Medicinal products for minors

-Different regulatory approaches and conduction of clinical trials on the example of antidiabetics-

Masterarbeit
Master‘s thesis

zur Erlangung des Titels
to obtain the Degree

“Master of Drug Regulatory Affairs, M.D.R.A”

der Mathematisch- Naturwissenschaftlichen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn

at the Faculty of Mathematics and Natural Sciences, Rhenish Friedrich-Wilhelms-University Bonn (Germany)

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Linguistic Notes

Throughout the entire thesis the British spelling `paediatric` is used. However, in cases where a fixed US term is used, the American spelling `pediatric` is retained instead. This also applies to all other words that have a British spelling and an American British spelling.

Abbreviations

Acc.	According to
AGPD	Arbeitsgemeinschaft Pädiatrische Diabetologie e.V.
ANZCTR	The Australian New Zealand Clinical Trials Registry
API	Active Pharmaceutical Ingredient
APSU	The Australian Paediatric Surveillance
ATC	Anatomic Therapeutic Code
ATTEMPT	Adolescent type 1 Diabetes Treatment with SGLT2i for Hyperglycaemia& Hyperfiltration
ARTG	The Australian Register of Therapeutic Goods
AusPAR	Australian Public Assessment Report for prescription medicines)
BCA	Best Pharmaceuticals for Children Act
BMI	Body Mass Index
CFR	Code of Federal Regulations
CHMP	Committee for Medical Products for Human Use
CTA	Clinical Trial Approval
CTIS	Clinical Trials Information System
CTN	Clinical Trial Notification
DCP	Decentralised Procedure
DDG	Deutsche Diabetes Gesellschaft
Dir.	Directive
DM	Diabetes Mellitus
E.g.	For example
Enpr-EMA	European Network of Paediatric Research at the European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practise
HC	Health Canada
HbA1c	Hämoglobin A_{1c}
HPFB	Health Products and Food Branch
HPRG	Health Products Regulation Group
HREC	Human Research Ethics Committee
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trial Registry Platform
ISPAD	International society for pediatric and adolescent diabetes
ISRCTN registry	International Standard Randomised Controlled Trial Number registry
JAPIC	Japan Pharmaceutical Information Center
JMA-CCT	Japan Medical Association Center for Clinical Trials
JRCT	Japan Registry of Clinical Trials
MAH	Marketing Authorisation Holder
MHLW	Ministry of Health, Labour and Welfare

MRP	Mutual Recognition Procedure
NIH	National Institute of Health
NIPH	Japan's National Institute of Public Health
NLM	Japan's National Institute of Public Health
NOC	Notice of Compliance
NPH	Neutral Protamine Hagedorn
PIP	Paediatric Investigation Plan
PDCO	Paediatric Committee
PMDA	Pharmaceutical and Medical Device Agency
PUMA	Paediatric-use marketing authorisation
PREA	Paediatric Research Equity Act
REG	Regulation
SPC	Supplementary protection certificate
SGLT2i	Sodium dependent glucose transporter-2 inhibitor
S3-Guideline	Third Stage Guideline
TGA	Therapeutic Goods Administration
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
UMIN	University Hospital Medical Information Network
WG	Working Group
WHO	World Health Organisation

1. Introduction

With the adoption of the Paediatric Regulation in 2006 and its entry into force in Europe in 2007, the primary objective was the improvement of children's health. Preferably, only drugs that were tested for safety and efficacy and were ethically researched as well as authorised should be used for paediatric therapy. The intension was to limit or even avoid off-label use of drugs that had only been proved in adults. The Europeans wanted to achieve this by strengthening the development and research of medicines for children and promoting more meaningful clinical trials. The goal has also been set to improve the information on the paediatric use of medicines.[1]

A report by the EU Commission in 2017 summarizing the decade of Paediatric Regulation concluded that the legislation "has had a *substantial impact on the development of paediatric medicines in the EU".*[2] According to the EU Commission, the success comes from an increase in paediatric research and in the number of new products with specific paediatric indications. For example, the number of paediatric trials increased from 8.30% in 2007 to 12.40% in 2016, as the EudraCT database has shown.[3]

What related developments have occurred in other industrialized countries – such as Australia, Canada and Japan? Did they take the European Paediatric Regulation or the US PREA (Pediatric Research Equity Act) and the BCA (Best Pharmaceuticals for Children Act) as a model? Have they therefore introduced a comparable law to improve the situation of children? Did the Paediatric Regulation actually lead to a higher number of children's trials and a higher number of medicines approved for children in Europe, compared to the other three countries? The measures and differences between the countries will be analysed in the following chapters.

In addition, it shall be examined whether and which types of clinical studies are carried out on children in these countries. Another aspect that will be considered encompasses the reasons for not conducting and failing a paediatric study as well as whether the data obtained from these studies can contribute to achieving approval for medicinal products

[1] Cf. European Medicines Agency, Paediatric Regulation.
[2] Cf. European Commission, State of Pediatric Medicines in the EU, p. 8.
[3] Cf. European Commission, State of Pediatric Medicines in the EU.

aimed at children. In this work, the situation of children will be examined with regard to antidiabetics.

1.1 Why antidiabetics?

Diabetes mellitus is a metabolic disease that can be divided into various types, such as diabetes mellitus type 1 and type 2. Type 1 is associated with the disruption of beta cells and results in an inability to produce insulin. This autoimmune disease usually occurs in childhood and is therefore called juvenile diabetes. Type 2 is often diagnosed in adults due to insulin resistance or insufficient insulin secretion. It often occurs in combination with obesity.[4]

The reason why this work deals with antidiabetics is that the disease has been spreading continuously, especially among children. The multicentre, twenty-year U.S. study SEARCH reveals a marked increase in children within both types from 2000 to 2020. Between 2002 and 2015, type 2 diabetes mellitus diagnoses in persons aged 10 to 19 years increased by 4.8% per year, the rate of type 1 diabetes mellitus diagnosed cases in children from 0 to 19 years of age by 1.9%.[5]

This is not only a problem pertaining to the USA. Increasing numbers of children suffering from diabetes mellitus have also been observed in European countries, India, China, Malaysia, and in parts of South America – according to the ISPAD (International Society for Pediatric and Adolescent Diabetes). This seemingly represents an important global health difficulty, especially in industrialized countries.[6]

In addition, it was discovered that paediatric type 2 diabetes mellitus exhibits a more rapid decline in pancreatic beta cells compared to adult T2DM (Type 2 diabetes mellitus). Adolescents who develop the disease have a significantly higher risk of morbidity and mortality in later adulthood than healthy children. It is therefore particularly important and

[4] Cf. Buttermore/Campanella/Priefer, The increasing trend of Type 2 diabetes in youth: An overview, 15, Diabetes & metabolic syndrome, 102253 (2021).
[5] Cf. Dabelea et al., Twenty years of pediatric diabetes surveillance: what do we know and why it matters, 1495, Annals of the New York Academy of Sciences, 99 (2021).
[6] Cf. P. Zeitler et al., ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth.

imperative that adequate as well as child-friendly therapy is made available and ensured.[7] Are there adequate treatment options for children in the EU, Australia, Japan, and Canada?

Currently, there are only three medicinal products with the active substances Metformin, Insulin, and Liraglutide approved by the FDA for the treatment of type 2 diabetes mellitus for paediatric use.[8] According to the TODAY study, *"the most effective approaches to treat youth with T2DM are not known".*[9]

This statement shows that there is great need for further investigation regarding the improvement of paediatric therapy options in the USA. What about the other industrialized countries?

1.2 Therapeutic recommendations using Germany as example

1.2.1 Type 1 diabetes mellitus

According to the S3-Guideline of the DDG (Deutsche Diabetes Gesellschaft) and AGPD (Arbeitsgemeinschaft Pädiatrische Diabetologie e.V.) from 2015, human insulin or insulin analogues should be used to treat type 1 diabetes mellitus in children. Both human insulin and its analogues are classified as equal.[10]

A combination of insulins is rarely used due to lack of flexibility.[11]

Nowadays, many children use insulin pumps, which contain short-acting insulin analogues. Otherwise, a combination of short-acting and long-acting insulin is recommended.[12]

Furthermore, Metformin is mentioned in the S3-Guideline of the DDG: It could be used in combination with insulin for the treatment of children and adolescents who suffer from

[7] Cf. Savic Hitt/Katz, Pediatric Type 2 Diabetes: Not a Mini Version of Adult Type 2 Diabetes, 49, Endocrinology and Metabolism Clinics, 679 (2020).
[8] Cf. Savic Hitt/Katz, Pediatric Type 2 Diabetes: Not a Mini Version of Adult Type 2 Diabetes, 49, Endocrinology and Metabolism Clinics, 679 (2020).
[9] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes, p. 74 (2007).
[10] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes (2007).
[11] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes (2007).
[12] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes (2007).

overweight, high insulin dose, or poor metabolic control. However, there is no general recommendation for the additive use of Metformin by the DDG, because in their option, the evidence for this is contradictory.[13]

1.2.2 Type 2 diabetes mellitus

Concerning therapy options of type 2 diabetes mellitus in children and adolescents, Metformin is the first-choice drug.[14]

Secondly, initial insulin therapy should be started if the initial HbA1c value is ≥ 9%, if spontaneous hyperglycaemia is ≥ 250 mg/dl, and if there are signs of absolute insulin deficiency (ketonuria, ketoacidosis).[15]

The DDG bases its recommendation of Metformin on the study results of the UK prospective diabetes study: Metformin is superior to sulfonylureas with the same metabolic control in terms of weight gain. However, this multicentre, prospective, randomised clinical trial was carried out in the 1990s, exclusively with type 2 diabetic patients aged 25-65 years.[16]

Have the medicinal products that are recommended for the therapy of children's diabetes mellitus and are part of the S3-Guideline also been approved in the other mentioned countries? This will also be analysed over the course of this work.

[13] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes, (2007).
[14] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes, (2007).
[15] Cf. P. Zeitler et al., Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes, 8, Pediatric diabetes, (2007).
[16] Cf. Deutsche Diabetes Gesellschaft, Diagnostik, Therapie und Verlaufskontrolle des Diabetes mellitus im Kindes- und Jugendalter. Aktualisierung 2015.

2. Regulatory authorities and systems

2.1 Canada

Health Canada is a federal department of the Canadian Ministry of Health and is responsible for the maintenance and improvement of the Canadian population's health.[17] Its portfolio includes the regulation of drugs, medical devices, consumer products, and food.[18]

Drug application reviews are performed by the national authority called Health Products and Food Branch (HPFB), which is part of Health Canada. It is also the authority's task to issue an approval in order to place the drugs on the market in form of a Notice of Compliance (NOC).[19]

In addition, HPFB is responsible for approving the conduction of a clinical trial in Canada and later reviewing information submitted after the clinical trial has been completed.[20]

In Canada, there are no regulations or laws that require the provision of information about the safety or efficacy of drugs for children when an adult drug is submitted for market access. Health Canada is only able to make a request to the pharmaceutical companies to conduct paediatric studies and therefore to provide data.[21]

In 2006, Health Canada found a way to incentivize research into paediatric indications. The department offers manufacturers of innovative drugs the opportunity to extend their eight-year data protection by six months, provided that results on safety and efficacy for paediatric use are available within five years after the receipt of the first Notice of Compliance (NOC). The information is then recorded on the label but must not lead to the approval of a paediatric indication. [22] [23]

Another measure is the establishment of the Office of Paediatric Initiatives and of the Paediatric Expert Advisory Committee (PEAC). PEAC was founded in 2009 and consists of experts who play an advisory role for the Health Products and Food Branch (HPFB). Their job is to support the development of paediatric information on health products, food and

[17] Cf. Canada, Health Portfolio - Canada.ca.
[18] Cf. Canada, Health Canada mandate and role: who we are and what we do - Canada.ca.
[19] Cf. Canada, How Drugs are Reviewed in Canada - Canada.ca.
[20] Cf. Canada, How Drugs are Reviewed in Canada - Canada.ca.
[21] Cf. Clarivate, How to Market Drugs for Pediatric Use (Canada).
[22] Cf. Health Canada, Health Canada's Clinical Trials Database - Canada.ca.
[23] Cf. Clarivate, How to Market Drugs for Pediatric Use (Canada).

nutrition, as well as the conduction of paediatric clinical trials to make health products safer. Thanks to the committee, there is a lively exchange of information and ideas between the different stakeholders, experts, and the agency.[24]

To help themselves, paediatricians and related healthcare professionals at the hospital of Toronto created a handbook called SickKids Drug Handbook & Formulary, which contains relevant information and recommendation on drug selection, use, and dosing for children. It is a collection of essential information from over 30 years of experience of paediatric medication.[25]

2.2 Japan

In Japan, after a period of reorganization and restructuring, the Pharmaceutical and Medical Device Agency (PMDA) was established in 2004. Since then, the agency's main tasks have included the consultation on clinical trials, regulatory and scientific review, as well as management of the approval of drugs and medical devices.[26]

PDMA is an independent regulatory agency that issues a recommendation for approval to the Ministry of Health, Labour and Welfare (MHLW) after reviewing the submission of a new pharmaceutical product or medical device. Both work hand in hand. The MHLW mostly follows the PMDA's recommendations.[27]

There is no law in Japan requiring clinical trials on children for newly-developed drugs. In addition, the companies that manufacture their drugs for the Japanese market are not required to develop drug formulations for children.[28]

Nevertheless, the Ministry of Health of Japan has taken the following measures to support medicinal products for the paediatric population:

- Creation of the Pediatric Pharmaceuticals Working Group in 2011.
- Creation of incentives for the companies in the form of extending the re-examination period.

[24] Cf. Clarivate, How to Market Drugs for Pediatric Use (Canada).
[25] Cf. SickKids, Pharmacy & Drug Formulary.
[26] Cf. PDMA, Services of PMDA | Pharmaceuticals and Medical Devices Agency.
[27] Cf. Satoru Magaska, Benjamin Lang, Mihoko Shintani, Sayaka Ueno, An Overview of Pharmaceutical and Medical Device Regulation in Japan.
[28] Cf. PDMA, Services of Pharmaceuticals and Medical Devices Agency.

- Establishment of the Council of Unapproved Drugs and Indications in 2010.
- Establishment of a clinical trial system.

The Paediatric Pharmaceuticals Working Group started its efforts in 2011, aiming to promote paediatric drug development. The WG's team of 16 members identifies and analyses paediatric issues and discusses them with different stakeholders, such as medical institutions and industry groups. The team's main efforts are focused on encouraging industries and investigators to develop paediatric medicines. Concerning the question of which developments have been achieved, a yearly report is published by the WG. As a result, the establishment of this WG appears to be an attempt by the authorities to improve and support paediatric drug development. It also seems that the WG has no influence and just exercises representative functions.[29]

A further effort is, for instance, the revision of the Pharmaceuticals and Medical Devices Act (PMD Act) from 2020. The revision's aim is to identify drugs with a high need in children and which are not indicated for use in paediatric patients. They will be defined as *"drugs for specific use"*[30] and will become candidates for a priority review. In the future, it shall become clear whether the revision was successful.[31]

Furthermore, there is a possibility to extend the re-examination period. The re-examination period of a medicinal product is the time during which the originator pharmaceutical company is protected against marketing of generic products. It can be equated with the marketing exclusivity and data protection in the EU and the U.S. This represents a great financial advantage for the holder of the marketing authorisation. How long the re-examination period lasts, depends on the medicinal product's properties (between four and ten years). In addition, during this period, the marketing authorisation holder is required to conduct a post-marketing study and report the results to the MHLW. The period can be extended to a maximum of ten years, if a clinical trial is planned, to find out the

[29] Cf. Pediatric Working Group in the PMDA, Current Situation and Challenges of pediatric clinical studies in Japan.
[30] Cf. PMDA, Latest trend of pharmaceutical and medicial device regulation in Japan, p. 7.
[31] Cf. PMDA, Latest trend of pharmaceutical and medicial device regulation in Japan.

children's dosage. This can be planned during or after the marketing authorisation's application.[32]

Apart from this, in 2010, a council of unapproved drugs and indications was established. Its aim is to give the MHLW advice regarding highly-needed unapproved drugs or indications in Japan, which are simultaneously being used in at least one of the following six countries: Australia, Canada, France, Germany, UK, or USA. It also includes paediatric indications or paediatric drugs. In actuality, no data is available to measure the action's success.[33]

Also, in 2010, the Pediatric Clinical Trials Network was established in order to support the promotion of drug development for minors. The founder hoped that an infrastructure would be built, that the network's resources would lead to an improvement of paediatric clinical trials' quality, and that this would speed up the conduction of clinical trials.[34]

2.3 Australia

The Australian regulatory authority for pharmaceuticals is called the Therapeutic Goods Administration (TGA). It is part of the Health Products Regulation Group (HPRG) in the Australian Government Department of Health and is responsible not only for medicines but also for biologicals and medical devices. These three categories are summarized as therapeutic goods.[35]

There is no law or regulation obliging pharmaceutical companies to develop medicinal products for children. The companies are only encouraged by the TGA to examine whether their drug is suitable for children or to examine the possibility of developing suitable paediatric formulations. Furthermore, the TGA does not offer any incentives in the form of an extended market exclusivity, for example.[36]

The Australian agency adopted European Union guidelines regarding paediatric topics to facilitate and support the generation of paediatric data and the extrapolation of data from one patient population to another. E.g., the *EU Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population*

[32] Cf. PMDA, Pediatric drug development in Japan and international regulatory collaboration.
[33] Cf. PMDA, Pediatric drug development in Japan and international regulatory collaboration.
[34] Cf. Pediatric Clinical Trials Network Office, Information Flyer about the Pediatric Clinical Trials Network.
[35] Cf. Therapeutic Goods Administration, TGA basics.
[36] Cf. Therapeutic Goods Administration, 1.10 Information relating to paediatrics.

(EMEA/SHMP/EWP/147013/2004) or the *Reflection Paper Formulation of Choice for the Paediatric Population* (EMEA/CHMP/PEG/194810/2005) have been accepted. [37] [38]

Among the Australian agency's different committees, there is no specific committee that deals with issues pertaining to medicines for paediatric use.[39]

The Australian Paediatric Surveillance Unit (APSU) could be mentioned here. Established in 1993, the APSU is the only Australian board or platform that collects data to facilitate active surveillance of childhood diseases, such as uncommon childhood illnesses, complications of common disorders, or adverse treatment effects. With its work, the APSU supports the development of clinical guidelines for paediatricians and research regarding children's health. It plays a major role in improving and ensuring the wellbeing of children. The study results and data are published annually through an APSU report. The diseases brought into focus depend on their public health implications and their impact on health resources.[40]

2.4 European Union

Since 2007, with the passing of the Paediatric Regulation No. 1901/2006, applicants for a marketing authorisation are required to develop a PIP (Paediatric Investigation Plan). A PIP is defined as a research and development programme that ensures that data are worked out for determining suitability of a medicinal product for the treatment in the paediatric population.[41]

The aim and purpose are to strengthen the development of medicines for children, improve information on the paediatric use of medicines and, at the same time, to avoid unnecessary clinical trials involving children.[42]

The obligation to carry out a PIP applies to medicinal products with a new application for authorisation in the EU, unless there is a reason for a waiver or deferral (Art. 7 REG No. 1901/2006). The obligation for a PIP also includes applications, e.g., for new indications or new dosage forms for drugs that are already authorised in the EU (Art. 8 REG No.

[37] Cf. Clarivate, How to Market Drugs for Pediatric Use (Australia).
[38] Cf. Therapeutic Goods Administration, 1.10 Information relating to paediatrics.
[39] Cf. Therapeutic Goods Administration, Committees.
[40] Cf. The Australian Paediatric Surveillance Unit at Kids Research, About the Australian Paediatric Surveillance Unit.
[41] Cf. European Medicines Agency, Paediatric investigation plans.
[42] Cf. European Medicines Agency, Paediatric investigation plans.

1901/2006). The regulation pertains to all applications for a marketing authorisation for medicinal products in the EU from 26 July 2008 onward.[43]

The extension of the lifetime of an SPC (Supplementary Protection Certificate) by a further six months serves as an incentive. The extension is given, when necessary results are submitted as part of an application of marketing authorisation, no matter whether a medicinal product is indicated for the use in the paediatric population. Generics, hybrids, biosimilars and well-established medicines are excluded.[44]

PIPs are assessed by the PDCO (Paediatric Committee). It is one of the committees of the EMA that was established when the Paediatric Regulation was passed. The PDCO is responsible for the activities regarding medicinal products for the paediatric population.[45]

One of the most important tasks of the PDCO is to review the PIPs to decide whether clinical trials involving children must be conducted or whether a waiver or deferral is required. Although the PDCO is not involved in the evaluation and the assessment of marketing authorisation applications, it has an advisory role for the CHMP and therefore represents a bottleneck for the authorisation of medicinal products. At the end of the procedure, it is the role of the CHMP to give a final opinion for marketing authorisation to the EC (European Commission). However, it is influenced by the PDCO.[46]

Another incentive to support the development of medicines for children is the PUMA (Paediatric-use marketing authorisation). This tool was also introduced under the Paediatric Regulation and can be used for drugs that are already authorised, drugs that are no longer covered by the SPC, or drugs developed for paediatric use only. For all these drugs, the MAH can submit an application for a new indication or an additional child-friendly formulation. As a reward, the MAH receives eight plus two years of data and market protection and the ability for access to the centralised procedure, while also benefiting from a partial fee exemption for a year.[47]

[43] Cf. European Medicines Agency, Paediatric investigation plans.
[44] Cf. European Medicines Agency, Paediatric investigation plans.
[45] Cf. European Medicines Agency, Paediatric Committee (PDCO).
[46] Cf. European Medicines Agency, Paediatric Committee (PDCO).
[47] Cf. European Medicines Agency, Paediatric-use marketing authorisations.

2.5 Overview of roles of the different committees and conclusion

The following table shows which competent authority has a committee that takes care of the needs of the paediatric population as a vulnerable group.

	Australia	Canada	Japan	EU
Committee available?	No specific committee	PEAC	Paediatric Pharmaceuticals Working Group	PDCO
Committee voice?	-	No, only advisory role and discussion with different stakeholders.	No, only identifies and analyses paediatric issues, discussions with different stakeholders.	Yes, it reviews the PIP and therefore is involved in the evaluation and assessment of marketing authorisation applications.

Table No. 1: Overview of the availability and the roles of the different committees (own representation based on sources in chapter 2.1.-2.4.).

Only EMA has the PDCO, whose main work contains the scientific evaluation and adoption of opinions on PIPs. Furthermore, the study results' evaluation is in compliance with an agreed PIP. As a result, it is an important player in the assessment of the approval documents and a co-decider for or against approval.

In contrast, the Canadian and Japanese committees can only be viewed as representative, since they have no say in the approval process.

2.6 Adoption of ICH E11

In 2000, the ICH created the E11 Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population. It aims to provide an overview of critical issues encountered in paediatric drug development. Another goal is to offer approaches on how to conduct a study safely, efficiently, and ethically. In 2017, the guidelines were updated due to new scientific and technical knowledge and new regulatory requirements.[48] [49]

[48] Cf. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Addentum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E1 (R1) 2017.
[49] Cf. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Efficacy Guidelines.

According to the ICH Health Canada, the EU and Japan have implemented the guideline. Australia is the only one of the countries addressed in this work that has not employed the paediatric guideline.[50] [51]

3. Methods

To research the medicinal products approved in the various countries the databases on the websites of the respective authorities were used. All databases and the search criteria used are presented in the sub-chapters of chapters 4 and 5. The information on paediatric approval could also be obtained from these sources, but also from the product information of the drugs. For this work, all medicinal products authorized between 01/2008 and 12/2021 were identified.

Information on clinical trials was obtained from the US clinicaltrials.gov database and in addition, from the national databases of the respective countries. The databases are presented in chapter 6 and 7. The work focused on the period from January 2008, the year in which the EU Paediatric Regulation was passed, to Dec. 2021. The search criteria used are also mentioned in the chapters.

4. Authorised medicinal products for the treatment of diabetes mellitus type 1 and 2

The following section shows which antidiabetics are generally accessible on the market in the individual countries and which sources are available to determine them.

In addition, annex No. 1 summarizes all antidiabetics that are authorised for the markets of the EU, Australia, Canada, and Japan.

[50] Cf. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Addentum to ICH E11: Clinical Investigation of Medicinal Products in the Pediatric Population E11 (R1) 2017.
[51] Cf. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Efficacy Guidelines.

4.1 Canada

The medicinal products that are approved or marketed in Canada can be found on the website of Health Canada. Therefore, a drug product database is available of all medicinal products marketed and authorised on the Canadian market. The keywords used in the database to find drugs for the treatment of diabetes mellitus have been the ATC (Anatomical Therapeutic Chemical) numbers A10A and A10B. A10A includes Insulin and analogues. A10B contains blood glucose lowering drugs, excluding insulin.[52]

The following entries have been found (Status 2021-12-03):[53]

- A10A: 103 entries.
- A10B: 474 entries.

Canadian authorised and marketed medicinal products, originator and generics for the treatment of diabetes mellitus type 1 and type 2 are collected and summarized in annex No. 2.

Those approved for children are marked in green. In addition, all information is listed pertaining to the reasons that led to a rejection of the paediatric application.

4.2 Japan

The Japanese health authority PDMA has listed all approved medicinal products for the Japanese market on its website, organised by the year in which they were approved. Related review reports can also be found on the PMDA website. Still, only review reports that have been translated into English are listed. Thus, the list of published review reports is not exhaustive. Important data about the indication or the use in the paediatric population are also often missing in these documents. This information is also documented in the column *review reports* of annex No. 3.[54]

In addition, PMDA provides package inserts for prescription drugs authorised for the Japanese market. Unfortunately, all documents are only available in the Japanese language. Additionally, little information about the drug authorisation status for children is

[52] Cf. Health Canada, Services and information.
[53] Cf. Government of Canada, Health Canada Public Affairs Consultation and Regions Branch, Drug Product Database Online Query.
[54] Cf. Pharmaceuticals and Medical Device Agency, Review reports: drugs.

provided. In most cases, section 9.7 merely states that no studies have been carried out on children. There is also no further justification for it.[55] [56]

The website RAD-AR can also be mentioned as a further information research tool. It is a website powered by the *Council for the Proper Use of Medicine* with the aim to enable the general public to have access to medicinal product information. Drug information sheets which are provided are almost similar to, e.g., the product information of European products. Information regarding the indication, usage, and dosage of most of the medicinal products on the Japanese market are included.[57]

Basically, it should be noted that very little information is available on approved antidiabetics and specifically for use in children. The data provided by the authority is very opaque. A big problem is that many documents are only provided in Japanese, very few of these documents are also translated into English. It is very difficult to find out which medicines are even approved for use in children. All data that could be collected from this website are available in the column *paediatric use* in annex No. 3. All other information that could be collected for this is summarized in this annex.

4.3 Australia

In Australia, an AusPAR has been created for each prescription drug. According to its definition, an AusPAR, an Australian Public Assessment Report for prescription medicines, is a report created by the TGA. It contains information about the evaluation of the drug and grounds for approval or refusal. It is comparable to the European Public Assessment Report (EPAR), which is issued by the European Medicines Agency (EMA).[58] [59]

All therapeutic goods, including medicinal products, are entered in the Australian Register of Therapeutic Goods (ARTG) after they are approved and authorised for delivery in Australia.[60] All medicines that require a prescription will be obligatorily registered in the

[55] Cf. Pharmaceuticals and Medical Device Agency, Prescription drug information retrieval.
[56] Cf. Pharmaceuticals and Medical Devices Agency, Information retrieval of ethical drug package inserts.
[57] Cf. RAD-AR, About the council.
[58] Cf. Therapeutic Goods Administration, Australian Public Assessment Reports for prescription medicines (AusPARs).
[59] Cf. Therapeutic Goods Administration, AusPARs: Questions & answers.
[60] Cf. Therapeutic Goods Administration, Australian Register of Therapeutic Goods.

ARTG. They are evaluated for efficacy. Most of the over-the-counter medicines are also registered.[61]

To identify which medicines have been prescribed and registered regarding the indication diabetes mellitus and that are pertinent to this work, it was necessary to search in the ARTG. Because there is no possibility to filter for the indication, the entire list had to be sifted through. Only the following filters could be set:[62] [63]

- Type: therapeutic good type: Medicines.
- ARTG category: Registered.
- Date: Start date after: 01.01.2008.

The database cannot be filtered for medicinal products that are also approved for use in children. Therefore, every ARTG document had to be reviewed for information on its use in paediatric patients.

All information that could be found for antidiabetics authorised in general and additionally for children is listed in annex No. 4.

4.4 European Union

The European public assessment report (EPAR) is a document published by the EMA after a medicinal product has been granted or refused marketing authorisation via the centralised procedure. An EPAR contains public information about the assessment and the grounds for the opinion by the agency.[64]

In the EMA's database, it is possible to search for EPARs of antidiabetics using the ATC codes A10A (Insulins and Analogues) and A10B (Antidiabetics, excl. Insulins) or using the filter for the therapeutic area *diabetes mellitus*.[65]

Furthermore, one may filter for PIPs, which are available for medicinal products authorised after 2007 or drugs that fall under the §8 of the Paediatric Regulation No. 1901/2006.

[61] Cf. Therapeutic Goods Administration, How we regulate medicines.
[62] Cf. TGA, ARTG search.
[63] Cf. Therapeutic Goods Administration, Search the TGA website.
[64] Cf. European Medicines Agency, European public assessment reports: background and context.
[65] Cf. European Medicines Agency, Medicines.

Information on the grounds for a refusal, a deferral, a waiver, or an approval for the paediatric population and the different age groups can be found in this document.[66]

All information from the EPARs and PIPs are collected in annex No. 5.

4.5 Conclusion of usage of databases and available information

It has proven to be rather difficult to obtain information about approved antidiabetic drugs. For example, the data provided by PMDA for the Japanese market is very opaque. It is to be regarded as problematic that many documents are only provided in Japanese language and only a few documents are translated from Japanese into English.

Additionally, little information is available on government websites about the drug authorisation status for children, not only for Japanese market but also for all other countries that are analysed. Often, there was no filter in the databases, making the search highly tedious.

Basically, the data situation is exceedingly confusing. Little information is provided pertaining to the use of medication by children. Direct requests toward the authorities regarding a list of approved antidiabetics in the countries and a list of medicines for children were rejected. The only response was a referral to the general authority's website.

Most of the required information was only provided on the EMA. The data situation is transparent and clear in comparison to the others.

5. Authorised medicinal products for the paediatric population

5.1 Canada

Annex No. 2 lists all antidiabetics that are currently authorised in Canada. Products with a green background are also authorised for children.

[66] Cf. European Medicines Agency, Medicines.

The following table provides an additional overview of all medicinal products currently authorised for children regarding the treatment of type 1 and type 2 diabetes mellitus by Health Canada. The active ingredients are in bold. The brand names are underneath.

Medicinal product/ API	Indication
Insulin aspart: 1: Kirsty/ Novorapid/ Trurapi 2: Fiasp	1: It is not mentioned that the product is authorised for children. However, there is the following statement for paediatrics from 2- 17 years of age: *"Evidence from clinical studies and experience suggests that use in the paediatric population is not associated with any differences in safety or effectiveness"*[67] – which also applies to adults. 2: Can be used in paediatric patients aged 2 years and above. Studies have been performed.[68]
Insulin degludec 1: Xultophy 2: Tresiba	1: Only for adults: no studies have been performed in patients below 18 years of age.[69] 2: Tresiba is indicated for the treatment of paediatric patients aged 2 years and older, but only for diabetes mellitus type 1.[70]
Insulin detemir Levemir	Is indicated for the treatment of paediatric population above 2 years of age. Statement for paediatrics (<18 years): *"Evidence from clinical studies and experience suggests that use in the paediatric population is not associated with any difference in safety or effectiveness."*[71]
Insulin glargine 1:Toujeo 2: Basaglar 3: Lantus	1: Safety and effectiveness have not been established for paediatric population.[72] 2: For children aged 6 years and older, only diabetes mellitus type 1. Safety and efficacy have been established for children over 6 years of age with type 1 diabetes mellitus.[73]

[67] Cf. BGP Pharma ULC, Kirsty Product Monograph, p. 4.
[68] Cf. Novo Nordisk Canada Inc., Fiasp Product Monograph 2020.
[69] Cf. Novo Nordisk Canada Inc., Xultophy Product Monograph 2020.
[70] Cf. Novo Nordisk Canada Inc., Tresiba Product Monograph 2021.
[71] Cf. Novo Nordisk Canada Inc., Levemir Product Monograph 2021, p. 4.
[72] Cf. Sanofi- Aventis Canada Inc., Toujeo SoloStar and Toujeo DoubleStar Product Monograph 2019.
[73] Cf. Eli Lilly Canada Inc., Basaglar Product Monograph 2021.

Medicinal product/ API	Indication
	3: Safety and effectiveness have been established regarding children over 6 years of age for treatment of type 1.[74]
Insulin glulisine Apidra	For use in children aged 6 years and older. Efficacy and safety have been established.[75]
Insulin human 1: Novolin 2: Humulin	1: No data available.[76] 2: If clinically indicated, may be used in children.[77]
Insulin lispro 1: Lyumjev 2: Admelog 3: Humalog	1: Clinical trials have been performed in children.[78] 2: Safety and efficacy in children have been established, authorised for children aged 3 years or older.[79] 3: Clinical trials have been performed with children aged 3 years and above.[80]
Liraglutide 1: Saxenda 2: Victoza	1: For children above 12 years of age. Safety and efficacy have been established.[81] 2: Authorised for children aged 10 or older.[82]

Table No. 2: overview of antidiabetics authorised for use in children in Canada (Own representation based on sources see footnotes).

This means that only eight of 32 available active pharmaceutical ingredients or the combination of two or more APIs are investigated and evaluated by Heath Canada for the treatment of diabetes mellitus in children and can be used for in-label use.[83]

For the treatment of type 2 diabetes mellitus, only Liraglutide is available as authorised therapeutic option. Liraglutide has been investigated in paediatric studies and deemed suitable regarding safety and efficacy.[84]

[74] Cf. Sanofi- Aventis Canada Inc., Lantus Product Monograph 2021.
[75] Cf. Sanofi- Aventis Canada Inc., Apidra Product Monograph 2021.
[76] Cf. Novo Nordisk Canada Inc., Novolin GE Product Monograph 2021.
[77] Cf. Eli Lilly Canada Inc., Humulin R, Humulin N, Humulin 30/70 Product Monograph 2021.
[78] Cf. Eli Liliy Canada Inc., Liprelog Product Monograph 2021.
[79] Cf. Sanofi- Aventis Canada Inc., Admelog and Admelog SoloStart Product Monograph 2021.
[80] Cf. Eli Liliy Canada Inc., Humalog 200 units/mL KwikPen, Humalog Mix25, Humalog Mix50 Product Monograph 2021.
[81] Cf. Novo Nordisk Canada Inc., Saxenda Product Monograph 2021.
[82] Cf. Novo Nordisk Canada Inc., Victoza Product Monograph.
[83] Cf. Annex No 2 Authorized medicinal products Canada.
[84] Cf. Annex No 2 Authorized medicinal products Canada.

Surprisingly, there is no paediatric approval for Metformin. According to the product information of the marketed products accessible on the Health Canada website, Metformin is only authorised for adults. In most cases, it is stated that no safety or efficacy studies have been carried out involving patients under 18 years of age. No further information is available in these documents.[85]

The only document that provides additional data is the product information of Janumet, the brand name of the fixed-dose combination product of Sitagliptin and Metformin. It reveals that clinical trials have been conducted with patients aged 10 to 17, in which the profile of adverse reactions was comparable to that in adults. Simultaneously, an increased risk of hypoglycaemia was observed. Other studies are not mentioned. Thus, it is not possible to determine whether any exist or what potential outcomes they had.[86]

In chapter 7.4 of this work a further discussion is held about Metformin in the different countries.

It can also be observed that there are active substances which differ in their approval for different age groups. For example, Xultophy, with the active ingredient Insulin degludec, is only authorised for adults. The product information reveals that *"no studies have been performed with Xultophy in patients below 18 years of age"*.[87] Compared to that, Tresiba, which contains the same API, has been investigated and indicated for the treatment of children above 2 years of age.[88]

The same situation can be observed for Insulin glargine: Toujeo is only indicated for adults. It is noted in the product information that safety and effectiveness have not been established for the paediatric population. In comparison, Basaglar can be used in children aged 6 and older. Within the product information of Lantus, it is mentioned that studies have been conducted with children over six years of age. However, it remains unclear whether there is an authorisation for the treatment of children from this age upward.[89] [90] [91]

[85] Cf. Sanofi- Aventis Canada Inc., Glucophage Product Monograph.
[86] Cf. Merck Canada Inc., Janumet and Janumet XR Product Monograph including Patient Medication Information.
[87] Cf. Novo Nordisk Canada Inc., Xultophy Product Monograph including Patient Medication Information, p. 4.
[88] Cf. Novo Nordisk Canada Inc., Tresiba Product Monograph 2021.
[89] Cf. Sanofi- Aventis Canada Inc., Toujeo SoloStar and Toujeo DoubleStar Product Monograph 2019.
[90] Cf. Sanofi- Aventis Canada Inc., Lantus Product Monograph 2021.
[91] Cf. Eli Lilly Canada Inc., Basaglar Product Monograph 2021.

The phenomenon that one and the same active ingredient in different preparations has different approvals for different age groups may be due to the fact that they differ, e.g., in their excipients or dosage forms. For different excipients or dosage forms, separate clinical trials are required. In these cases, it is perplexing why no paediatric studies have been carried out for Toujeo, or if the conducted studies failed.[92]

For Insulin human, there is no concrete statement regarding the age limit. In many countries, Insulin human is normally part of the standard therapy for the treatment of type 1 diabetes in children of all ages. In the Canadian product information, it is only stated that there is no data available for the paediatric population (Insulin human Novonordisk) [93] or that *"Humulin may be used in children and adolescents, if clinically indicated"*[94] but without any specifications.

Most of the reasons why there is no approval for the paediatric population are the following:

- Safety and efficacy in paediatric patients or in patients under 18 years of age have not been established.[95]
- The drug has not been studied in paediatric patients or pharmacokinetics and pharmacodynamics in the paediatric and adolescent population have not been studied.[96]

However, in none of the product information, it is mentioned why safety and efficacy could not be established. Perhaps studies have been performed, but the results show that the medicines should not be used in children, or no children were included in the studies at all.

Health Canada has published an administrative list of all medicinal products authorised and marketed, which have paediatric information about the safety and efficacy or are authorised for the use in children. The list contains the following antidiabetics: [97]

[92] Cf. Sanofi- Aventis Canada Inc., Toujeo SoloStar and Toujeo DoubleStar Product Monograph 2019.
[93] Cf. Novo Nordisk Canada Inc., Novolin GE Product Monograph.
[94] Cf. Eli Lilly Canada Inc., Humulin R, Humulin N, Humulin 30/70 Product Monograph 2021, p. 8.
[95] Cf. Annex No 2 Authorized medicinal products Canada.
[96] Cf. Annex No 2 Authorized medicinal products Canada.
[97] Cf. Health Canada, List of therapeutic products with paediatric information available in their labelling.

Brand name	API	Paediatric indication
Apidra	Insulin glulisine	>6 years of age
Humalog (not for Humalog MIX25 or MIX50)	Insulin lispro	>3 years of age
Humulin R/N/ 30/70	Insulin human	Yes (no more data)
Levemir	Insulin detemir	>2 years of age
Victoza	Liraglutide	No, but there are clinical trials.

Table No. 3: list of approved antidiabetics for children in Canada (Own representation based on source, see footnote)[98]

Providing the list seems like a good measure to get an overview without studying the product information of each medicinal product. However, the list was last updated in November 2014 and appears to be out of date.[99]

According to the list, no medicinal products are available for the treatment of type 2 diabetes mellitus in children. For Liraglutide, it is only stated that clinical trials have been conducted. Still, there is no paediatric authorisation.[100]

Furthermore, it should be mentioned that the list of HC does not contain Insulin aspart, Insulin degludec, and Insulin glargine.[101]

Perhaps all four drugs were authorised for children after 2014. All in all, it can be said that this list is not complete and does not offer any help for the choice of therapy, especially not for the therapy of type 2 diabetes mellitus.

5.2 Japan

The following table shows all medicinal products that are currently authorised for children regarding the treatment of type 1 and type 2 diabetes in Japan. Additionally, annex No. 3

[98] Cf. Health Canada, List of therapeutic products with paediatric information available in their labelling.
[99] Cf. Health Canada, List of therapeutic products with paediatric information available in their labelling.
[100] Cf. Health Canada, List of therapeutic products with paediatric information available in their labelling.
[101] Cf. Health Canada, List of therapeutic products with paediatric information available in their labelling.

lists all antidiabetics that are authorised for the Japanese market. Products with a green background are also authorised for the paediatric population.

Medicinal product/ API	Indication
Insulin degludec Tresiba	For the treatment of diabetes mellitus in general, also for children.[102]
Metformin Melbin, Glycoran, Metgluco	Since 2014, the drug can be used in children for the treatment of type 2 diabetes mellitus. Additionally, there is a paediatric dosage recommendation. However, it is mentioned that no studies have been conducted.[103] [104]

Table No. 4: overview of antidiabetics for use in children in Japan (own representation based on sources see footnotes).

Only Metformin is authorised for children for the treatment of type 2 diabetes mellitus. In the documents, it is delineated that studies involving children over 10 years of age have been conducted. Additionally, in the Metgluco document, it is revealed that there are limited experiences with children under 10 years of age and that clinical trials for infants, newborn, low weight infants and young children are currently not given. Limited experience with children under the age of 10. No further information has been made available, not even about the studies' outcomes or the age limit for the medicinal product. The information is paradoxical and misleading. It cannot be concluded whether the medicine is authorised for use in children above 10 years of age or not.[105]

Amaryl with Glimepirid as an active substance deserves a mention. According to the documents, studies with children from 9 to 16 years of age have been performed. The data were insufficient. There have only been uncontrolled studies. Furthermore, it is stated that the administration to children aged below 9 years of age is not recommended due to the lack of safety data. Consequently, it cannot be concluded whether the medicine is authorised for use in children or not, because there is no clear statement on the status of approval and the age limit for children.[106]

[102] Cf. Pharmaceuticals and Medical Device Agency, Review Report for Tresiba FlexTouch and Tresiba Penfill.
[103] Cf. Pharmaceuticals and Medical Device Agency, New Drugs Approved in FY 2014.
[104] Cf. RAD-AR, Metformin Tablets 250 Drug Information.
[105] Cf. Pharmaceuticals and Medical Device Agency, Metformin 250mg and 500mg, Product information.
[106] Cf. Sanofi, Amaryl 3mg Product information.

According to the documents that are available, Insulin degludec is the only further drug approved in addition to Metformin. In the product information of Tresiba, it is indicated that the drug can be used for *"Diabetes mellitus where treatment is required"*.[107] It can be interpreted that Tresiba is for the treatment of diabetes mellitus in general, also for children. There is no further information.[108]

In most of the cases, the drugs' product information confirms that no studies have been conducted in children or, alternatively, that there is no experience of their application regarding children.[109]

In general, it should be noted that not much data and information from the PMDA are publicly available. Only a limited amount of data are available in English. It is difficult to believe that only two drugs are approved for therapy in children and, above all, that only one insulin is available.

5.3 Australia

The following table depicts all medicinal products that are currently authorised for children regarding the treatment of type 1 and type 2 diabetes in Australia. Additionally, annex No. 4 lists all antidiabetics that are authorised for the Australian market. Products in the annex with a green background are also authorised for children.

Medicinal product/ API	**Indication**
Insulin aspart/ degludec Ryzodeg	Ryzodeg can be used in children and adolescents from the age of 6 years. Clinical trials performed/data are available.[110]
Insulin detemir Levemir	Authorised from the age of 2 years; data is available acc. product information.[111]

[107] Cf. Pharmaceuticals and Medical Device Agency, Review report for Tresiba FlexTouch and Tresiba Penfill, p.3.
[108] Cf. Pharmaceuticals and Medical Device Agency, Review report for Tresiba FlexTouch and Tresiba Penfill.
[109] Cf. Annex No 3 Authorized medicinal products Japan.
[110] Cf. Therapeutic Goods Administration, Australian Product Information Ryzodeg 70/30 FlexTouch and Penfill.
[111] Cf. Therapeutic Goods Administration, Australian Product Information Levemir FlexPen and Levemir Penfill.

Medicinal product/ API	Indication
Insulin glargine 1: Toujeo Max SOLOSTAR 2: Optisulin 3: Basaglar KwikPen 4: Toujeo Solostar	1: Only for adults, no studies performed.[112] 2: From age of 6 years, below not demonstrated.[113] 3: For treatment of type 1 diabetes mellitus in adults and children.[114] 4: Safety and efficacy have been demonstrated. Authorised for children aged 6 years and above.[115]
Insulin human Mixtard, Protaphane	Dosage for children available in the Product information, but it is also stated that for paediatric use *"data were not assessed as part of this medicine registration"*.[116]
Insulin lispro Humalog	Can be used from ages 3 years and upward; clinical studies involved children.[117]
Metformin 1: Metcip, Apo- Metformin, Cipla-Metformin, Diaformin, Emnorm, Metmin 2: Metformin STR 3: Apx Metformin 4: Pharmacor Metformin, Diaxemet	1: From 10 years of age.[118] 2: It is only written down in the product information that the drug can be used for the treatment of diabetes mellitus type 2, no age statement.[119] 3: Not recommended for use in children.[120]

[112] Cf. Therapeutic Goods Administration, Australian Product Information- Toujeo Max Solostar (Insulin glargine).
[113] Cf. Therapeutic Goods Administration, Australien Product Information- Optisulin/ Optisulin Solostar (Insulin glargine).
[114] Cf. Therapeutic Goods Administration, Public Summary Basaglar KwikPen Insulin glargine 100IU/ml.
[115] Cf. Therapeutic Goods Administration, Australian Product Information- Toujeo Solostar (Insulin glargine).
[116] Cf. Therapeutic Goods Administration, Australian Product Information Actrapid, Mixtard, Protaphane, p. 6.
[117] Cf. Therapeutic Goods Administration, Australian Product Information Humalog U200 Kwikpen (Insulin lispro).
[118] Cf. Therapeutic Goods Administration, Australian Product Information- APO Metformin 500, 850, 1000).
[119] Cf. Therapeutic Goods Administration, Public Summary Metformin STR Metformin HCl 1000mg.
[120] Cf. Therapeutic Goods Administration, Australian Product Information- APX Metformin (Metformin HCl) Tablets.

Medicinal product/ API	Indication
	4: Only for adults, absence of paediatric data available.[121]

Table No. 5: overview of antidiabetics for use in children in Australia (own representation based on sources, see footnotes).

In Australia, only the different types of Insulin – Insulin detemir and Insulin glargine as well as the combination of Insulin aspart and Insulin degludec, Insulin human, Insulin lispro and, additionally, Metformin – are authorised for the use in children regarding the treatment of diabetes mellitus. Therefore, Metformin is the only active pharmaceutical ingredient authorised for the treatment of diabetes mellitus type 2 in children.[122]

Based on the available documents on Insulin aspart, it is not possible to make an exact statement as to whether the active ingredient is approved for use in children or not.

On the one hand, the product information of Truvelog mentions that no data are available for paediatric use. On the other hand, it is stated that *"care should be taken, especially in children, to match insulin doses".*[123] This does not exclude the use in children, but it is not clear if Truvelog is authorised by the competent authority for paediatric use.[124]

Furthermore, there are data available for Novorapid, confirming that studies in children have been conducted, but safety and effectiveness have not been assessed due to limited information and limited clinical experience.[125]

So, consequently, no statement can be made about the status of the paediatric approval. Paradoxically, however, the combination of Insulin aspart and Insulin degludec is authorised for children.[126]

[121]Cf. Therapeutic Goods Administration, Australian Product Information Diaxemet XR 500, Diaxemet XR 570 and 1000.
[122] Cf. Annex No 4 Authorized medicinal products Australia.
[123] Cf. Therapeutic Goods Administration, Australian Product Information- Truvelog and Truelog Solostar (Insulin aspart), p. 5.
[124] Cf. Therapeutic Goods Administration, Australian Product Information- Truvelog and Truelog Solostar (Insulin aspart).
[125] Cf. Therapeutic Goods Administration, Australian Product Information Novorapid and Novomix (Insulin aspart).
[126] Cf. Therapeutic Goods Administration, Australian Product Information Ryzodeg 70/30 FlexTouch and Penfill (Insulin degludec/Insulin aspart).

Four products containing Insulin glargine could be found, which have an authorisation for paediatric use. All of them can be used for paediatric patients above 6 years of age. It is noted that safety and efficacy could be demonstrated in clinical trials. Apart from this, there is the medicinal product Toujeo Max Solostar with the same active substance, which is only approved for the use in adults. The product information informs that no clinical trials have been conducted and, consequently, no safety profile could be established.[127]

It makes sense not to perform unnecessary studies involving children, when data already exist. It is inconceivable that the data cannot be shared, so that Toujeo can also be approved for children. Accordingly, there are more medicinal products on the market that are available for children. However, it could also be assumed that the two products differ in, e.g., their excipients or in their dosage form. Therefore, no data can be shared.[128]

The same situation can be found for the products containing Metformin. Some of the products are approved for paediatric use; others are not. In similar cases, data is not sufficient and specified.[129]

Insulin human is not authorised for the treatment of diabetes in children because, according to the documents of Mixtard and Protaphane, no data for paediatric use have been assessed. Nevertheless, information about the dosage for children is available.[130]

In general, a lot of the product information of medicinal products for the treatment of diabetes mellitus does not contain any information regarding the use in children, not even whether studies have been carried out in these age groups or not. Often, only the dosage for adults is given. Sometimes, it is only mentioned that the medicinal product is authorised for diabetes mellitus instead of an age statement.[131]

The most common reason why a medicinal product is not approved for children is that there are no data available. In these cases, the following is included in the product information:[132]

[127] Cf. Annex No 4 Authorized medicinal products Australia.
[128] Cf. Annex No 4 Authorized medicinal products Australia.
[129] Cf. Annex No 4 Authorized medicinal products Australia.
[130] Cf. Therapeutic Goods Administration, Australian Product Information Actrapid, Mixtard, Protaphane.
[131] Cf. Annex No 4 Authorized medicinal products Australia.
[132] Cf. Annex No 4 Authorized medicinal products Australia.

- No studies have been conducted in children.
- Safety and effectiveness have not been established.

Hence, it is not clear whether studies have been carried out. Still, the results in children have been insufficient due to lack of efficacy or safety – or the studies have not been performed at all. The information and sources can be consulted in annex No. 4.[133]

5.4 European Union

The following table displays all medicinal products currently authorised for children regarding the treatment of type 1 and type 2 diabetes mellitus via Centralised Procedure. Additionally, annex No. 5 lists all antidiabetics that are approved for the European market. The products that are also authorised for children are marked with a green background.

API and medicinal products (via Centralised Procedure)	
Type 1	**Type 2**
Insulin aspart: Fiasp/Kirsty/Sanofi/Novorapid: From 1 year of age, for type 1 and type 2 diabetes mellitus.[134] [135] [136] [137]	**Liraglutide:** Victoza: Authorised from 10 years of age for type 2 diabetes mellitus. No data available for children below 10 years of age.[138]
Insulin aspart and degludec: Ryzodeg: For children from 2 years of age, type 1 and 2.[139]	**Dapagliflozin:** Edistride, Forxiga: Both medicinal products are indicated in adults and children aged 10 years and above

[133] Cf. Annex No 4 Authorized medicinal products Australia.
[134] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Fiasp.
[135] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics, Kirsty.
[136] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Insulin aspart Sanofi, INN - insulin aspart.
[137] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics NovoRapid, INN-insulin aspart.
[138] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Victoza, INN-liraglutide.
[139] Cf. European Medicines Agency, Summary of Product Characteristics Ryzodeg, INN-insulin degludec/insulin aspart).

API and medicinal products (via Centralised Procedure)	
Type 1	**Type 2**
	regarding the treatment of diabetes mellitus type 2.[140] [141]
Insulin degludec: Tresiba: for children aged 1 year or older for treatment of type 1 and from age of 10 for the treatment of type 2 diabetes mellitus.[142]	
Insulin detemir: Levemir: for children aged 1 year or older for treatment of type 1 and from age of 10 for the treatment of type 2 diabetes mellitus.[143]	
Insulin glargine: Abasaglar/Lantus: for children over the age of 2 and adults for type 1 and for children aged 10 or older for treatment of type 2 diabetes mellitus.[144] [145] Toujeo: from age of 6 years.[146]	
Insulin glulisine: Apidra: from 6 years of age, type 1 and type 2 diabetes mellitus.[147]	
Insulin human: Insulatard/Protaphane/Actrapid/Actraphane/Mixtard: for the treatment of diabetes mellitus in children and adults.[148]	

[140] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Edistride, INN-dapagliflozin.
[141] Cf. European Medicines Agency, Summary of Product Characteristics Forxiga, INN-dapagliflozin.
[142] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Tresiba, INN-insulin degludec.
[143] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Levemir, INN-insulin detemir.
[144] Cf. European Medicines Agency, Summary of Product Characteristics Abasaglar,INN-insulin glargine.
[145] Cf. European Medicines Agency, Summary of Product Characteristics Lantus, INN-insulin glargine.
[146] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Toujeo.
[147] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Apidra, INN-insulin glulisine.
[148] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Insulatard, INN-insulin human (rDNA).

API and medicinal products (via Centralised Procedure)	
Type 1	**Type 2**
Insulin lispro: Humalog/Liprolog/Sanofi: For the treatment of diabetes mellitus in children and adults, there is no age limit.[149] [150] [151]	
Glibenclamid: Amglidia: For treatment of neonatal diabetes mellitus, for use in newborns, infants, and children. No formulation is available.[152]	
Glucagon: Baqsimi: for diabetes mellitus, from 4 years of age.[153] Ogluo: for diabetes mellitus, from 2 years of age.[154]	

Table No. 6: overview of antidiabetics for use in children in Europe (own representation based on sources, see footnotes).

For the treatment of type 1 diabetes mellitus, all medicinal products approved for adults are also available for use in children. This fact is to be rated as very positive.[155]

Only for insulin human with the commercial product Insuman, it is stated in the EPAR that data are not available, and that safety and efficacy have not been established. This statement is surprising, given that insulin human is the standard therapy for the treatment of type 1 diabetes in children.[156]

[149] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Humalog, INN-insulin lispro.
[150] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Liprolog, INN-insulin lispro.
[151] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Insulin lispro Sanofi, INN-insulin lispro.
[152] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Amglidia, INN-glibenclamide.
[153] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Baqsimi, INN-glucagon.
[154] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Ogluo, INN-glucagon.
[155] Cf. Annex No 5 Authorized medicinal products Europe.
[156] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Insuman, INN-insulin human.

For type 2 diabetes mellitus in paediatric use, only Dapagliflozin and Luraglutide are authorised. Metformin is not authorised for children via the Centralised Procedure but via MCP or DCP. Subsequently, it is not listed in this section.[157]

Additionally, Glibenclamid should be mentioned, which is authorised for the treatment of neonatal diabetes mellitus in new-borns, infants, and children.[158]

All other medicinal products available and authorised for the treatment of diabetes mellitus are only for the use in adults.[159]

The most common reasons for a waiver are listed in the following:

1. On the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).[160]

   The following medicinal products in the list are included:

API and medicinal product	**Age**
Glutide: Albiglutide (Eperzan)[161]; Dulaglutide (Trulicity)[162]; Liraglutide (Victoza)[163]; Semaglutide (Ozempic)[164]	Children from birth to less than 10 years of age.

[157] Cf. Annex No 5 Authorized medicinal products Europe.
[158] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics AMGLIDIA, INN-glibenclamide.
[159] Cf. Annex No 5 Authorized medicinal products Europe.
[160] Cf. Annex No 5 Authorized medicinal products Europe.
[161] Cf. European Medicines Agency, European Medicines Agency decision P/0272/2016 of 7 October 2016 on the acceptance of a modification of an agreed paediatric investigation plan for albiglutide (Eperzan), (EMEA-001175-PIP01-11-M04).
[162] Cf. European Medicines Agency, European Medicines Agency decision P/0175/2020 of 13 May 2020 on the acceptance of a modification of an agreed paediatric investigation plan for dulaglutide(Trulicity), (EMEA-000783-PIP01-09-M05).
[163] Cf. European Medicines Agency, European Medicines Agency decision P/0218/2017 of 9 August 2017 on the acceptance of a modification of an agreed paediatric investigation plan for liraglutide (Victoza), (EMEA-000128-PIP01-07-M08).
[164] Cf. European Medicines Agency, European Medicines Agency decision P/0137/2020 of 18 April 2020 on the acceptance of a modification of an agreed paediatric investigation plan for semaglutide (Ozempic) (EMEA-001441-PIP01-13-M03).

API and medicinal product	Age
DPP4-Inhibitor: Alogliptin (Vipidia)[165]; Linagliptin (Trajenta)[166]; Saxagliptin (Onglyza)[167]; Sitagliptin (Januvia)[168]	Children from birth to less than 10 years of age.
Gliflozine: Canagliflozin (Invokana)[169]; Ertugliflozin (Steglatro)[170]	Children from birth to less than 10 years of age.
Exenatide (Bydureon, Byette) [171]	Children from birth to less than 10 years of age.
Insulin detemir (Levemir):[172] Only waiver for type 2 DM	Type 2: children from birth to less than 10 years of age.
Insulin degludec (Tresiba)[173]	Type 1: children from birth to less than 12 months of age. Type 2: children from birth to less than 10 years of age.
Insulin glargine (Lantus/ Toujeo)[174] [175]	Children less than 10 years of age.
Lixisenatide (Lyxumia)[176]	Children from birth to less than 10 years of age.

[165] Cf. European Medicines Agency, European Medicines Agency decision P/0257/2020 of 15 July 2020 on the acceptance of a modification of an agreed paediatric investigation plan for alogliptin (Vipidia), (EMEA-000496-PIP01-08-M08).
[166] Cf. European Medicines Agency, European Medicines Agency decision P/0088/2021 of 19 March 2021 on the acceptance of a modification of an agreed paediatric investigation plan for linagliptin (Trajenta), (EMEA-000498-PIP01-08-M09).
[167] Cf. European Medicines Agency, European Medicines Agency decision P/0277/2019 of 16 August 2019 on the acceptance of a modification of an agreed paediatric investigation plan for saxagliptin (Onglyza), (EMEA-000200-PIP01-08-M08).
[168] Cf. European Medicines Agency, European Medicines Agency decision P/0358/2019 of 4 October 2019 on the acceptance of a modification of an agreed paediatric investigation plan for sitagliptin (Januvia (and associated names)), (EMEA-000470-PIP01-08-M11).
[169] Cf. European Medicines Agency, European Medicines Agency decision P/0464/2020 of 1 December 2020 on the acceptance of a modification of an agreed paediatric investigation plan for canagliflozin (Invokana), (EMEA-001030-PIP01-10-M08).
[170] Cf. European Medicines Agency, European Medicines Agency decision P/0141/2019 of 17 April 2019 on the acceptance of a modification of an agreed paediatric investigation plan for ertugliflozin (Steglatro), (EMEA-001533-PIP01-13-M02).
[171] Cf. European Medicines Agency, European Medicines Agency decision P/0064/2021 of 18 February 2021 on the acceptance of a modification of an agreed paediatric investigation plan for exenatide (Byetta, Bydureon), (EMEA-000689-PIP01-09-M11).
[172] Cf. European Medicines Agency, European Medicines Agency decision P/0172/2014 of 11 July 2014 on the acceptance of a modification of an agreed paediatric investigation plan for insulin detemir (Levemir), (EMEA-000412-PIP01-08-M01).
[173] Cf. European Medicines Agency, 000456-PIP01-08-M02 Decision Insulin degludec (Tresiba).
[174] Cf. European Medicines Agency, Decision and Opinion Lantus Insulin glargine 000387-PIP01-08.
[175] Cf. European Medicines Agency, Decision and Opinion Optisulin Insulin glargine 000396-PIP01-08.
[176] Cf. European Medicines Agency, Decision on the acceptace of a modifation of an agreed pediatric investigation plan for lixisenatide (Lyxumia), (EMEA-000916-PIP01-10-M07).

API and medicinal product	Age
Vildagliptin (Galvus)[177]	Children from birth to 10 years of age and from 10 to 18 years of age.

Table No. 7: list of drugs with a waiver on grounds that the disease does not occur in this age group (own representation based on sources see footnotes).

2. In comparable cases, studies were performed for, e.g., Komboglyze, Trajenta, and Glyxambi. However, due to a small number of participants, the data situation is insufficient, so that no paediatric approval can be obtained.[178] [179] [180]

3. On the grounds that the specific medicinal product is likely to be unsafe or on the grounds that the specific medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population.

   The following medicinal products in the list are included:

API and medicinal product	Age
Dapagliflozin (Forxiga)[181]	Children from birth to less than 2 years.
Empagliflozin (Jardiance)[182]	Children from birth to less than 18 years of age.

Table No. 8: list of drugs with waiver on the grounds that the drugs are unsafe or ineffective (own representation based on sources see footnotes.).

4. On the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

   The following medicinal products in the list are included:

[177] Cf. European Medicines Agency, EMA Decision on Galvus 000700-PIP02-10.
[178] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Komboglyze, INN-saxagliptin, metformin.
[179] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Trajenta, INN-linagliptin.
[180] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Glyxambi, INN-empagliflozin/linagliptin.
[181] Cf. European Medicines Agency, EMA decision on the granting of a product specific waiver for dapagliflozin (Forxiga), (EMEA 000694-PIP04-18) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.
[182] Cf. European Medicines Agency, EMA decision on the acceptance of a modification of an agreed paediatric investigation plan for empagliflozin (Jardiance), (EMEA-000828-PIP04-16-M03) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

API and medicinal product	Age
Glucagon (Baqsimi)[183]	Children from birth to less than 1 year of age.
Insulin aspart/ Insulin degludec (Ryzodeg)[184]	Children from birth to less than 12 months of age.
Insulin detemir (Levemir)[185] Grounds for type 1 diabetes mellitus.	Children from birth to less than one year of age.
Insulin glargine (Lantus/ Toujeo) [186] [187] Grounds for type 1 DM and type 2 DM.	Type 1: children less than one year of age and children from 6 to less than 18 years of age. Type 2: children from 10 to less than 18 years of age.
Metformin/ Sitagliptin (Velmetia/ Efficib/ Janumet)[188] [189] [190]	Children of all ages.
Metformin/ Vildagliptin (Eucreas)[191]	Children from birth to less than 18 years of age.
Lixisenatide (Lyxumia)[192]	Children from 10 to less than 18 years.

[183] Cf. European Medicines Agency, EMA decision on the acceptance of a modification of an agreed paediatric investigation plan for glucagon (Baqsimi), (EMEA-001657-PIP01-14-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.
[184] Cf. European Medicines Agency, EMA decision on the acceptance of a modification of an agreed paediatric investigation plan for insulin degludec / insulin aspart (Ryzodeg), (EMEA-000479-PIP01-08-M03) in accordance with Regulation(EC) No 1901/2006 of the European Parliament and of the Council.
[185] Cf. European Medicines Agency, EMA decision on the acceptance of a modification of an agreed paediatric investigation plan for insulin detemir (Levemir), (EMEA-000412-PIP01-08-M01) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.
[186] Cf. European Medicines Agency, Decision and Opinion Lantus Insulin glargine 000387-PIP01-08.
[187] Cf. European Medicines Agency, Decision and Opinion Optisulin Insulin glargine 000396-PIP01-08.
[188] Cf. European Medicines Agency, EMA decision of 1 December 2008 on the application for agreement of a Paediatric Investigation Plan for sitagliptin phosphate monohydrate, metformin hydrochloride (Velmetia) EMEA-000212-PIP01-07 in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended.
[189] Cf. European Medicines Agency, EMA decision of 1 December 2008 on the application for agreement of a Paediatric Investigation Plan for sitagliptin phosphate monohydrate, metformin hydrochloride (Efficib) EMEA-000213-PIP01-07 in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council as amended.
[190] Cf. European Medicines Agency, EMA decision on the application for agreement of a Paediatric Investigation Plan for sitagliptin phosphate monohydrate, metformin hydrochloride (Janumet) EMEA-000165-PIP01-07.
[191] Cf. European Medicines Agency, EMA decision on the granting of a product specific waiver for vildagliptin / metformin hydrochloride (Eucreas), (EMEA-000703-PIP01-09).
[192] Cf. European Medicines Agency, Decision on the acceptace of a modifation of an agreed pediatric investigation plan for lixisenatide (Lyxumia), (EMEA-000916-PIP01-10-M07).

API and medicinal product	Age
Semaglutide (Ozempic)[193]	Children from birth to less than 6 years of age.

Table No. 9: list of drugs with waiver on the grounds that the drug does not benefit children (own representation based on sources see footnotes).

5.4.1. No information about studies can be found

As can be discerned in table No. 7 above, there is a waiver for DPP4-inhibitors, Glitazones, and Dulaglutide from birth to 10 years of age. Children from 10 to less than 18 years are excluded from the waiver. For this paediatric population, the EMA requires studies. Nevertheless, no information about the studies has been published, neither about the outcome nor the studies' conduction.[194]

For instance, Invokana with the API Canagliflozin is only authorised for adults, as stated in the product information. Studies involving children aged 10 to under 18 years are required, according to EMA's PIP decision report. Therefore, a paediatric phase 1 pharmacokinetics and pharmacodynamics study has been performed. Although the results show that the pharmacokinetic and pharmacodynamic responses were similar to those in adults, there is actually no approval for paediatric use. It is not clear whether additional studies have been or will be conducted for further investigation. Unfortunately, no more data are available to explore the reason for not submitting the paediatric approval.[195]

5.4.2 Fixed- dose combination medicinal products

As is visible in annex No. 5, no fixed-dose combination drug has been approved for the use in children. According to Art. 7 of the Paediatric Regulation, a PIP is only mandatory if the fixed-dose combination medicinal product was not yet authorised when the Regulation came into force in 2008. This also applies to the individual medicinal products in the fixed-dose combination. Conversely, if the individual components were authorised before 2008, and the pharmaceutical form of the individual medicinal products corresponds to that of

[193] Cf. European Medicines Agency, EMA decision on the acceptance of a modification of an agreed paediatric investigation plan for semaglutide (Ozempic) (EMEA-001441-PIP03-17-M01).
[194] Cf. Annex No 5 Authorized medicinal products Europe.
[195] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Invokana, INN-canagliflozin.

the fixed-dose combination, these are referred to as one global marketing authorization. Subsequently, neither article 7 nor 8 apply.[196]

The medicinal products Glyxambi (Empagliflozin/Linagliptin) and Synjardy (Empagliflozin/Metformin) do not fall under the exclusion of Art. 7 and 8. Consequently, a PIP must be required for them.[197] [198]

In the case of Glyxambi, a paediatric Phase 1 trial for Empagliflozin and a paediatric Phase 2 trial for Linagliptin have been performed to examine pharmacokinetics and pharmacodynamics of Empagliflozin in children aged 10 to 18. The results were consistent with those found in adults. [199]

In the product information pertaining to Synjardy, it is asserted that safety and efficacy in children from 0 to 18 years of age have not been established and that no data is available. In the same document, a few studies are mentioned, such as a paediatric Phase 1 study of Empagliflozin. The observed results of pharmacokinetics and -dynamics were equal to those in adult subjects. Secondly, there has been a single dose study involving Metformin, which shows that the pharmacokinetic profile was similar to that in healthy adults.[200]

In both cases, a waiver has been granted by the EMA, although studies that were mentioned have been successful.[201] [202]

Also, for the combination of Linagliptin and Metformin (Jentadueto), a phase 2 study and a single dose study have been performed in children. Nevertheless, it is stated in the EPAR that safety and efficacy have not been established. The studies' results are unknown and have not been published by the EMA. It is therefore not clear why there was no approval for paediatric use.[203]

[196] Cf. European Medicines Agency, Paediatric investigation plans: questions and answers.
[197] Cf. European Medicines Agency, Glyxambi.
[198] Cf. European Medicines Agency, Synjardy.
[199] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Glyxambi, INN-empagliflozin/linagliptin.
[200] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Synjardy, INN-Empagliflozin + Metformin.
[201] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Synjardy, INN-Empagliflozin + Metformin.
[202] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Glyxambi, INN-empagliflozin/linagliptin.
[203] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Jentadueto, INN-Linagliptin/Metformin.

5.4.3. The disease does not occur in the specified paediatric subset(s)

For Canagliflozin, a waiver has been applied for children from birth to under 10 years of age, with the argument *"that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s)"*[204].

The reason that the disease does not occur in this age group can also be found, for instance, in the cases of Tesavel and Januvia (both Sitagliptin), Byetta (Exenatide), Insulin degludec, and several other medicinal products pertaining to the indication of diabetes mellitus (Table No. 7). This justification is given in many cases by the EMA to grant a waiver for medicinal products and, as a consequence, prevent studies on children.[205]

However, given the steadily increasing number of type 2 diabetes mellitus in children, this justification seems outdated.

5.4.4. Small number of study participants

Komboglyze (Metformin/Saxagliptin) is indicated only for adults with type 2 diabetes mellitus. A waiver was granted to exclude children from participating in clinical trials. No safety or efficacy studies were conducted in children under 18 years of age. Reasons for the exclusion of minors from the clinical trials could not be determined.[206]

A study was, as a matter of fact, performed to evaluate the pharmacokinetics of Saxagliptin and Metformin in children aged between 10 and 17 years with type 2 diabetes mellitus. The study was not part of the European PIP (Paediatric Investigational Plan) but a post-marketing requirement of the FDA. Nevertheless, it appears at the EMA website, as it is required to submit all paediatric data that is generated in or outside the EU. Due to a small number of study participants, efficacy results could only be reported for one subject. Safety results could only be reported for two subjects. In general, Komboglyze was deemed safe

[204] Cf. European Medicines Agency, European Medicines Agency decision P/0464/2020 of 1 December 2020 on the acceptance of a modification of an agreed paediatric investigation plan for canagliflozin (Invokana), (EMEA-001030-PIP01-10-M08), p. 7.
[205] Cf. Annex No 5 Authorized medicinal products Europe.
[206] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Komboglyze, INN-saxagliptin, metformin.

and tolerated by the subjects. Due to the study's limited value, the company decided not to present any results.[207]

Glyxambi (Empagliflozin, Linagliptin): both Empagliflozin and Linagliptin were studied separately from one another to examine the pharmacokinetics and pharmacodynamics in children aged 10 to 18 years. The results were consistent with those in adults. Nevertheless, the agency granted a waiver for the paediatric population due to a *"limited nature of the data set"*[208]. Glyxambi is not recommended for use in children. This information was obtained by the product information on the EMA website.[209]

Linagliptin: The same situation can be found for Trajenta (Linagliptin). A phase 2 study examined pharmacokinetics and pharmacodynamics of children aged 10 to 18 years and yielded the same results as in adults. However, due to *"the limited nature of the data set"*[210], linagliptin cannot be recommended for the treatment of type 2 diabetes mellitus in this age group.[211]

5.5 Conclusion and evaluation of the grounds for not conducting clinical trials involving children

With the ever-increasing number of children developing type 2 diabetes mellitus, it seems paradoxical that studies are not being conducted on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s). As already mentioned above, studies such as multicentre, twenty-year study SEARCH show how the number of children with type 2 diabetes mellitus is steadily increasing.[212]

[207] Cf. European Medicines Agency, Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 for Komboglyze.
[208] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Glyxambi, INN-empagliflozin/linagliptin.p. 24
[209] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Glyxambi, INN-empagliflozin/linagliptin, p. 13.
[210] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Trajenta, INN-linagliptin, p. 13.
[211] Cf. European Medicines Agency, Annex 1 Summary of Product Characteristics Trajenta, INN-linagliptin.
[212] Cf. Dabelea et al., Twenty years of pediatric diabetes surveillance: what do we know and why it matters, 1495, Annals of the New York Academy of Sciences, 99 (2021).

Despite the passage of the EU Paediatric Regulation, the problem of patient recruitment persists, not only outside the EU. Many studies cannot be completed or evaluated after completion, since a representative number of paediatric participants did not take part.

In some documents, paediatric studies and their results are described. They often show positive results in children, which are comparable to the studies in adults. However, it is often the case that there is still no paediatric drug approval. It is difficult to understand why there was no submission for approval despite successful studies. Criticism of the lack of transparency and non-traceability is appropriate, especially on part of the Japanese, Canadian, and Australian authorities.

At the same time, it looks as if the information gained from the children's studies will not be used further. It is often said that studies were won with results, but in the end, a waiver was granted by the EMA. The aim of the Paediatric Regulation's adoption was, among other things, to avoid unnecessary studies on children and to carry out only as many studies as necessary.

5.6 Approvals in Germany, including MRP and DCP

The following table lists all antidiabetics that are authorised for the paediatric population in Germany, according to the Gelbe Liste.

For example, Metformin and Glimepiride are highlighted here as authorised medicinal products. Both are not displayed in table 6 because they were not approved via the central procedure but via MRP (Mutual Recognition Procedure) or DCP (Decentralised Procedure).

Therefore, a total of three drugs for the treatment of type 2 are available for in-label use: Glimeprid, Dapagliflozin, and Metformin. Seven types of Insulin are approved in Germany and are available for the treatment of diabetes mellitus for type 1. In addition, Gliblenclamid can be used for the treatment of neonatal diabetes mellitus.

API and medicinal product	**Paediatric use and age range**
Dapagliflozin (Forxiga)	Forxiga is indicated for the treatment of insufficiently controlled

API and medicinal product	Paediatric use and age range
	type 2 diabetes mellitus in addition to dietary advice and exercise in adults and children from 10 years of age and above.[213]
Insulin aspart (Sanofi)	Insulin aspart Sanofi can be used for the treatment of diabetes mellitus in adults, adolescents, and children from aged 1 year and above.[214]
Insulin aspart (NovoMix)	NovoMix® 30 can be used for the treatment of diabetes mellitus in adults, adolescents, and children from 10 years of age and above.[215]
Insulin aspart (Novorapid)	NovoRapid® can be used for the treatment of diabetes mellitus in adults, adolescents, and children aged 1 year and above.[216]
Insulin aspart (Fiasp)	For the treatment of diabetes mellitus in adults, children and adolescents from the age of 1 year and above.[217]
Insulin degludec (Tresiba)	For the treatment of diabetes mellitus from the age of 1 year and above.[218]
Insulin detemir (Levemir)	Levemir® can be used for the treatment of diabetes mellitus in adults, children, and adolescents from the age of 1 year and above.[219]
Insulin glargine (Abasaglar)	For the treatment of diabetes mellitus in adults, adolescents, and children from the age of 2 years and above.[220]

[213] Cf. AstraZeneca, Fachinformation Forxiga 5mg und 10mg Filmtabletten.
[214] Cf. Sanofi Aventis Deutschland GmbH, Fachinformation Insulin aspart Sanofi 100 Einheiten/ml Durchstechflasche, Fertigpen, Patrone.
[215] Cf. Novo Nordisk, Novomix Penfill und FlexPen.
[216] Cf. Novo Nordisk, Novorapid.
[217] Cf. Novo Nordisk, Fiasp Flexpen, Penfill und Durchstechflasche.
[218] Cf. Novo Nordisk, Tresiba Injektionslösung 100 Einheiten/ml.
[219] Cf. Novo Nordisk, Levemir Penfill, Flexpen, Flextouch.
[220] Cf. Lilly Deutschland GmbH, Abasaglar 100 Einheiten/ml Patrone und Kwikpen.

API and medicinal product	Paediatric use and age range
Insulin glargine (Lantus)	For the treatment of diabetes mellitus in adults, adolescents, and children from the age of 2 years and above.[221]
Insulin glargine (Toujeo)	For the treatment of diabetes mellitus in adults, adolescents, and children from the age of 6 years and above.[222]
Insulin glargine (Semglee)	For the treatment of diabetes mellitus in adults, adolescents, and children from the age of 2 years and above.[223]
Insulin glulisin (Apidra)	For the treatment of diabetes mellitus in adults, adolescents, and children from the age of 6 and above, in cases where insulin therapy is required.[224]
Insulin human/NPH (Actraphane)	Actraphane® can be used in children and adolescents.[225]
Insulin human (Protaphane)	Protaphane® can be used in children and adolescents. [226]
Insulin human (Huminsulin, Humulin, Insultard, Mixtard)	For the treatment of patients with diabetes mellitus requiring insulin for maintenance normal glucose homeostasis.[227]
Insulin human (Actrapid)	Actrapid® can be used in adolescents and children.[228]
Human insulin (Berlinsulin)	For the treatment of patients with diabetes mellitus requiring insulin for maintenance normal glucose homeostasis.[229]
Insulin lispro (Liprolog)	For the treatment of diabetes mellitus in adults, adolescents, and children who need insulin for a normal

[221] Cf. Sanofi, Lantus Durchstechflasche, Patrone und Solostart Fertigpen.
[222] Cf. Sanofi, Toujeo Doublestar und Solostar.
[223] Cf. Viatris Healthcare GmbH, Semglee 100 Einheiten/ml Injektionslösung in einem Fertigpen.
[224] Cf. Sanofi, Apidra Durchstechflasche, Patrone, Fertigpen.
[225] Cf. Novo Nordisk, Actraphane.
[226] Cf. Novo Nordisk, Protaphane.
[227] Cf. Lilly Deutschland GmbH, Humulin Durchstechflasche, Kwikpen.
[228] Cf. Novo Nordisk, Actrapid Durchstechflasche, Patrone, Fertigpen.
[229] Cf. Berlin Chemie Menarini, Berlinsulin Pen Patronen.

API and medicinal product	Paediatric use and age range
	glucose balance. Liprolog is also displayed during initial setup of diabetes mellitus.[230]
Insulin lispro (Humalog, Sanofi)	Humalog can be used in children and adolescents.[231]
Glimepirid (Amaryl)	No data available for the treatment of Glimepirid in patients younger than 8 years. Concerning children aged 8 to 17, only little data is available for Glimepirid as single therapy. The available data regarding safety and efficacy for the paediatric population is insufficient and, therefore, the use is not recommended.[232]
Glimepirid (Abz)	No data is available regarding the use of Glimepiride in patients less than 8 years of age. For children aged 8 to 17, there are conditional data on Glimepiride as monotherapy. Available data on safety and efficacy for the treatment in children are insufficient and not recommended.[233]
Glibenclamid (Amglidia)	AMGLIDIA can be used in new-borns, babies, and children for the treatment of neonatal diabetes mellitus.[234]
Liraglutide (Victoza)	Victoza® can be used for the treatment of uncontrolled type 2 diabetes mellitus in adults, adolescents, and children from the age of 10 years as an addition to dietary advice and physical activity.[235]

[230] Cf. Berlin Chemie Menarini, Liprolog Durchstechflasche, Patrone und Fertigpen.
[231] Cf. Lilly Deutschland GmbH, Humalog Durchstechflasche, Patrone und Kwikpen.
[232] Cf. Sanofi Aventis Deutschland GmbH, Amaryl Tabletten.
[233] Cf. Abz Pharma, Glimepirid Abz Tabletten 2mg und 3mg.
[234] Cf. Ammtek, Amglidia 0,6 mg/ml Suspension zum Einnehmen/ AMGLIDIA 6 mg/ml Suspension zum Einnehmen.
[235] Cf. Novo Nordisk, Victoza® 6 mg/ml Injektionslösung in einem Fertigpen.

API and medicinal product	Paediatric use and age range
Metformin (Glucophage, Siofor)	For the treatment in children from the age of 10 years and above as monotherapy or in combination with insulin.[236] [237]

Table No. 10: approved antidiabetics in Germany for children, according to the Gelbe Liste (own representation based on sources see footnotes)

6. Clinical trial systems

6.1 Trial registration in general

In general, it is important for maintaining transparency that a clinical trial is registered by the sponsor or the responsible person. To meet the requirements, which are determined by the International Committee of Medical Journal Editors (ICMJE), sponsors are encouraged to register their trials in a Primary Registry or in an ICMJE-approved registry. A Primary Registry is part of the WHO Registry Network.[238]

To become part of the WHO Registry Network and to be called a Primary Registry, a national registry must meet certain criteria of the International Clinical Trial Registry Platform (ICTRP) in terms of the content, quality, validity, accessibility, unambiguous identification, technical capacity, administration, and governance.[239]

6.2 Clinical trials and clinical trials database in Canada

In Canada, Health Canada is responsible for the review of clinical trial applications of human pharmaceutical and biological drugs of phase I-III and also for the review of the results. Trials must be conducted according to Division 5 of the Food and Drugs Regulations and Good Clinical Practice, in alignment with the ICH E6 Guidance: Good Clinical Practice. [240] [241]

[236] Cf. Merck Healthcare GmbH Germany, Glucophage® 500 mg/- 850 mg/- 1000 mg.
[237] Cf. Berlin Chemie Menarini, Siofor Retardtabletten.
[238] Cf. World Health Organization, Trial registration- Why is trial registration Important?.
[239] Cf. World Health Organization, WHO Registry Criteria.
[240] Cf. Health Canada, Health Canada's Clinical Trials Database.
[241] Cf. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Efficacy Guidelines.

The trials, which are authorised by the authority, have been listed in the Health Canada Clinical Trials Database as of April 1, 2013. Only basic information is published on the database. Completeness is not guaranteed. Still, according to the information on the HC website, the Clinical Trials Database is not a registry. Furthermore, registration is not mandatory for sponsors conducting clinical trials in Canada. Instead, the competent authority encourages sponsors to register their clinical trials and keep their study results and data in registries, such as clinicaltrials.gov or ISRCTN registry.[242] [243]

6.3 Clinical trials and clinical trials databases in Japan

In Japan, the Pharmaceutical Affairs Law regulates clinical trials. In addition, clinical trials must be conducted according to the Japan Good Clinical Practice guideline, which is harmonized with the ICH GCP guideline, coupled with some Japan-specific additions.[244]

Before the start of the trials, sponsors must submit an initial notification and study protocol to the PMDA. PMDA later will also conduct the scientific review of the application for the completed clinical trial.[245]

In Japan, there are four registry centres in which a clinical trial or clinical research can be registered and accessed:[246]

- UMIN (University Hospital Medical Information Network) is a database that largely deals with clinical research conducted within academia, such as in university hospitals.
- JAPIC (Japan Pharmaceutical Information Center) is a database that is often used for the registration of clinical trials conducted by pharmaceutical companies.
- JMA-CCT (Japan Medical Association Center for Clinical Trials) is a database that is mainly used for the registration of investigator-initiated clinical trials (IITs).
- JRCT (Japan Registry of Clinical Trials) is the registry of the Ministry of Health, Labour and Welfare, established in 2018.

[242] Cf. Health Canada, Health Canada's Clinical Trials Database.
[243] Cf. Health Canada, Clinical trials and drug safety.
[244] Cf. Credevo, Japan – Clinical Trial Regulatory Process.
[245] Cf. Credevo, Japan – Clinical Trial Regulatory Process.
[246] Cf. Shiokawa, Background, introduction and activity of the Japan Primary Registries Network.

For the first three registries UMIN, JAPIC, and JMA-CCT, registration and publication began in 2005 in parallel. The portal that supports the searching for information in all three registries is called the NIPH Clinical Research Portal. It is hosted by Japan's National Institute of Public Health (NIPH) and was established in 2007. A short time later, the three registers were combined into a cooperation system called Japan Primary Registries Network (JPRN). This became a WHO Primary Registry in 2008. Since then, information on clinical trials is also submitted to the ICTRP. The data are offered in Japanese as well as in English.[247]

In 2018, the Clinical Trial Act came into force, which also led to the introduction of a new register: the JRCT. Since then, sponsors are required to upload the contents of the trial plan to the registry website, if the clinical trials are conducted under the new Clinical Trial Act. It is assumed that with the obligation to register clinical trials at the JRCT, the other three registers will be merged into the JRCT in the future.[248]

6.4 Clinical trials and clinical trials databases in Australia

Therapeutic goods used in clinical trials in Australia are subject to the Therapeutic Goods Administration (TGA). This requires that the drugs used in the clinical trials follow ICH Guidelines for Good Clinical Practice. Furthermore, there is an *Australian clinical trial handbook*, which provides guidance on conducting clinical trials in Australia when they contain *unapproved* therapeutic goods.[249]

Before a clinical trial can be conducted with unapproved therapeutic goods in Australia, the sponsor must submit a CTN (Clinical Trial Notification) scheme or a CTA (Clinical Trial Approval) scheme. Which scheme is used depends on the trial type and the choice of sponsor. The TGA does not evaluate the application at the time of submission. In both cases, CTN or CTA, it is only the HREC (Human Research Ethics Committee) that makes a scientific and ethical review of the trial protocol's risk and harm and is also responsible for overseeing the trial's conduct. [250]

[247] Cf. Shiokawa, Background, introduction and activity of the Japan Primary Registries Network.
[248] Cf. Nakamura/Shibata, Regulatory changes after the enforcement of the new Clinical Trials Act in Japan.
[249] Cf. Therapeutic Goods Administration, Australian clinical trial handbook.
[250] Cf. Therapeutic Goods Administration, Clinical trials.

The Australian New Zealand Clinical Trials Registry (ANZCTR) is the Primary Registry for clinical trials conducted in Australia since 2007. It can also include clinical trials conducted in New Zealand and in other parts of the world. Information about the trials are passed on to WHO ICTRP. For registering a trial as well as its accuracy and completeness, the trial's sponsor is responsible. All data of a registered clinical trial entered in the registry are published.[251]

Because the sponsors are not required by the Australian agency to register their clinical trials, and registration is a voluntary measure. The register is not complete. Nevertheless, sponsors are encouraged by the TGA to register clinical trials that meet the WHO/ICMJE definition. In addition, there is a possibility to register the Australian clinical trial in clinicaltrials.gov. This is also not mandatory.[252]

6.5 Clinicaltrials.gov

Clinicaltrial.gov is a U.S. database provided by the National Library of Medicine (NLM) at the National Institute of Health (NIH), the US national's medical research agency founded in 1997. It is called a registry and contains information on publicly and privately supported clinical studies. The responsibility to provide and update the information lies with the clinical studies' sponsor or investigator. The database contains both clinical trials (interventional studies) and observational studies.[253]

But clinicaltrials.gov does not list all clinical studies conducted in the USA. Registration on clinicaltrials.gov is mandatory for studies that meet the definition of an *applicable clinical trial* (ACT) and started after or were still ongoing in 2007. For example, the definition includes interventional studies of FDA-regulated drugs, biological products, or certain medical devices that are conducted in the US or under an FDA investigational new drug application (42 CFR 11.10). Observational studies are not included. But many sponsors and investigators voluntarily register their studies, including registrations from around the world. [254]

[251] Cf. Australian New Zealand Clinical Trials Registry, What is the ANZCTR?.
[252] Cf. Australian New Zealand Clinical Trials Registry, What is the ANZCTR?.
[253] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, ClinicalTrials.gov Background.
[254] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, ClinicalTrials.gov Background.

For certain trials, it is also required to submit the results, such as all ACTs of approved, licensed, or cleared products that were completed after December 2007 or for ACTs of unapproved, unlicensed, or uncleared products that were completed after January 2017.[255] [256]

6.6 EU clinical trial register

The EU Clinical Trial Register contains the following information: [257]

- Interventional clinical trials, which are conducted in the EU and in the EEA (European Economic Area).
- You can also find clinical trials that are conducted outside the EU/EEA. These are related to the development of European medicines for children. In this case, the clinical trial is part of a paediatric investigation plan (PIP). Alternatively, the clinical trial is carried out to generate data in order to obtain EU marketing authorisation for drugs intended for use in children.

The register lists all interventional clinical trials, which were started after 1 May 2004. The EudraCT database contains all information about a trial. After a clinical trial protocol is authorised, the national competent authority loads protocol-related information into the database. So, every trial that fulfils the requirements is registered in the EudraCT.[258]

Furthermore, it is the responsibility of the sponsor to enter the trial results. After the sponsor has validated the data, the latter will be published in the EU Clinical Trials Register.[259]

The EudraCT database was established with the entry into force of the Directive 2001/20/EC and is mentioned in Article 11. Furthermore, in accordance with the Paediatric Regulation No. 1901/2006, information on paediatric clinical trials must be submitted. Since 2011, the EU Clinical Trial Register has obtained the status of a primary registry of the WHO's Registry Network.[260]

[255] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, ClinicalTrials.gov Background.
[256] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, FDAAA 801 and the Final Rule.
[257] Cf. Europea Medicines Agency; EU Clinical Trials Register, Clinical Trials.
[258] Cf. European Medicines Agency, EU Clinical Trials Register.
[259] Cf. European Medicines Agency, EU Clinical Trials Register.
[260] Cf. European Medicines Agency, EU Clinical Trials Register.

Since 2014, sponsors are required to post their clinical trial results no later than six or twelve months after the end of the trial, depending on the trial's type.[261]

6.6.1 New Clinical Trials Regulation No. 536/ 2014

With the new regulation, sponsors are encouraged to use the Clinical Trials Information System (CTIS) since 31 January 2022. The CTIS is a system used to apply for authorisation to run a clinical trial. New and advantageous is that just one single portal and one single online application are needed for the conduction of trials in all 30 EEA countries. There is a transition period of three years. I.e., from 31 January 2025 onward, every clinical trial must be in compliance with the new Clinical Trials Regulation and must be recorded in CTIS. All data and information submitted through the CTIS EU portal are then stored in the EU database EudraCT.[262] [263]

With the new regulation, it is also hoped that the conduction of clinical trials will be easier with just one portal and that more studies will be carried out as a result. Electronic communication, predetermined timelines, and replacing country-by-country decision with one single decision led to a more efficient and faster way of working. Furthermore, it shall support and increase transparency of clinical trials, especially for the public.[264] [265]

It is hoped that, with the new regulation as well as the associated Europe-wide cooperation and more efficient/quicker working methods, more meaningful studies can be carried out on children. The number of study participants will – as is expected – increase, so that meaningful and significant results can be gathered.

6.7 Overview CT registries

	Australia	**Canada**	**Japan**	**EU**
Name of register	ANZCTR	Health Canada's Clinical Trials	UMIN, JAPIC, JMA-CCT and JRCT	EU Clinical Trial Register

[261] Cf. European Medicines Agency, EU Clinical Trials Register.
[262] Cf. European Medicines Agency, Clinical Trials Information System.
[263] Cf. European Medicines Agency, Clinical Trials Regulation.
[264] Cf. Parkins, EU Clinical Trial Regulation: what you need to know.
[265] Cf. Ruediger Pankow et al., Six top tips to prepare for the new EU Clinical Trial Regulation.

	Australia	Canada	Japan	EU
		Database →No official registry		
Registration mandatory?	No	No	Yes, at JRCT acc. New Clinical Trial Act in 2018.	Yes, since 2001 in acc. Dir. 2001/20/EC.

Table No. 11: overview of clinical trials registries of the different countries (own representation based on sources in chapter 6.1-6.6).

In the EU and in Japan, it is mandatory for sponsors to register their clinical trials in a register provided by the authority. For these countries, traceability and transparency regarding the implementation of all clinical studies are possible, which can be considered an important and correct step in the right direction.

Unfortunately, the EU database only includes interventional studies, so that there is no traceability or transparency for observational and further studies.

In Japan, the registrational obligation was only introduced in 2018, with the launch of the JRCT. Therefore, data collection has only been complete for three years.

Data from Canadian and Australian studies obtained from clinicaltrials.gov most likely do not represent the exact number of studies that were actually carried out, because their registration is not mandatory in any of the registers.

Consequently, the following evaluation is only based on approximate data.

7. Clinical studies conducted in the different countries

The number of studies with antidiabetics conducted in the various countries according to the database of clinicaltrial.gov are analysed in this section. The exact numbers of studies and the search criteria which have been used can be found in the tables of annexes 8 to 11.

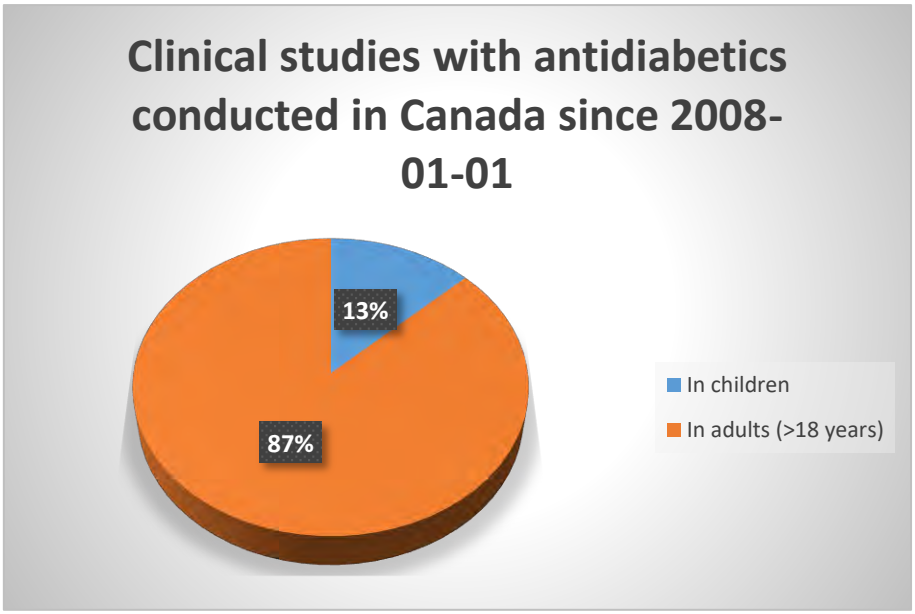

Figure No. 1: clinical studies with antidiabetics conducted in Canada since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[266]

According to clinicaltrials.gov, 87% of all clinical studies conducted in Canadian sites since the beginning of 2008 have been conducted in adults. This corresponds to 937 studies. 13% of the clinical studies have been performed in children (139 clinical studies) since 2008.

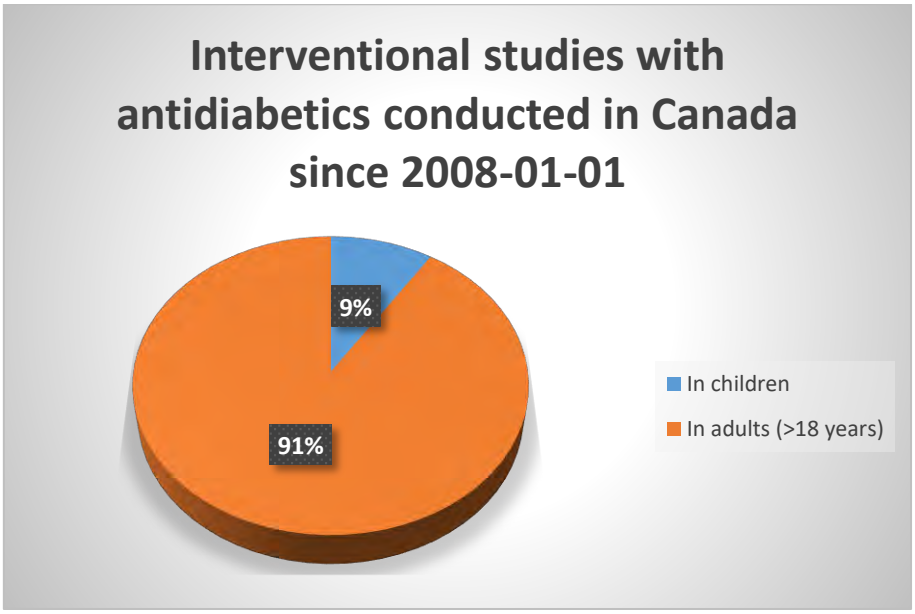

Figure No. 2: interventional studies with antidiabetics conducted in Canada since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[267]

[266] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Canada, all studies, since 2008-01-01.
[267] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Canada, interventional studies, since 2008-01-01.

Looking at the interventional studies since 2008, 91% were conducted in adults (801 clinical trials). Children were involved in 9% of the interventional studies, which corresponds with 81 clinical trials.

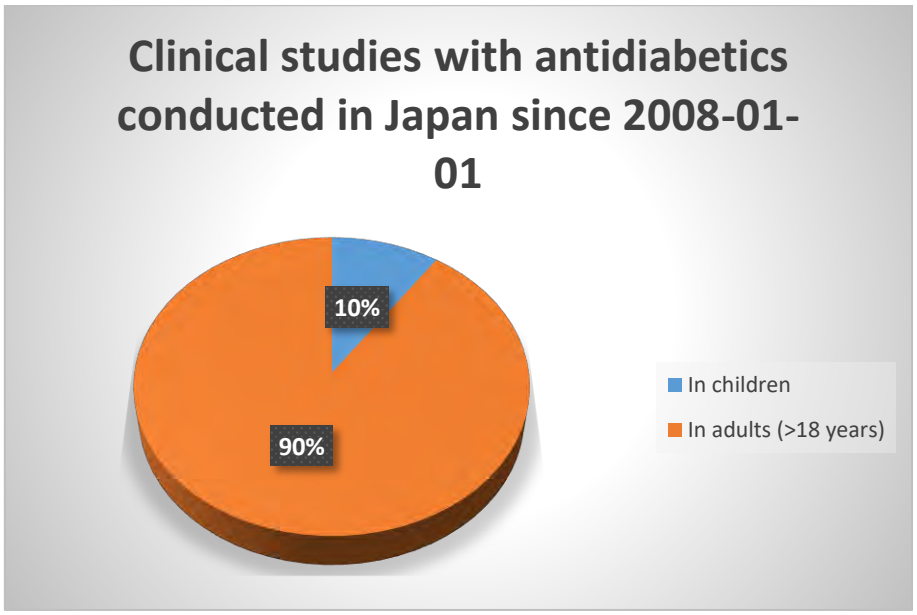

Figure No. 3: clinical studies with antidiabetics conducted in Japan since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[268]

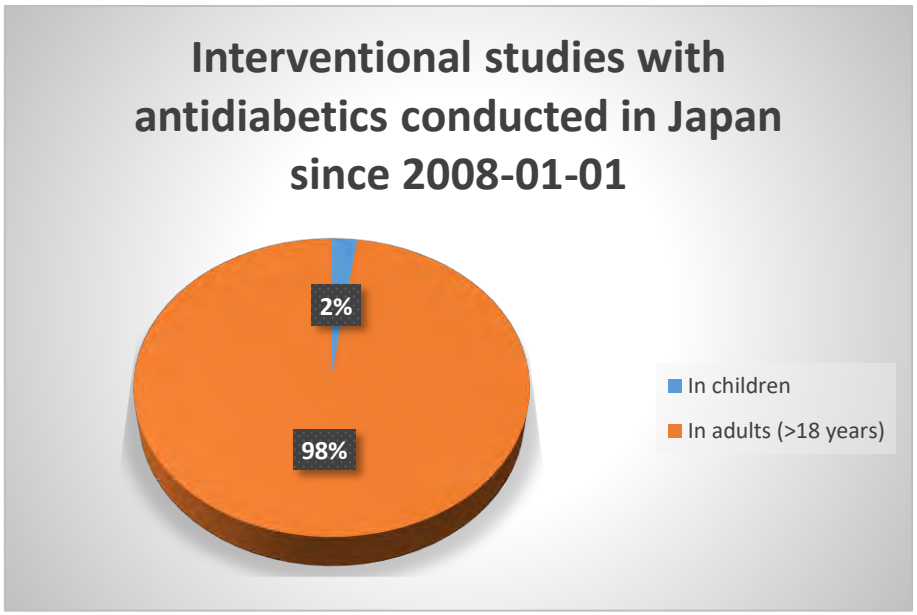

Figure No. 4: interventional studies with antidiabetics conducted in Japan since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[269]

[268] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Japan, all studies, since 2008-01-01.
[269] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Japan, interventional studies, since 2008-01-01.

According to the clinicaltrial.gov registry, 359 clinical trials have been conducted in Japan since 2008, 90% of them with adult patients and 10% with children. The situation is different for the interventional studies: the percentage of paediatric clinical trials is 2% and that of adults is 98%.

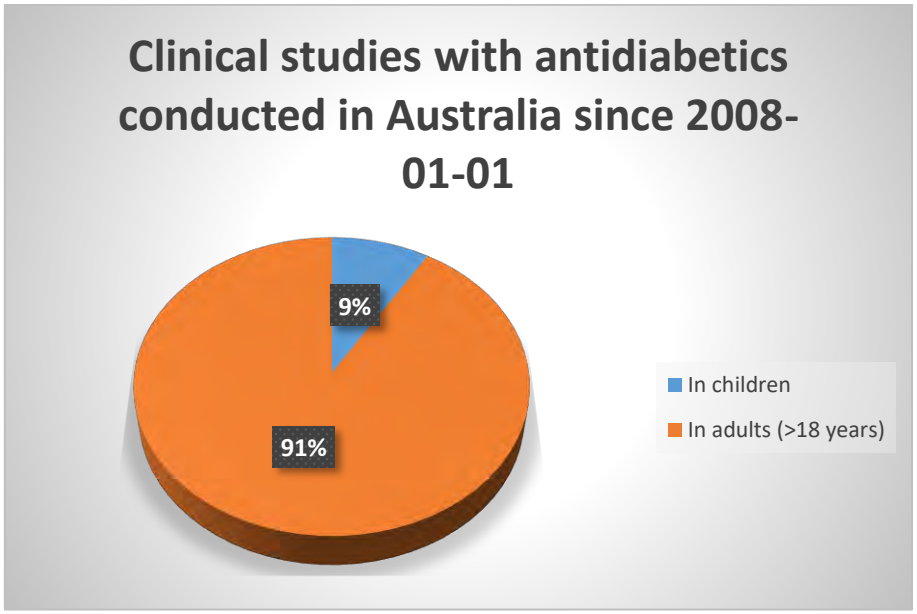

Figure No. 5: clinical studies with antidiabetics conducted in Australia since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[270]

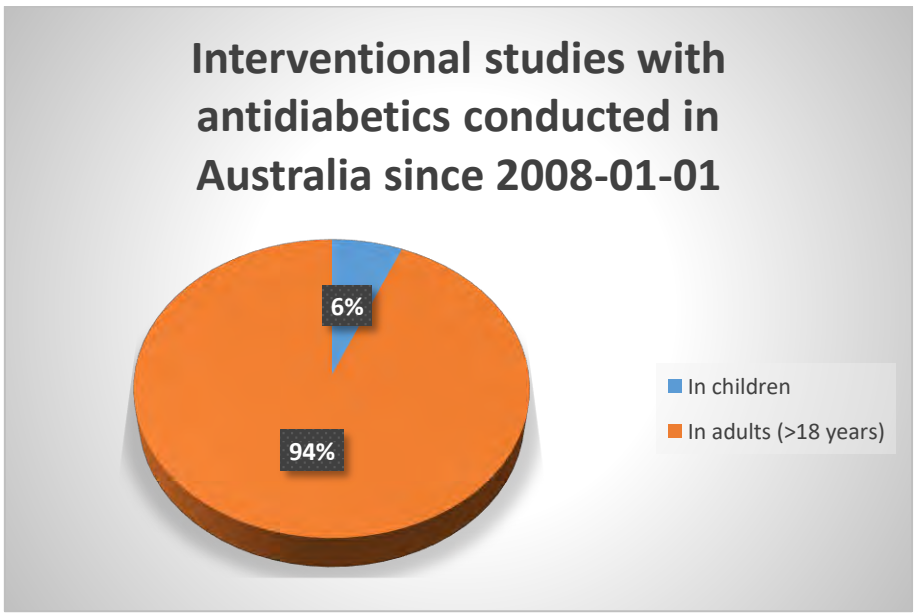

Figure No. 6: interventional studies with antidiabetics conducted in Australia since 2008-01-01, in percent, status 31.12.2021 (own representation based on date from clinicaltrials.gov).[271]

[270] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Australia, all studies, since 2008-01-01.
[271] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Australia, interventional studies, since 2008-01-01.

According to clinicaltrials.gov, 91% of all clinical studies conducted in Australian sites since the beginning of 2008 have been conducted in adults. This corresponds to 239 clinical studies. 6%, which means a study number of 23, have been carried out in children within 14 years.

Looking at the interventional studies since 2008, 94% were conducted in adults (223 clinical trials). Children were involved in 6% of the interventional studies, which corresponds with 15 trials.

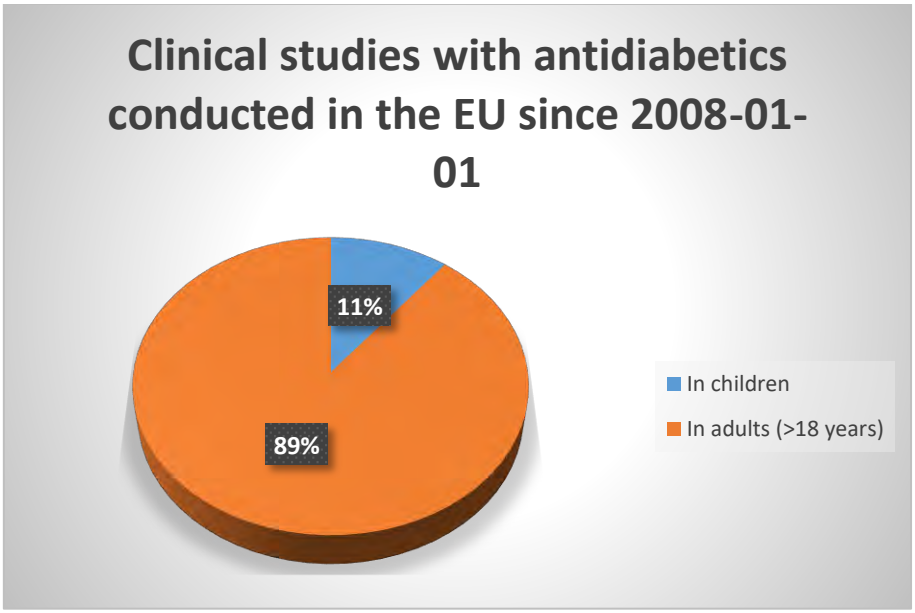

Figure No. 7: clinical studies with antidiabetics conducted in the EU since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[272]

[272] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Europe, all studies, since 2008-01-01.

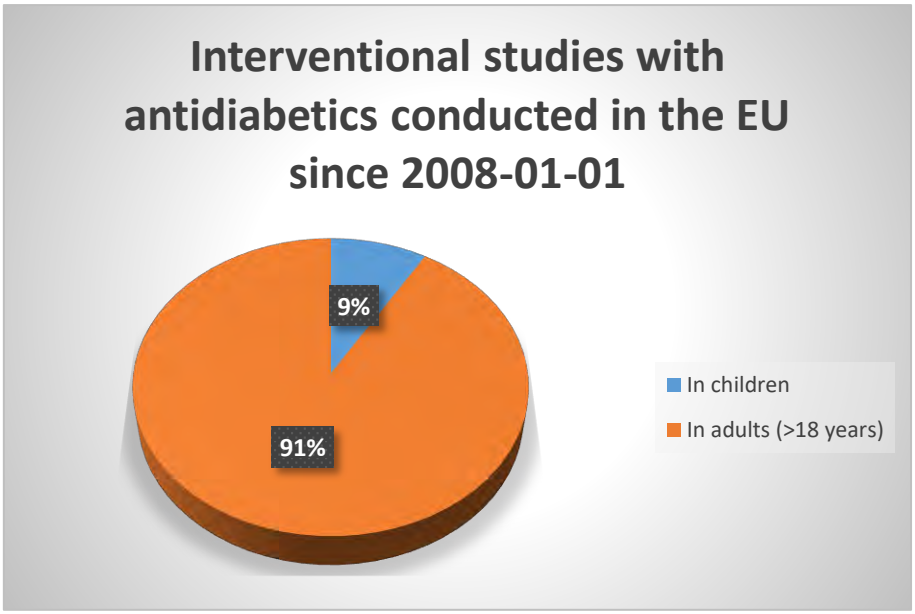

Figure No. 8: interventional studies with antidiabetics conducted in the EU since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[273]

In Europe, 11% of all clinical studies and 9% of the interventional studies were carried out with the participation of children. Approximately 90% of the studies conducted always involved adults.

7.1 Conclusion of the clinicaltrials.gov results for clinical studies on DM

Since January 2008, approximately 9% of all interventional studies on the subject of diabetes mellitus in the EU have been conducted with children. One might assume that the number would be significantly higher given the passage of the Paediatric Regulation. Nevertheless, the percentage of clinical trials conducted on children is higher than that of Australia and Japan. In Australia, interventional clinical trials account for 6% of the total amount of studies conducted. In Japan, this applies to a measly 2%. Canada has the highest value at 9% and, therefore, has the same percentage as Europe.

13% of all studies conducted in Canada have been carried out with children. In Australia, it was 9% and in Japan 10 %. That is 3 percentage points more in Australia (6% compared to 9%) and even 8 percentage points more in Japan (2% compared to 10%).

[273] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, Europe, interventional studies, since 2008-01-01.

Observational studies can only be conducted within the authorised indication. It is prohibited to investigate off-label use. It can be assumed that children and their parent are more willing to participate in clinical studies with already approved drugs, in observational studies, than to take part in interventional studies, where safety and efficacy still have to be proven.

Nevertheless, it is difficult to make a comparison of conducted clinical trials of the different countries because it is not mandatory for sponsors to enter their trials into the clinicaltrial.gov registry. It cannot be ruled out or even assumed that the true values deviate from this result. No global registry is available, in which registration is mandatory for all countries, so that a comparison would make sense. Nor does it make sense to use the values of the national registers for comparison, because in two out of four countries, the studies' registration is also not obligatory. Furthermore, it is worth noting that registration in the Japanese JRCT has been mandatory for merely three years. That means that just data from three years are complete. Only in the EU, registration has been a binding requirement of the EMA since 2001, which has already been shown in table 11 (the registry's overview).

Additionally, the number of studies includes both those with medication as well as those that deal with behaviour, other dosage forms, or other dosages.

7.2 EU and EudraCT results and comparison to clinicaltrials.gov results

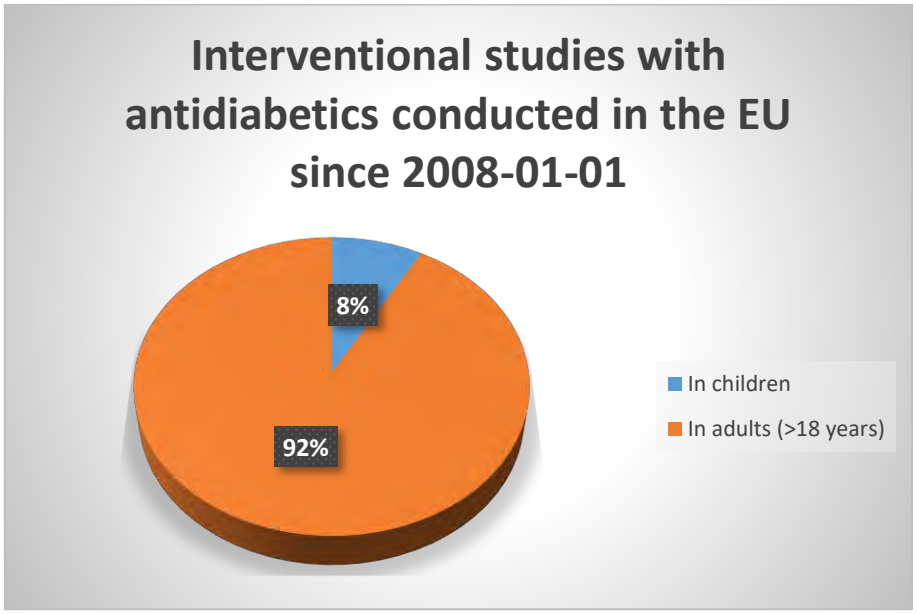

Figure No. 9: interventional studies with antidiabetics conducted in the EU since 2008-01-01, in percent, status 31.12.2021 (own representation based on data from EudraCT).[274]

According to the EudraCT register, 8% (140 studies) of the interventional studies conducted in the EU or for the EU have been carried out with children. 92% of the clinical trials only involved adult participants since 2008, which corresponds with 1580 clinical trials.

As already mentioned, only data of interventional clinical trials are available in the EudraCT database. Therefore, only this type of studies could be compared between the clinicaltrial.gov and the EudraCT database. The following keywords were used: the condition *Diabetes mellitus*, study type *interventional studies*, the time range *since 01-01-2008.* There was no filter for the EU in the clinicaltrial.gov database, so the data for the individual EU states had to be summed up.

It turned out that significantly more interventional studies are conducted and registered in the clinicaltrials.gov database: Since the beginning of 2008, a total of 3283 interventional studies researching antidiabetics have been registered. Children were involved in 302 studies. In contrast, only 140 studies involving children were registered in the European database. A total of 1682 interventional studies were carried out in Europe during this period. The exact numbers ca be found in annex 11 and annex 12.

[274] Cf. EudraCT, keywords: Diabetes mellitus, interventional studies, since 2008-01-01.

It is difficult to understand why the number of registered studies in the US database is significantly higher, since in the EU all interventional studies are notifiable and the entry in the clinicaltrials.gov database is voluntary.

7.3 Relevant clinical trials in children for the treatment of diabetes mellitus

Relevant clinical trials conducted in the various countries according to the database of clinicaltrial.gov and regional databases are analysed in this section.

7.3.1 Australia

Regarding to the keywords *child* and *interventional study*, there are 22 studies available at clinicaltrials.gov register. Only 15 interventional studies have been conducted in Australia with children on the topic of diabetes mellitus since January 2008. This represents 6 % of all Australian interventional studies. Only 9 of them have been completed.

According to the ANZCTR website, only 7 interventional studies dealing with the disease of diabetes mellitus in children have been conducted since January 2008.

All numbers of studies from clinicaltrials.gov and the ANZCTR database can be found in annex 13.

The studies of both registries which are relevant for this work are presented in the following table. Only those studies are listed that deal with the evaluation of medication for the treatment of diabetes mellitus in the paediatric population. They will be examined more in detail.

Study	
1	**Title:** Rosiglitazone and insulin in T1DM adolescent[275] **Age:** 10-18 years **Active substances:** Rosiglitazone **Status:** completed, interventional and Phase 4, last update 09/2006

[275] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Rosiglitazone and Insulin in T1DM Adolescents.

	Aim: to test treatment with rosiglitazone (an oral medication used frequently in type 2 diabetes), will reduce the insulin resistance of adolescence and improve the control of type 1 diabetes during puberty **Results:** no results posted
2	**Title:** study to evaluate safety and efficacy of Dapagliflozin and Saxagliptin in patients with type 2 DM[276] **Age:** 10-18 years **Active substances:** Dapagliflozin, Saxagliptin, and Placebo **Status:** recruiting (Since 2017), interventional study **Aim:** to evaluate safety and efficacy of D. and S. in children **Results:** not posted
3	**Title:** a research study to compare a new medicine oral Semaglutide to a dummy medicine in children and teenagers with type 2 diabetes[277] **Age:** 10-17 years **Active substances:** Semaglutide and Placebo **Status:** recruiting (First posted 10/2020) **Aim:** to compare S. and Placebo **Results:** not posted
4	**Title:** efficacy and safety of Liraglutide in combination with Metformin, compared to Metformin alone, in children and adolescents with type 2 DM[278] [279] **Age:** 10-17 years **Active substances:** Liraglutide and Placebo **Status:** completed (Last update 07/2021) **Aim:** see above **Results:** in children and adolescents with type 2 diabetes, Liraglutide, at a dose of up to 1.8 mg per day (added to Metformin, with or without basal insulin), was efficacious in improving glycaemic control over 52 weeks. This efficacy came at the cost of an increased frequency of gastrointestinal adverse events.

Table No. 12: relevant clinical studies conducted in Australia (own representation based on data from clinicaltrials.gov and ANZCTR).

[276] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Study to Evaluate Safety and Efficacy of Dapagliflozin and Saxagliptin in Patients With Type 2 Diabetes Mellitus Aged 10 to Below 18 Years Old.
[277] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, A Research Study to Compare a New Medicine Oral Semaglutide to a Dummy Medicine in Children and Teenagers With Type 2 Diabetes (PIONEER TEENS).
[278] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™).
[279] Cf. Tamborlane et al, Ellipse Trial Investigators, Liraglutide in Children and Adolescents with Type 2 Diabetes.

There are merely four studies dealing with the evaluation of safety and efficacy of medicinal products in children. These drugs have already been approved for adults. They deal with the question whether they are relevant, safe, and effective for treating children.

Study 1: the first study dealt with the investigation of Rosiglitazone and whether there is a reduction of insulin resistance and, therefore, an improvement of the control of type 1 diabetes mellitus. Unfortunately, no results were posted. Consequently, the study's conduction and results cannot be evaluated. Obviously, the results regarding children were negative, as there is no approval for Rosiglitazone in this population. The reasons for this could not be determined due to lack of data.

Study 2: the second study mentioned deals with the evaluation of Dapagliflozin and Saxagliptin as well as their safety and efficacy in children with type 2 diabetes mellitus. The study began in 2017. Since then, the recruiting phase has been running. It is possible that too few children agreed to participate in the study. This indicates a common and major problem, i.e., why many studies on children fail and cannot be completed.

Study 3: study No. 3 aimed to compare Semaglutide with a placebo for the evaluation of its safety and efficacy. Just like study No. 2, the recruiting phase is still being carried out, so that results are missing.

Study 4: study No. 4 was initiated with the aim to get more information about the efficacy and safety of Liraglutide in combination with Metformin. The combination is compared to Metformin with placebos for the treatment of diabetes mellitus type 2 in the paediatric population. The results show that the combination of both decreases the mean glycated haemoglobin level, which presented the primary efficacy end point. In the placebo group, however, the value increased. Unfortunately, there was a higher rate of side effects among the Liraglutide group in contrast to the control group. Nevertheless, it is not clear whether sufficient data were obtained from this study and whether they were positive to be used for a regulatory submission.

As a conclusion, it can be said that there are only four studies that deal with the investigation of medicinal products for the treatment of diabetes mellitus in children.

Also, recruitment of paediatric participants seems to be very difficult. In cases where children are enrolled, it seems very difficult to get an adequate number of paediatric study

participants. This can be seen, for example, in studies 1 and 2: The last update for study 1 was in 2006. Since then, no further data or results were added. Recruitment for study 2 has been going on since 2017.

Most of the remaining studies deal with topics such as behavioural measurements, e.g., diet and physical activity, meant to prevent diabetes mellitus or to improve the course of the disease. Additionally, studies exist that evaluate new and innovative formulations, including Insulin pumps or intranasal and oral Insulin.

7.3.2 Canada

Regarding the keywords *child* and *interventional study*, there are 111 studies available at clinicaltrials.gov. 81 interventional studies have been conducted in Canada with children on the topic of diabetes mellitus since January 2008. This represents 9% of all Canadian interventional studies. 50 of them are complete.

In the HC database, only 21 results regarding paediatric clinical trials can be found since 2008-01-01. Six of them are already closed. The used keywords are *Diabetes* and *pediatric studies*. The keyword *interventional study* cannot be selected, because the registry contains only phase 1-3 clinical trials. There is no possibility to filter for a special study type.

All numbers of studies from clinicaltrials.gov and the HC database can be found in annex 14.

Relevant studies of the two databases with medication are mentioned and presented in the table below:

Study	
1	**Title:** activity and Metformin intervention in obese adolescents (REACH) (interventional study, DM type 2)[280] [281] **Age:** 10-16 years **Active substances:** Metformin, placebo, exercises **Status:** completed **Aim:** reduction in BMI **Results:** no differences between MXR and control group, exercise is crucial

[280] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Activity and Metformin Intervention in Obese Adolescents (REACH).
[281] Cf. Clarson et al, Effects of a Comprehensive, Intensive Lifestyle Intervention Combined with Metformin Extended Release in Obese Adolescent,.

2	**Title:** adolescent type 1 diabetes. Treatment with SGLT2i for hyperglycaemia and hyperfiltration trial (ATTEMPT)[282] **Age:** 12-18 years **Active substances:** Dapagliflozin (Forxiga) and placebo **Status:** recruiting **Aim:** effect of Dapagliflozin compared to placebo (and in combination with Insulin) **Results:** no results available yet
3	**Title:** a trial investigating the efficacy and safety of Insulin degludec/Insulin aspart once daily, plus Insulin aspart for remaining meals vs. Insulin detemir once or twice daily, plus mealtime insulin aspart in children and adolescents with type 1 DM[283] [284] **Age:** 1-17 years **Active substances:** Insulin degludec and Insulin aspart **Status:** completed **Aim:** to investigate safety and efficacy of insulin degludec/aspart **Results:** IDegAsp + IAsp was non-inferior to IDet + IAsp regarding HbA1c, had similar hypoglycaemia rates and required fewer injections.
4	**Title:** efficacy and safety of Liraglutide in combination with Metformin compared to Metformin alone, in children and adolescents with type 2 DM (Ellipse)[285] [286] **Age:** 10-17 years **Active substances:** Liraglutide, Metformin, Placebo **Status:** Completed **Aim:** To assess the efficacy and safety of Liraglutide in paediatric population **Results:** In children and adolescents with type 2 diabetes, Liraglutide, at a dose of up to 1.8 mg per day (added to Metformin, with or without basal insulin), was efficacious in improving glycaemic control over 52 weeks. This efficacy came at the cost of an increased frequency of gastrointestinal adverse events.
5	**Title:** Ertugliflozin type 2 diabetes mellitus paediatric study[287] **Age:** 10-17 years **Active substances:** Ertugliflozin, Metformin, Insulin, placebo **Status:** Recruiting **Aim:** to evaluate the safety and efficacy of Ertugliflozin in paediatric population with t2DM on Metformin with and without Insulin

[282] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Adolescent Type 1 Diabetes Treatment With SGLT2i for hyperglycEMia & hyPerfilTration Trial (ATTEMPT).
[283] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, A Trial Investigating the Efficacy and Safety of Insulin Degludec/Insulin Aspart Once Daily Plus Insulin Aspart for the Remaining Meals Versus Insulin Detemir Once or Twice Daily Plus Meal Time Insulin Aspart in Children and Adolescents With Type 1 Diabetes Mellitus.
[284] Cf. Battelino et al, Efficacy and safety of a fixed combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes: A randomized trial.
[285] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™).
[286] Cf. Tamborlane et al, Ellipse Trial Investigators, Liraglutide in Children and Adolescents with Type 2 Diabetes.
[287] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Ertugliflozin Type 2 Diabetes Mellitus (T2DM) Pediatric Study (MK-8835/PF-04971729) (MK-8835-059).

	Results: Results are not available yet
6	**Title:** diabetes study of Linagliptin and Empagliflozin in children and adolescents (DINAMO)[288] [289] **Age:** 10-18 years **Active substances:** Linagliptin, Empagliflozin, placebo **Status:** recruiting **Aim:** to evaluate the efficacy and safety of Empagliflozin dosing and dose of linagliptin **Results:** no results are available yet
7	**Title:** study to evaluate safety and efficacy of Dapagliflozin and Saxagliptin in patients with type 2 DM [290] [291] **Age:** 10-18 years **Active substances:** Dapagliflozin and Saxagliptin **Status:** active, not recruiting **Aim:** to evaluate efficacy and safety pf Dapagliflozin and Saxagliptin **Results:** -
8	**Title:** finding a safe and effective dose of Linagliptin in pediatric patients with type 2 diabetes mellitus[292] [293] **Age:** 10-17 years **Active substances:** Linagliptin and placebo **Status:** completed **Aim:** to identify the dose of Linagliptin **Results:** limitation of the trial, such as small number of subjects analysed or technical problems leading to unreliable data (73 participants)
9	**Title:** a multicentre, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of Saxagliptin in combination with Metformin IR or Metformin XR in paediatric patients with type 2 diabetes who have inadequate glycaemic control on Metformin alone[294] [295] **Age:** 10-17 years **Active substances:** Saxagliptin and Metformin **Status:** completed

[288] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Diabetes Study of Linagliptin and Empagliflozin in Children and Adolescents (DINAMO)TM.
[289] Cf. European Medicines Agency, A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks.
[290] Cf. ClinicalTrials.gov, Study to Evaluate Safety and Efficacy of Dapagliflozin and Saxagliptin in Patients With Type 2 Diabetes Mellitus Aged 10 to Below 18 Years Old.
[291] Cf. European Medicines Agency, A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin.
[292] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Finding a Safe and Effective Dose of Linagliptin in Pediatric Patients With Type 2 Diabetes.
[293] Cf. European Medicines Agency, A randomised, double-blind, placebo-controlled, parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus.
[294] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination With Metformin IR or Metformin XR in Pediatric Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.
[295] Cf. European Medicines Agency, A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin IR or metformin XR in pediatric patients with type 2 diabetes who have inadequate glycemic control on metformin alone.

	Aim: to evaluate efficacy, safety, tolerability of Saxagliptin in combination with Metformin **Results:** limitation of the trial, such as small number of subjects analysed or technical problems leading to unreliable data (6 participants)

Table No. 13: relevant clinical studies conducted in Canada (own representation based on data from clinicaltrials.gov and database of Health Canada).

Study 1: the first study mentioned is called REACH study, an acronym that stands for Activity and Metformin Intervention in Obese Adolescents. It investigated the combination of Metformin and comprehensive, intensive lifecycle intervention, as well as their impact on the BMI in obese adolescents, compared to an identical lifestyle intervention with a placebo. The study was conducted as a randomized and double-blind trial. There had already been studies for this topic, but these studies were limited to a maximum of 12 months and could only show moderate positive impact on BMI. With the REACH study as a long-term project of 24 months, the sponsors hoped for sustainable improvements in BMI.

The study found out that the effect of Metformin was most evident in the first 6 months and decreased in effectiveness over time. Consequently, the sponsors recommend combining Metformin with a lifecycle intervention for the first 6 to 12 months, as both together resulted in an initial decrease in BMI. After that, it is advisable to switch to a sustained lifestyle modification as a sole therapy in the long term.[296]

Nevertheless, despite this result, there is no authorisation for Metformin for the treatment of diabetes mellitus in children or adolescents in Canada but in the other three countries, which are within scope of this work.

Study 2: the study called ATTEMPT (Adolescent type 1 diabetes treatment with SGLT2i for hyperglycaemia & hyperfiltration trial) means to investigate the effect of Dapagliflozin compared to placebo beside an insulin therapy in patients with diabetes mellitus type 1. It is a randomized, double-blinded study with US-American and Canadian children aged 12 to 18 years. The recruitment started in December 2020 and is still ongoing, so that no results have been posted yet.

Study 3: this multicentre study was conducted in Canada among other sites. The study evaluated the combination of Insulin aspart and Insulin degludec as well as its safety and

[296] Cf. Clarson et al., Effects of a Comprehensive, Intensive Lifestyle Intervention Combined with Metformin Extended Release in Obese Adolescents.

efficacy profile in children aged 2 to 17 years with diabetes mellitus type 1. The combination was actually authorised in Australia and the EU.

The study revealed that the combination of Insulins degludec and Insulin aspart once daily with Insulin aspart on demand is non-inferior to the therapy of Insulin detemir with Insulin aspart as single preparations regarding the reduction of HbA1c in children. Furthermore, the combination represents a benefit for patients, because fewer injections need to be administered. Nevertheless, Rhyzodeg is not approved for children in Canada. However, it was not possible to find out why no application was made.[297]

Study 4: this study dealt with the evaluation of Liraglutide with Metformin and its combined effect on children and adolescents. This study was already mentioned in the section pertaining to Australia. In conclusion, the study found out that the combination of both effects a reduction of mean glycated haemoglobin level, compared to Metformin with a placebo and a decrease in fasting plasma glucose. This led to an improved glycaemic control. It is an indication that Liraglutide is superior to placebos. Nevertheless, safety outcomes show a higher rate of adverse events with Liraglutide.[298]

The globally conducted study has already ended, but no approval has been granted to date for the combination, neither in Australia nor in Canada.

As monotherapy, Liraglutide is only authorised in Canada for children aged 10 years and older with the medicinal product Victoza and for children aged 12 or older with Saxenda. However, in Australia, there is no authorisation for Liraglutide as single preparation.

Compared to that, a paediatric authorisation for Metformin is missing in Canada.

In addition, it must be mentioned that, according to the study protocol, there were recruitment difficulties. Due to the lack of paediatric participants, the protocol had to be adjusted to facilitate recruitment, which further led to a delay in conducting the study. Instead of 150 randomized subjects, only 94 patients took part.

Study 5: the interventional phase 3 study is poised to deal with the evaluation of Ertugliflozin concerning children who suffer from type 2 diabetes mellitus and take

[297] Cf. Battelino et al., Efficacy and safety of a fixed combination of insulin degludec/insulin aspart in children and adolescents with type 1 diabetes: A randomized trial.
[298] Cf. Tamborlane et al., Liraglutide in Children and Adolescents with Type 2 Diabetes.

Metformin with or without Insulin. The study aims to show that the addition of Ertugliflozin to the basic treatment with Metformin is superior to Metformin with a placebo. The first post was in July 2019. The recruitment phase is still ongoing. Therefore, no results have yet been published.

The same situation can be found in phase 3 **studies 6 and 7**. The recruitment phase of study 6, which evaluates the treatment of Linagliptin and Empagliflozin, began February 2018 and is still ongoing. Therefore, unfortunately, no results have been posted, yet – neither at clinicaltrials.gov nor in the EU clinical trial registry.

Study 7, which investigates the safety and efficacy of Dapagliflozin and Saxagliptin, is active but has not recruited since April 2022. No results have been published.

Study 8: this study was conducted to determine a safe and effective dose of Linagliptin for children 10 to 17 years of age with diabetes mellitus type 2. It was conducted as a randomized, double-blind and placebo-controlled study and completed in 2017. Results from 1 and 5 mg Liraglutide were positive, showing a decrease in mean HbA1c and a decline in mean fasting plasma glucose. The results are comparable with the clinical efficacy and safety profile in adults. Nevertheless, Linagliptin is not approved for children by Health Canada, because according to the product information of Saxenda, safety and effectiveness have not been established in children.

Additionally, the difficulty of recruiting was also pointed out in the study report. It took 56 months to recruit just 40 children according to clinicaltrials.gov. Providentially, this number is sufficient for the assessment. Nevertheless, it was estimated that 117 patients would be needed for the analysis of improvements in metabolic control.[299]

Study 9: the aim of this study was to assess the safety and tolerability of Saxagliptin by adding it to a Metformin therapy in children aged 10 to 17 years. The study failed, because fewer patients could be recruited than necessary. Approximately 236 subjects were needed for an evaluation, but only six subjects could be randomized and treated. It was a global study, and no subject could be recruited from Canada.

[299] Cf. Tamborlane et al., Randomized, double-blind, placebo-controlled dose-finding study of the dipeptidyl peptidase-4 inhibitor linagliptin in pediatric patients with type 2 diabetes.

Remaining studies:

Most of the studies addressed exercise, dietary intervention, or the comparison between different dosage forms of insulin preparations. There have been few studies aimed at gaining knowledge about a medication. In addition, few studies have been conducted on the subject of type 2 diabetes mellitus.

There are some studies that are carried out with all age groups. In these cases, it was difficult to see whether, how many children, and what ages took part.[300] [301] [302]

7.3.3 Japan

For Japan, only clinical studies of the registry clinicaltrials.gov will be considered and analysed in the following section, because the ministry's registry JRCT has only existed since 2018 and its results are not comparable.

All interventional studies that have been carried out since 2008 are examined in more detail. According to clinicaltrials.gov, a total of 50 studies with antidiabetics have been carried out in children at all. That accounts for 10% of all Japanese studies investigating antidiabetics.

7 interventional studies have been performed since January 2008 that represents 2% of all interventional studies for the treatment of diabetes mellitus. Six of them are complete. Since not all studies are registered with clinicaltrials.gov, as it is not mandatory, it is difficult to assess whether so few studies have actually been conducted over the last 16 years.

Studies out of the 7 that will no longer be considered:

- One study has the status *unknown* and will therefore not be considered further.
- In one of the studies, instead, retinopathy, a secondary disease of diabetes mellitus, is discussed, which means that the study no longer plays a role in this analysis.

[300] Cf. Health Canada, Health Canada's Clinical Trials Database.
[301] Cf. U.S. National Library of Medicine, ClinicalTrials.gov.
[302] Cf. European Medicines Agency, EU Clinical Trials Register.

- One study discusses the efficacy and safety of desmopressin. Desmopressin is not primarily intended for the treatment of diabetes, so the study is no longer the focus of this analysis.

Consequently, only 4 studies remain for analysis. All numbers of studies from clinicaltrials.gov can be found in annex 15.

Study	
1	**Title:** comparison of the safety and efficacy of HOE901-U300 with Lantus in children and adolescents with type 1 diabetes mellitus (Edition junior)[303] [304] **Further information:** phase 3, interventional stud, multicentre (USA, Canada, EU and more.) **Age:** from 6 to 17 years **Active substances:** Insulin glargine (HOE901-U300 = Insulin glargine U300 new formulation) **Status:** completed **Aim:** to compare the efficacy of a new formulation of Insulin glargine (HOE901-U300) to Lantus in terms of change of HbA1c from baseline to endpoint (month 6) in children and adolescents with type 1 diabetes mellitus. **Results:** Gla-300 (Insulin glargine U300) provided similar glycaemic control and safety profiles to Gla-100 in children and adolescents with type 1 diabetes, indicating that Gla-300 is a suitable therapeutic option in this population. **Sources:**
2	**Title:** a trial investigating the efficacy and safety of Insulin degludec in children and adolescents with type 1 diabetes mellitus (BEGIN). Further information: phase 3 study, multicentre study (Africa, Asia, EU, USA), interventional study[305] [306] **Age:** 1-17 years **Active substances:** Insulin degludec, Insulin detemir, Insulin aspart **Status:** completed **Aim:** the aim is to investigate the efficacy and safety of Insulin degludec in children and adolescents with type 1 diabetes mellitus **Results:** in conclusion, this trial showed that IDeg offers a valuable new addition to the treatment of T1D in children, with the potential to deliver similar glycaemic control to IDet, achieved with comparable safety, but reduced hyperglycaemia with ketosis in a single daily injection.

[303] Cf. Danne et al, Efficacy and Safety of Insulin Glargine 300 Units/mL (Gla-300) Versus Insulin Glargine 100 Units/mL (Gla-100) in Children and Adolescents (6-17 years) With Type 1 Diabetes: Results of the EDITION JUNIOR Randomized Controlled Trial.
[304] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Comparison of the Safety and Efficacy of HOE901-U300 With Lantus in Children and Adolescents With Type 1 Diabetes Mellitus (EDITION JUNIOR).
[305] Cf. Thalange et al, Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes.
[306] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, A Trial Investigating the Efficacy and Safety of Insulin Degludec in Children and Adolescents With Type 1 Diabetes Mellitus (BEGIN™).

3	**Title:** a study comparing LY900014 to Insulin lispro (Humalog) in children and adolescents with type 1 diabetes (PRONTO-Peds) **Further information:** interventional study, multicentre (USA, China, EU, Japan, Mexico, Russia and more), phase 3 study[307] [308] **Age:** 1-17 years **Active substances:** LY90014 (Lyumjev, insulin lispro/Citrate/Treprostinil), Insulin lispro, Insulin glargine, Insulin degludec **Status:** completed **Aim:** to compare the study drug LY900014 to Insulin lispro (Humalog) in children and adolescents with type 1 diabetes **Results:** no results posted
4	**Title:** efficacy and safety of faster-acting insulin aspart compared to NovoRapid both in combination with insulin degludec in children and adolescents with type 1 diabetes[309] [310] **Further information:** phase 3 study, interventional study, multicentre (USA, EU, Japan, etc.) **Age:** 1-17 years **Active substances:** faster-acting Insulin aspart, Insulin aspart, Insulin degludec **Status:** completed **Aim:** to investigate efficacy and safety of faster- acting insulin aspart compared with insulin degludec **Results:** in children and adolescents with type 1 diabetes, mealtime, and post meal faster aspart with insulin degludec provided effective glycaemic control with no additional safety risks versus IAsp. Mealtime faster aspart provided superior HbA1c control compared with IAsp.

Table No. 14: relevant clinical studies conducted in Japan (own representation based on data from clinicaltrials.gov).

All in all, there are only studies that deal with the investigation of type 1 diabetes mellitus in children. None of them discuss the disease of type 2. All of them are multicentre studies and carry out examinations with various insulin preparations.

Study 1: according to the results of study 1, both Insulin glargine Gla-100 and Gla-300 provide similar glycaemic control. Both are safe in children and adolescents. Consequently,

[307] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, A Study Comparing LY900014 to Insulin Lispro (Humalog) in Children and Adolescents With Type 1 Diabetes (PRONTO-Peds).
[308] Cf. European Medicines Agency, A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-PEDS.
[309] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Efficacy and Safety of Faster-acting Insulin Aspart Compared to NovoRapid® Both in Combination With Insulin Degludec in Children and Adolescents With Type 1 Diabetes (onset®7).
[310] Cf. Bode et al, Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec, in Children and Adolescents With Type 1 Diabetes: The onset 7 Trial.

both are suitable therapeutic options in this population. Therefore, it is incomprehensible why Insulin glargine has not been approved for children in the Japanese market.

Study 2 shows that Insulin degludec and Insulin detemir are both comparable regarding their efficacy and safety in type 1 diabetes mellitus. However, only Insulin degludec is authorised for the treatment of type 1 diabetes mellitus in children.

Study 3: in study 3, a new formulation with Insulin lispro was investigated and compared with an already existing Insulin lispro formulation Humalog and with Insulin glargine und Insulin degludec. Actually, no Insulin lispro, neither Humalog nor the new formulation LY90014, are available for use in children in Japan. Furthermore, due to lack of results published, no further statement can be made.

Study 4: the fourth study deals with the comparison between a faster-acting Insulin aspart and Insulin aspart and degludec already on the Japanese market. Insulin aspart is currently not approved for use in children. The results show that the combination of faster aspart and Insulin degludec are equivalent in efficacy to Insulin aspart without additional safety risks. Additionally, regarding HbA1c control, the faster-acting Insulin aspart is superior to conventional Insulin aspart.

All published results show that the studies in children were successful. The drugs tested are effective and safe in children. However, none of the drugs, with the exception of Insulin degludec, have been approved for the paediatric population in Japan. Since no further data are available, no further statement can be made in this regard.

The small number of paediatric clinical trials carried out clarifies and underpins what the diagram *interventional clinical trials conducted in Japan since 2008-01-01* already shows: 2% of all conducted clinical trials have been performed involving children. That clearly is not enough.

7.3.4 European Union

According to the EU Clinical Trials Register, there are 72 trials registered with an EudraCT protocol. The keywords used for the search are the following:

- In the search field: diabetes mellitus.
- Select Country: No filter → that means that all countries of the EU and outside the EU/EEA are included.
- Select Age Range: under 18.
- Select Date Range: 2008-01-01.
- Results Status: trials with results.

Overview of study results	
Clinical trials without results are excluded due to the lack of further information (trials without results) (EudraCT Keywords: diabetes mellitus, under 18, 2008-01-01, trials without results)	**68 studies** are affected
54 of the 72 clinical trials are already completed.	
How many of these 72 studies are for the indication of type 2 diabetes mellitus?	**22 studies** of these 72 studies
How many of these 72 studies are for the indication of type 1 diabetes mellitus?	**31 studies** of these 72 studies
How many of these 72 studies are listed but not relevant for indication of diabetes mellitus?	**16 studies** of these 72 studies
How many studies were conducted exclusively outside the EU/ EEA?	**12 studies** of these 56 (72-16) studies

Table No. 15: clinical trials conducted in the EU, status 31.12.2021 (own representation based on data from EudraCT).[311]

Relevant studies with results are listed in the following table:

Study	
1	**Title:** a randomized, multi-center, parallel group, single-dose, pharmacokinetics and pharmacodynamics study of Dapagliflozin in children and adolescents aged 10 to 17 years with type 2 diabetes mellitus[312] [313] **Further information:** conducted in USA and Mexico, type 2, interventional study **Age:** 10-17 years **Active substances:** Dapagliflozin **Status:** completed, global end of trial date: 13 Sep. 2014 **Aim:** to evaluate the pharmacokinetics of Dapagliflozin **Results:** administration of a single oral dose of dapagliflozin was generally well tolerated, no unexpected or clinically significant safety findings.
2	**Title:** a randomized, double-blind, placebo-controlled trial to

[311] Cf. European Medicines Agency, EU Clinical Trials Register.
[312] Cf. European Medicines Agency, A Randomized, Multi-Center, Parallel Group, Single-Dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus.
[313] Cf. Tirucherai et al, Pharmacokinetics and pharmacodynamics of dapagliflozin in children and adolescents with type 2 diabetes mellitus.

	assess safety and tolerability, pharmacokinetics and pharmacodynamics of Liraglutide in paediatric (10 – 17 years old) subjects with type 2 diabetes [314] [315] **Further information:** conducted in USA and EU etc. **Age:** 10- 17 years **Active substances:** Liraglutide **Status:** completed, global end of trial date: 30 Sep. 2011 **Aim:** to assess the safety and tolerability of different doses of Liraglutide **Results:** Liraglutide was well tolerated, safety, tolerability and pharmacokinetics profiles were similar to profiles in adults
3	**Title:** efficacy and safety of Liraglutide in combination with Metformin versus Metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes[316] [317] **Further information:** conducted in EU and Canada, type 2 study **Age:** 10- 17 years **Active substances:** Liraglutide, Metformin and basal insulin **Status:** completed, global end of trial date: 22 Nov. 2013 **Aim:** to confirm the superiority of Liraglutide versus placebo when added to Metformin with or without basal insulin **Results:** Liraglutide was efficacious in improving glycaemic control, but increasing adverse events
4	**Title:** a 52-week, multinational, multi-centre, open-labelled, randomised, parallel, efficacy and safety comparison of Insulin detemir and NPH Insulin in children and adolescents aged 2-16 years with type 1 diabetes on a basal-bolus regimen with Insulin aspart as bolus insulin[318] [319] **Further information:** conducted in EU and Russia **Age:** 2-17 years **Active substances:** Insulin aspart, Insulin detemir, NPH **Status:** completed, global end of trial date 03 Sep. 2008 **Aim:** to compare HbA1c of Insulin detemir + Insulin aspart with NPH Insulin + Insulin aspart **Results:** Insulin detemir is as safe and efficacious as NPH
5	**Title:** A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of Insulin detemir versus Insulin Neutral Protamine Hagedorn in combination with the maximum tolerated dose of Metformin and diet/exercise on glycaemic control in

[314] Cf. European Medicines Agency, A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10 – 17 years old) Subjects with Type 2 Diabetes.
[315] Cf. Klein et al, NN2211-1800 Study Group, Liraglutide's safety, tolerability, pharmacokinetics, and pharmacodynamics in pediatric type 2 diabetes: a randomized, double-blind, placebo-controlled trial.
[316] Cf. European Medicines Agency, Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes.
[317] Cf. Tamborlane et al, Ellipse Trial Investigators, Liraglutide in Children and Adolescents with Type 2 Diabetes.
[318] Cf. European Medicines Agency, A 52-Week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin.
[319] Cf. Thalange et al, Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus.

	children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of Metformin ± other oral antidiabetic drug(s) ± basal insulin[320] **Further information:** conducted in EU, USA, Brazil, Russia, and more. **Age:** 10-17 years **Active substances:** Metformin, Insulin detemir, NPH **Status:** completed, global end of trial date 14 Jun. 2016 **Aim:** to compare the efficacy of Insulin detemir in combination with Metformin with NPH in combination with MTD of Metformin **Results:** -
6	**Title:** a phase 3, double-blind, placebo-controlled, randomized, multi-center study to assess the safety and efficacy of Exenatide once weekly in adolescents with type 2 diabetes[321] **Further information:** conducted in USA, EU, Israel, Mexico **Age:** 2-17 years **Active substances:** Exenatide **Status:** completed, global end of trial date: 05 May 2021 **Aim:** to assess the effect on glycaemic control of Exenatide compared with placebo. **Results:** -

Table No. 16: relevant clinical trials conducted in the EU (own representation based on data from EudraCT).

Study 1: investigations have been conducted with Dapagliflozin for the treatment in children aged 10 to 17 years. According to the study report, children from birth to <10 years of age were excluded, because the disease would not occur in this paediatric population. Furthermore, it is a published fact that enrolment of patients was difficult.

Nevertheless, the single-dose study was successful, since it could be confirmed that Dapagliflozin is well tolerated among this age group. No significant safety issues occurred. Therefore, the conduction of further studies, such as safety and efficacy, was recommended in the study report. All the studies with Dapagliflozin appear to have been successful, as dapagliflozin has been approved for the treatment in children in the EU.

Unfortunately, no children from Australia, Canada, or Japan were included. Dapagliflozin is actually not authorised for use in children in these countries, according to the research.

[320] Cf. European Medicines Agency, A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin Neutral Protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin.

[321] Cf. European Medicines Agency, A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes.

Study 2: a similar situation exists with Liraglutide, mentioned in the table as study 2: Clinical trial results for the medicinal product can be found in the EU register. In study 2, which was carried out exclusively in the EU, it could be shown that Liraglutide was well tolerated in patients from 10 to 17 years of age and that safety, tolerability, and pharmacokinetic profiles were similar to profiles in adults. Consequently, Liraglutide was granted an approval for the paediatric population between 10 and 17 years of age by the EU.

Although no study with Liraglutide could be found in the registry of clinicaltrials.gov nor in the EU registry, which was carried out on Canadian soil, Liraglutide got an approval for the treatment of type 2 diabetes mellitus in Canada. Maybe they were able to fall back on European study data, or studies were conducted without a registration and without a publication of results.

Study 3: Liraglutide was further investigated in combination with Metformin, as is shown in the table as study 3. The aim of the study was to confirm the superiority of Liraglutide against a placebo when added to Metformin. Ultimately, superiority and efficacy could be proven, but this was associated with an increased incidence of adverse event reports. It can be assumed that the application for approval failed, as the drug is actually not available for children on the market.

There is also no approval for the combined preparation in Canada, where the study was also carried out.

Study 4: because of a low number of patients aged from 2 to 5 years, no formal statistical analyses have been made. Nevertheless, it can be concluded that Insulin detemir is equal in its safety and efficacy to NPH. It was the first study that included subjects younger than 6 years of age.

Study 5: although this was a global study, an insufficient number of participants was recruited. According to the report of the EU register, the study ended earlier than planned. The study results must be analysed with caution, since the number of study participants was not sufficient for an accurate evaluation.

Study 6: the multicentre study was ended with the analysis of 64 children. Due to the lack of subjects, it is difficult to accurately interpret the data. Consequently, no data can be processed and used for a submission.

For all other study reports found in the EU registry, no results were published. All the reports just stated that there have been limitations of the study due to small numbers of participants or that technical problems led to unreliable data.

All data that could be collected regarding the relevant studies of the 54 completed clinical trials of the EU register are available in annex No. 6. The studies marked in yellow have also been conducted in Canada, Australia, or Japan.

7.3.5 Conclusion of the clinicaltrials.gov results for clinical studies with antidiabetics

In Australia, since 2008, very few clinical studies in children have been carried out. Given the high demand for approval of medicinal products for the use in children and the high demand for clinical trials dealing with new and adapted dosage forms, it is truly appalling how few clinical trials are actually conducted or completed to generate the necessary data for a submission for a paediatric marketing authorisation.

Additionally, it has not been made transparent what happens to the studies' data and whether they were used for a submission.

Furthermore, recruitment of paediatric participants seems to be very difficult.

Comparatively many studies were carried out in Canada, but the data is sparse. Some studies were successful. However, it remains unclear what was done with the results and whether they could be used for approval.

According to a study of Peterson et al., sometimes, there are clinical trials conducted in Canada with Canadian children, but these trials' data and results were not made available to Health Canada. The data is generated for the submission and further for the approval of drugs by the FDA. The only beneficiaries of this system are U.S. American children, not Canadian children. Paradoxically, this means that sometimes drugs are approved for paediatric use in US, while those same drugs are declared as insufficient for the use in children in Canada. [322]

[322] Cf. Peterson et al., Industry's neglect of prescribing information for children.

Almost no child studies have been conducted in Japan since 2008. According to clinicaltrial.gov, there were 7 in total, 6 of which were completed. The number must be analysed with caution, as registration of studies conducted in Japan at clinicaltrial.gov is not mandatory. However, since it was generally not mandatory to register a study in Japan until 2018, it is difficult to estimate the actual number of studies conducted. However, the studies found in clinicaltrial.gov only address type 1 diabetes mellitus. No studies have been conducted with children suffering from type 2 diabetes mellitus. Since type 2 is often associated with obesity, it can be assumed that there are not so many cases in Japan since the obesity problem in Japan is much smaller than in the other countries.

Most of the studies found in the EU registers have also failed. The reason given in these reports is the following sentence: "*Limitations of the trials such as small numbers of subjects analysed or technical problems leading to unreliable data".*[323]

Often it was not clear why it failed specifically. It can be assumed that the study was terminated due to an insufficient number of enrolled patients, since not enough study participants could be enrolled. There are only a few studies with concrete study results that are stored and published in the EU register.

In general, however, it can be observed that more studies in children are being conducted on type 1 diabetes mellitus than on type 2.

7.4 Metformin as an example

Metformin is approved in three out of four countries for the treatment in type 2 diabetes mellitus in children. Only Health Canada has not authorised drug products containing Metformin for paediatric use. This is surprising, given the fact that there have been some Metformin studies involving Canadian children. An example of this is the REACH study, which was already mentioned in chapter 7.3.2 and listed there as study 1. Despite the recommendation of the sponsors of the REACH study combining Metformin with lifecycle intervention, no authorisation could be reached.[324]

[323] Cf. Annex 6 clinical trials in EudraCT for the European Union.
[324] Cf. U.S. National Library of Medicine, ClinicalTrials.gov, Activity and Metformin Intervention in Obese Adolescents (REACH).

It is also surprising that Canadian children were also involved in studies in which combinations of different antidiabetic drugs were examined, which always also contained Metformin. Although Metformin is not even approved as API of a single medicinal product in Canada, Canadian children have been participants of clinical trials that have investigated two or more antidiabetics in combination. An overview is provided by annex No. 7. It lists three studies investigating Metformin in combination with Saxaglitin, Sitagliptin, and Liraglutide. The participation of the Canadian children is said to be superfluous, as it does not bring any benefit to them in form of a paediatric authorisation.

The annex also lists studies that were conducted in Canada and dealt with the evaluation of Metformin alone as active ingredient versus a placebo or behavioural interventions.

In Australia and the EU, Metformin is approved from the age of 10 years and above. It is believed that the biguanide is also available on the Japanese market from the age of 10 years. The only indication that was found was a dose for children over 10 years of age in the product information of Metugluco. Still, a description of the age limit is missing.[325]

7.5 Comparison of type 1 and type 2 in the different countries acc. clinicaltrials.gov

The following two figures provide an overview of clinical trials for the treatment of diabetes mellitus conducted in the different countries regarding type 1 and type 2, according to clinicaltrials.gov.

[325] Cf. RAD-AR- Medicine Proper Use Council, Medicinal product informatio of Metformin Tablets 250mg.

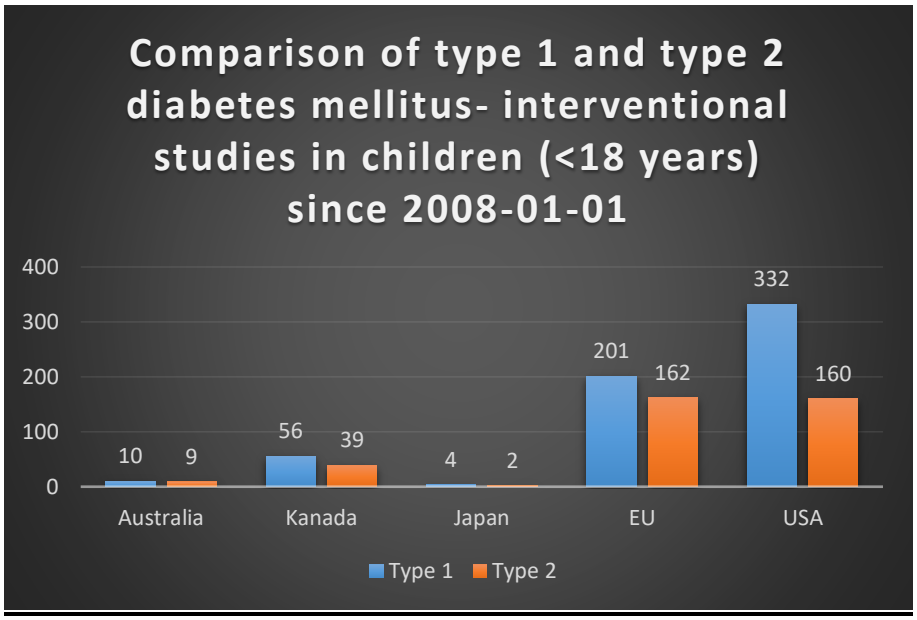

Figure. No. 10: comparison of interventional studies for type 1 and type 2 in children since 2008, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[326]

In all countries, more type 1 than type 2 studies have been conducted involving children.

In general, most studies are conducted in the USA, followed by Europe.

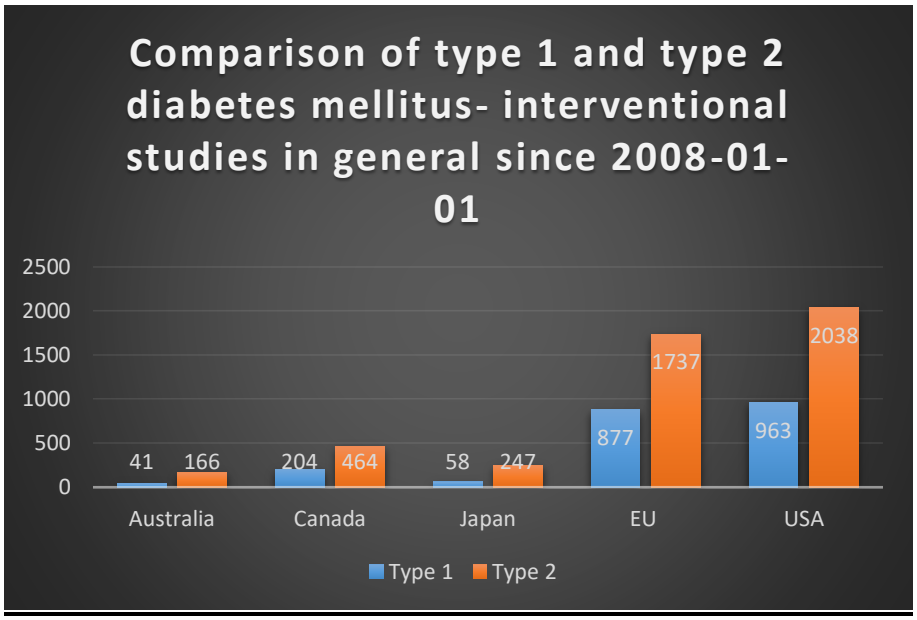

Figure. No. 11: comparison of interventional studies for type 1 and type 2 in general since 2008, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[327]

Considering all the studies, both those involving children and those involving adults, it can be observed that more studies are being conducted on type 2 diabetes mellitus. This is

[326] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, interventional studies, children, since 2008-01-01.
[327] Cf. U.S. National Library of Medicine, Clinicaltrials.gov, keywords: Diabetes mellitus, interventional studies, since 2008-01-01.

probably because more clinical trials are being conducted in adults, and adults almost exclusively develop type 2 diabetes mellitus rather than type 1.

Compared to the other countries, most trials are conducted in the USA, followed by Europe.

All numbers can be found in annex 16.

7.6 Comparison type 1 and type 2 in EU acc. EudraCT

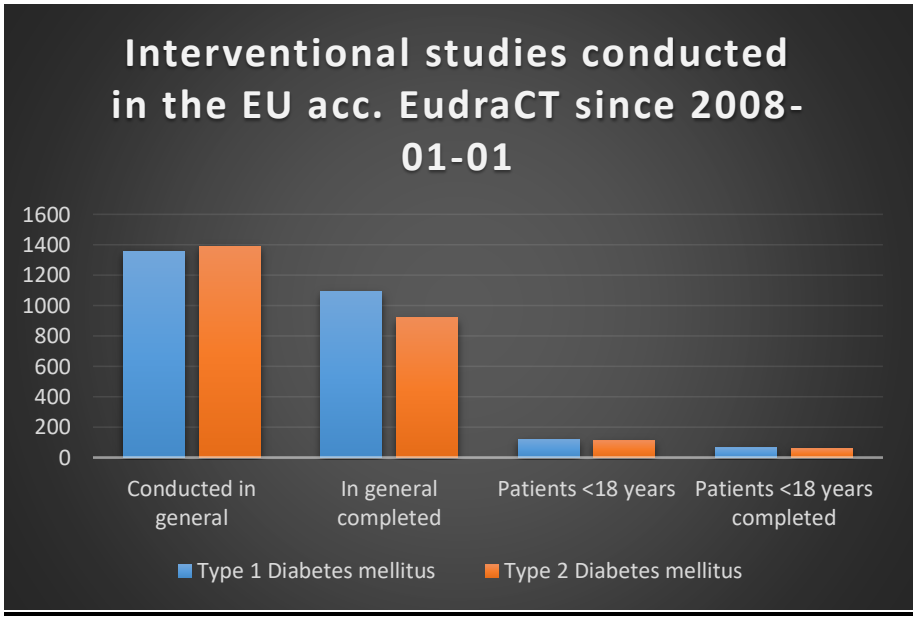

Figure. No. 12: comparison of interventional trials conducted in the EU since 2008, status 31.12.2021 (own representation based on data from EudraCT).[328]

According to the EudraCT database, about the same number of studies are being carried out for type 1 and type 2 diabetes mellitus. This is in contrast to the data from clinicaltrials.gov, which found a difference in the number of studies conducted between type 1 and type 2 in the European Union. The reasons for this are unclear. The exact numbers of studies can be found in annex 17.

[328] Cf. European Medicines Agency, Clinical Trials Register, keywords: interventional studies, EU, since 2008-01-01.

8. Conclusion

8.1 Outcome of the analysis of the different regulatory systems

None of the three analysed countries have introduced a law comparable to the EU Paediatric Regulation since its entry into force. All countries have recognized the problem that more antidiabetic drugs for the treatment of children urgently need to be approved and research on children must be promoted. As a result, Japan and Canada have introduced programmes, established working groups, and created incentives of various kinds to reverse the trend. However, no notable successes were reported.

Australia, on the other hand, was not very active. The country doesn't even have a paediatrics council to draw attention to the high demand and problems.

8.2 Conclusion of usage of databases and available information on authorised medicinal products for children

Obtaining information about which antidiabetic drugs are approved for use in general and especially in children has proved to be very difficult. Little information is provided pertaining to the use of medication by children. Most of the databases provided by the authorities are not exceedingly user-friendly, which has made searching rather tedious.

Direct requests toward the authorities regarding a list of approved antidiabetics in the countries and a list of medicines for children were rejected. The only response was a referral to the general authority’s website.

For example, the data provided by PMDA for the Japanese market is very opaque. A big problem is that many documents are only provided in Japanese language. Only a few are translated into English.

The fact that an AusPAR is being produced for every prescription drug in Australia raised hopes that this would provide more information on approval or disapproval, including paediatric use. However, this turned out to be a mistake. The Australian authority's database no longer contained information on the approval of antidiabetic drugs. The AusPARs usually only contain the information that no studies were carried out on children.

Overall, for Canada, Australia, and Japan, exceptionally little information has thus far been published about the reasons for not conducting clinical trials in children or for rejecting submissions for an antidiabetic drug for therapy in children.

Even if the information provided by the EMA for EU medicines is sometimes not entirely clear regarding why an approval was not obtained or why a waiver for certain age groups was approved for certain antidiabetics, it still offers much more information and ensures much more transparency and traceability in the form of PIPs, EPARs, or product information than the other three countries.

In the EU, eight drugs for the treatment of type 1 diabetes mellitus in children and two antidiabetic drugs for the treatment of type 2 are currently approved via the Centralised Procedure. Two others are available through the MRP or DCP: Metformin for paediatric type 2 therapy and Glibenclamide for the treatment of neonatal diabetes mellitus.

In contrast, in Australia, only 6 different Insulins and Metformin are approved for the therapy of type 2 in children. According to the available data, only two antidiabetics are available in Japan for therapy in children: Insulin degludec and Metformin.

Comparatively more antidiabetics for children have been approved for the Canadian market: seven insulin types for use in type 1 diabetes mellitus and Liraglutide for the treatment of type 2 diabetes mellitus.

Furthermore, it is worrying that in Canada and Japan it is not possible to provide an in-label therapy according to the S3-Guideline for children suffering type 2 diabetes mellitus due to the lack of approval for Metformin.

8.3 Outcome of the analysis of the clinical studies

Only half of the countries analysed are obliged to register the clinical trials that are carried out in a specified database. The Japanese authority only introduced the obligation to register in 2018 with the new registry JRCT. In contrast, Canada does not even have its own national registry. Because registration is not mandatory in all of these countries, there is no exact data on the number of studies actually carried out. This makes the analysis much

more difficult in this work. It is not possible to estimate how high the actual numbers of the studies that have been carried out are. All data should be treated with caution.

With the data obtained from the regional registers and the data from clinicaltrials.gov, the following statements could be made:

- It seems that the EU and Canada have the highest percentage of child studies compared to adult studies than the other countries. Nevertheless, there should be many more. In Japan, according to clinicaltrials.gov, almost no studies are conducted on children.
- However, few antidiabetic drugs are approved for use in children in Canada. The suspicion seems to be true that many studies are being conducted in Canada, but the data are being used for approval in the USA.
- It seems like more observational studies are being done in children than intervention studies.
- The proportion of interventional child studies in the total studies registered in clinicaltrials.gov and EudraCT is almost the same at 8% and 9%, respectively. However, the US registry contains more than twice as many EU studies as the EudraCT.

  In addition, according to clinicaltrials.gov, there are more paediatric type 1 diabetes mellitus studies than paediatric type 2 studies. In general, however, more studies are being conducted on type 2 diabetes mellitus involving adults and children. The reason could be that, in general, the rate of adult participants is significantly higher and this population group suffers almost exclusively from type 2.

  This statement is in contrast to the EudraCT data. According to the EU register, the number of studies for type 1 and type 2 are almost identical.
- Due to the poor data situation, it is difficult to make a general statement regarding the numbers and type of the clinical studies, the failure or non-conduction of the studies and the utilization of the data. There is still a lot of catching up to do here so that exact data can be generated.
- The most common reason why a study failed was due to the small number of study participants. Recruitment of paediatric participants seems to be a big challenge.

- There are also studies that were successful and could be completed. Sometimes, however, it is not understandable why EU studies were not approved, either.

9. Outlook

Children are difficult to recruit. They and presumably especially their parents are frequently unwilling to participate in clinical research studies. Above all, this problem can be observed in clinical studies that investigate type 2 diabetes mellitus. It is estimated that there is a need of minimum of 3800 paediatric patients to conduct studies agreed upon with EMA to date. This is a large number, given the comparatively low prevalence of type 2 diabetes mellitus in the paediatric population, especially in Europe.

Another problem is the lack of adequate developed infrastructure for conducting paediatric clinical research in most of the countries.[329]

An approach to solve the problem of the small number of paediatric study participants could be the idea of partial efficacy extrapolation. According to the FDA and EMA, extrapolation from adults to the paediatric population is possible, if there are similarities in the disease, and the criteria specified by the FDA and EMA are met. Similarities exist, for instance, in the basic pathophysiology of insulin resistance or progressive beta cell dysfunction, when considering the disease of type 2 diabetes mellitus.[330]

Another idea is the conduction of multi-arm trials: instead of testing each new agent in a separate clinical trial, efficacy and safety of multiple new agents added to the standard of care are evaluated against a shared control in one single trial. The advantage of that shared single control is a reduction of the total number of paediatric patients.[331]

Furthermore, there is a high need of international cooperation. Therefore, in 2007, the so-called Pediatric Cluster was established. Regulators of FDA and EMA have started monthly teleconferences to discuss issues of paediatric development. With their meetings, they aim to ensure that paediatric studies are carried out scientifically and ethically on the one hand,

[329] Cf. Food and Drug Administration, Joining Forces: A Call for Greater Collaboration To Study New Medicines in Children and Adolescents With Type 2 Diabetes.
[330] Cf. Food and Drug Administration, Joining Forces: A Call for Greater Collaboration To Study New Medicines in Children and Adolescents With Type 2 Diabetes.
[331] Cf. Food and Drug Administration, Joining Forces: A Call for Greater Collaboration To Study New Medicines in Children and Adolescents With Type 2 Diabetes.

and only as many studies as necessary are carried out on the other. Topics are, e.g., decision of PIPs or choice of study endpoints or results of paediatric studies.[332]

Since 2009 and 2010 respectively, the Japanese PMDA and Health Canada have started to join these telecons and take on the role of observers. The TGA has participated since 2014 and is now an active member. They worked out so-called Common Commentary with which they inform sponsors about their opinion on PIPs. However, the comments are not binding.[333]

The number of topics that are discussed between the different countries increases steadily. It is positive that there is a regular exchange of information, which has been increasing annually.[334]

Additionally, the European Network of Paediatric Research, which is part of the EMA, has created a platform for investigators, academia, and pharmaceutical industry to network as well as collaborate on clinical studies in children. The aim is to exchange good practices and to promote research on medicines for children, also involving stakeholders from outside Europe. For example, Enpr-EMA hold annual meetings and workshops, the results of which they publish in a report. Members from Canada and Japan can also be found in the database.[335]

A great deal has been achieved in the last 15 years to advance the development of paediatric medicines like never before, especially in Europe and the USA. However, this should only be a start to significantly improve the situation for children all over the world.

10. Summary

The issue of the lack of paediatric research is commonly known. Europe addressed this problem by introducing the Paediatric Regulation in 2006. The aim of this master's thesis was to analyse the legal situation and development that has taken place in other industrialised countries, such as Australia, Japan and Canada in comparison to the EU. As

[332] Cf. Food and Drug Administration, International Collaboration / Pediatric Cluster.
[333] Cf. Food and Drug Administration, International Collaboration / Pediatric Cluster.
[334] Cf. PMDA, Pediatric drug development in Japan and international regulatory collaboration.
[335] Cf. European Medicines Agency, European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA).

part of this, the number of approved drugs and the number of clinical studies using the example of antidiabetics for children were considered.

No law similar to the EU Paediatric Regulation has been passed in the three countries, but there are only different support programs that point in the right direction.

In these regions, over 20 medicinal products are authorised for the treatment of type 1 and type 2 diabetes mellitus, apart from the combination products. Of these more than 20 products, only two are approved for the paediatric population in Japan. For Canadian and Australian children, only two drugs other than insulins are available. In addition, in Canada and Japan, it is not possible to provide an in-label therapy according to the S3-Guideline for children suffering type 2 diabetes mellitus due to the lack of approval for Metformin.

Reasons for not granting a child approval are usually based on an authority's waiver with the grounds that the disease does not occur in the paediatric population or due to the lack of paediatric study results. For most of the medicines marketed in Canada, Japan and Australia, no information for the non-existence of the children's approval are available, only the EU provides partial data.

In the EU, 11% of all clinical studies and 9% of all interventional clinical trials were conducted with paediatric participation. In Canada, the number of children participating in clinical studies for diabetes mellitus is even higher: 13%. As many Canadian children take part in interventional clinical trials as in Europe. Japan and Australia bring up the rear (Japan 10% and 2%, Australia 9% and 6%). The most common reason given for not conducting or failing a study is the small number of paediatric participants. Recruiting paediatric participants appears to be a major challenge. Furthermore, justifications are commonly missing and there is a lack of traceability and transparency with regard to the further use of the study data, including whether the studies contribute to the submission of approval for a drug.

Unfortunately, the data from the registers should be treated with caution, as registration of a clinical study is not mandatory in Canada and Australia. In Japan, registrational requirement only started in 2018. Since interventional trials conducted in the EU have been registered since 2004, the EudraCT is considered to be the most comprehensive, most complete and most transparent of all the registers presented.

The number of children suffering from diabetes mellitus has increased significantly in recent years. Although the issue has been tackled more consciously and vigorously since the beginning of the 21st century and the development of paediatric medicines has progressed at unprecedented levels, especially in Europe and the USA, this should only be a start to considerably improve the situation for children all over the world.

Annex 1: List of authorised antidiabetics in general in the four countries[336]

Australia		Canada		Japan		EU (Centralized procedure)	
Type 1	Type 2	Type 1	Type 2	Type 1	Type 2	Type 1	Type 2
Insulin aspart	Acarbose	Insulin aspart	Acarbose	Insulin aspart	Acarbose	Insulin aspart	Alogliptin
Insulin detemir	Alogliptin	Insulin degludec	Alogliptin	Insulin degludec	Alogliptin	Insulin degludec	Canagliflozin
Insulin glargine	Empagliflozin	Insulin detemir	Canagliflozin	Insulin detemir	Amargliptin	Insulin detemir	Dapagliflozin
Insulin human	Exenatide	Insulin glargine	Dapagliflozin	Insulin glargine	Anagliptin	Insulin glargine	Dulaglutide
Insulin lispro	Dulaglutide	Insulin glulisine	Dulaglutide	Insulin glulisine	Canagliflozin	Insulin glulisine	Empagliflozin
	Glipizide	Insulin human	Empagliflozin	Insulin human	Dapagliflozin	Insulin human	Ertugliflozin
Insulin aspart/ degludec	Gliclazide	Insulin lispro	Exenatide	Insulin lispro	Dulaglutide	Insulin lispro	Exenatide
	Glimepiride		Gliclazide		Empagliflozin	Sotagliflozin	Glibenclamide
	Linagliptin		Glimepiride		Exenatide		Glucagon
	Liraglutide		Linagliptin		Glimepride	Insulin aspart/ degludec	Linagliptin
	Metformin		Liraglutide		Imeglimin		Liraglutide
	Pioglitazone		Lixisenatide		Ipragliflozin		Lixisenatide
	Saxagliptin		Metformin		Linagliptin		Nateglinide
	Sitagliptin		Pioglitazone		Liraglutide		Pioglitazone
	Vildagliptin		Repaglinide		Lixisenatide		Repaglinide
			Rosiglitazone		Luseogliflozin		Saxagliptin
	Alogliptin/Pioglitazon		Saxagliptine		Metformin Miglito		Semaglutide
	Empagliflozin/ Linagliptin		Semaglutide		Mitiglinide		Sitagliptin
	Dapagliflozin/ Saxagliptin		Sitagliptin		Nateglinide		Sotagliflozin
	Insulin glargine/ Lixisenatide				Pioglitazone		Vildagliptin
	Metformin/ Alogliptin		Empagliflozin/ Linagliptin		Repaglinide		
	Metformin/ Linagliptin		Dapagliflozin/ Saxagliptin		Saxagliptin		Alogliptin/ Pioglitazone
	Metformin/ Sitagliptin		Liraglutide/ Insulin degludec		Semaglutide		Empagliflozin/ Linagliptin
	Metformin/ Empagliflozin		Lixisenatide/ Insulin glargine		Sitagliptin		Ertugliflozin/ Sitagliptin
	Metformin/ Dapagliflozin		Metformin/ Alopgliptin		Teneligliptin		Glimepirid/ Pioglitazone
	Metformin/ Saxagliptin		Metformin/ Canagliflozin		Tofogliflozin		Insulin degludec/ Liraglutide
	Metformin/ Vildagliptin		Metformin/ Dapagliflozin		Treiagliptin		Insulin glargine/ Lixisenatide
			Metformin/ Linagliptin		Vildagliptin		Metformin/ Alogliptin
			Metformin/ Empagliflozin		Vogibose		Metformin/ Canagliflozin
			Metformin/ Saxagliptin				Metformin/ Dapagliflozin
			Metformin/ Sitagliptin		Canagliflozin/ Teneligliptin		Metformin/ Empagliflozin
					Empagliflozin/ Linagliptin		Metformin/ Ertugliflozin
					Insulin degludec/ Liraglutide		Metformin/ Linagliptin
					Metformin/ Alogliptin		Metformin/ Pioglitazone
					Metformin/ Anagliptin		Metformin/ Saxagliptin
					Metformin/ Vildagliptin		Metformin/ Sitagliptin
							Metformin/ Pioglitazone
							Saxagliptin/ Dapagliflozin

[336] Cf. Own representation based on sources see references to all annexes.

Annex 2: Authorised antidiabetics in Canada

Active Ingredient	Name	Indication	Paediatric use	Grounds
Acarbose	**Acarbose/ Glucobay/ Mar-Acarbose**	Diabetes mellitus type 2	Only adults	-*"recommended for use in children under 18 years of age."*[337] -*"Safety and effectiveness of GLUCOBAY in patients under 18 years of age have not been established."*[338]
Alogliptin	**Nesina**	Diabetes mellitus type 2	Only adults	-*"Safety and efficacy of NESINA in pediatric patients have not been established. Therefore, NESINA should not be used in children."*[339] -*"Pharmacokinetics of alogliptin in patients under 18 years old have not yet been established."*[340]
Canagliflozin	**Invokana**	Diabetes mellitus type 2	Only adults	-*"Safety and efficacy of INVOKANA® in pediatric patients under 18 years of age have not been established. Therefore, INVOKANA® should not be used in children."*[341] *"An open-label, sequential, multiple-dose, multicentre pediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥11*

[337] Cf. Bayer Inc., Product Monograph Glucobay, p.26.
[338] Cf. Bayer Inc., Product Monograph Glucobay, p.3.
[339] Cf. Takeda Canada Inc., Product Monograph Nesina, p.3.
[340] Cf. Takeda Canada Inc., Product Monograph Nesina, p.19.
[341] Cf. Janssen Inc., Product Monograoh Invokana, p.37.

				to < 18 years of age (mean age 14.6 years) with type 2 diabetes mellitus who were on a stable dose of metformin."[342]
Canagliflozin/ Metformin	**Invokamet**	Diabetes mellitus type 2	Only adults	*"The safety and efficacy of INVOKAMETÒ in pediatric patients under 18 years of age have not been established. Therefore, INVOKAMETÒ should not be used in this population."*[343] *"Based on the data submitted and reviewed by Health Canada, the safety and efficacy of canagliflozin in pediatric patients <18 years of age have not been established; therefore, Health Canada has not authorized an indication for pediatric use. An open-label, sequential, multiple-dose, multicentre pediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥11 to <18 years of age (mean age 14.6 years) with type 2 diabetes mellitus who were on a stable dose of metformin. The mean body weight was 107.15 kg (range: 48.5 to 168.6 kg). The patients were treated with canagliflozin once-daily 100 mg or 300 mg for 14 days."* [344]

[342] Cf. Janssen Inc., Product Monograph Invokana, p.42ff.
[343] Cf. Janssen Inc., Product Monograph Invokamet, p.4.
[344] Cf. Janssen Inc., Product Monograph Invokamet, p.48ff.

Dapagliflozin	**Forxiga**	Diabetes mellitus type 2	Only adults	"*Pediatrics (<18 years of age): Safety and efficacy of FORXIGA have not been established in patients under 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use.*" [345] *Pediatrics: "Pharmacokinetics in the pediatric and adolescent population have not been studied."* [346]
Dapagliflozin/ Saxagliptin	**Qtern**	Diabetes mellitus type 2	Only adults	*"Pediatrics (<18 years of age): QTERN should not be used in pediatric patients. Safety and effectiveness of QTERN or its monocomponents have not been established in this patient population."* [347] *"Pediatrics (<18 years of age): QTERN should not be used in pediatric patients. Pharmacokinetics in the pediatric population have not been studied."*[348]
Dapagliflozin/ Metformin	**Xigduo**	Diabetes mellitus type 2	Only adults	"*Pediatrics (<18 years of age): XIGDUO should not be used in pediatric patients. Safety and efficacy of XIGDUO have not been established in patients under 18 years of age."* [349]

[345] Cf. AstraZeneca Canada Inc, Product Monograph Forxiga, p.4.
[346] Cf. AstraZeneca Canada Inc, Product Monograph Forxiga, p.32.
[347] Cf. AstraZeneca Canada Inc, Product Monograph Qtern, p.30.
[348] Cf. AstraZeneca Canada Inc, Product Monograph Qtern, p.3.
[349] Cf. AstraZenec Canada Inc., Product Monograph Xigduo, p.4

				"Pediatrics (<18 years of age): Dapagliflozin XIGDUO is contraindicated in this patient population. No studies were conducted in the pediatric population. Age: No dosage adjustment for dapagliflozin is recommended on the basis of age. The effect of age (young: ≥18 to <40 years [n=105] and elderly: ≥65 years [n=224]) was evaluated as a covariate in a population pharmacokinetic model and compared to patients ≥40 to <65 years using data from healthy subject and patient studies). The mean dapagliflozin systemic exposure (AUC) in young patients was estimated to be 10.4% lower than in the reference group (90% CI: 87.9, 92.2%) and 25% higher in elderly patients compared to the reference group (90% CI: 123,129%). These differences in systemic exposure were considered not to be clinically meaningful. Metformin hydrochloride: Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients." [350]
Dulaglutide	**Trulicity**	Diabetes mellitus type 2	Only adults	"*The safety and efficacy of TRULICITY have not been studied in pediatric patients. Therefore, TRULICITY should not be used in this patient*

[350] Cf. AstraZeneca Canada Inc., Product Monograph Xigduo, p.39 ff.

				population. *The safety and effectiveness of TRULICITY have not been studied in pediatric patients.* *TRULICITY is not indicated for use in pediatric patients. Studies characterizing the pharmacokinetics of dulaglutide in pediatric patients have not been performed."* [351]
Empagliflozin	**Jardiance**	Diabetes mellitus type 2	Only adults	*"JARDIANCE should not be used in pediatric patients. Safety and effectiveness of JARDIANCE have not been studied in patients under 18 years of age."* [352] *"Studies characterizing the pharmacokinetics of empagliflozin in pediatric patients have not been performed."* [353]
Empagliflozin/ Metformin	**Synjardy**	Diabetes mellitus type 2	Only adults	*"SYNJARDY should not be used in pediatric patients. Safety and effectiveness of SYNJARDY have not been studied in patients under 18 years of age. Studies characterizing the pharmacokinetics of empagliflozin and metformin in paediatric patients have not been performed. Therefore, SYNJARDY should not be used in this patient population."* [354]

[351] Cf. Eli Lilly Canada Inc., Product Monograph Trulicity, p. 4ff.
[352] Cf. Boehringer-Ingelheim Canada Ltd., Product Monograph Jardiance, p.7.
[353] Cf. Boehringer-Ingelheim Canada Ltd., Product Monograph Jardiance, p.31.
[354] Cf. Boehringer- Ingelheim Canada Ltd., Product Monograph Synjardy, p. 3.

Empagliflozin/ Linagliptin	**Glyxambi** **Cancelled post market**	Diabetes mellitus type 2	Only adults	*"GLYXAMBI should not be used in pediatric patients. The safety and effectiveness of GLYXAMBI or its individual components have not been established in this patient population. Studies characterizing the pharmacokinetics of empagliflozin or linagliptin in pediatric patients have not been performed."* [355]
Exenatide	**Bydureon**	Diabetes mellitus type 2	Only adults	*"The safety and efficacy of BYDUREON have not been established in pediatric patients. Therefore, BYDUREON should not be used in pediatric patients. BYDUREON has not been studied in pediatric patients."* [356]
	Byetta	Diabetes mellitus type 2	Only adults	*"Pediatrics (<18 years of age): The safety and efficacy of BYETTA have not been established in pediatric patients. Therefore, BYETTA should not be used in this patient population."* [357]
Gliclazide	**Diamicron**	Diabetes mellitus	Only adults	*"Pediatrics (< 18 years of age): Safety and effectiveness of DIAMICRON® MR in children have not been established. DIAMICRON® MR is therefore not recommended for use in children and adolescents."* [358]

[355] Cf. Boehringer- Ingelheim Canada Ltd., Product Monograph Glyxambi, p. 10.
[356] Cf. AstraZeneca Canada Inc., Product Monograph Bydureon, p.4.
[357] Cf. AstraZeneca Canada Inc., Product Monograph Bydureon, p. 3.
[358] Cf. Servier Canada Inc., Product Monograph Diamicron, p. 3.

	APO- Gliclazide	Diabetes mellitus	Only adults	*"Pediatrics (< 18 years of age): Safety and effectiveness of Gliclazide modified release tablets in children have not been established. Gliclazide modified release tablets is therefore not recommended for use in children and adolescents."* [359]
Glimepiride	**Sandoz Glimepiride**	Diabetes mellitus type 2	Only adults	*"Pediatrics (<18 years of age): Safety and efficacy in pediatric type 2 diabetes patients have not been established."* [360]
Insulin aspart	**Kirsty** **Only approved not marketed**	Diabetes mellitus	Authorised for children? No clear information Approved not marketed	*"Pediatrics (2 – 17 years of age): Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness."*[361] *Pediatrics: The pharmacokinetic properties of insulin aspart and regular human insulin were investigated in 18 children (6-12 years, n=9) and adolescents (13-17 years, n=9) with type 1 diabetes. The relative difference in pharmacokinetics and Kirsty® Product Monograph Page 28 of 60 pharmacodynamics in type 1 diabetic children and adolescents between insulin aspart and regular human insulin correlated well with*

[359] Cf. APOTEX Inc., Product Monograph APO-Gliclazide, p. 3.
[360] Cf. Sandoz Canada Inc., Product Monograph Sandoz Glimepiride, p. 3.
[361] Cf. BGP Pharma ULC, Product Monograph Kirsty, p. 4.

				those in healthy adult subjects and type 1 diabetic adults." [362]
	Fiasp	Diabetes mellitus	For children older than 2 years	*"Fiasp: Fiasp® can be used in pediatric patients aged 2 years and above. There is no clinical experience with the use of Fiasp® in pediatric patients with type 1 diabetes mellitus below the age of 2 years or in patients with type 2 diabetes mellitus below the age of 18 years."* [363] *"Safety and efficacy have been investigated in a therapeutic confirmatory trial in children with type 1 diabetes mellitus aged 2 to less than 18 years. In the trial, 519 pediatric patients were treated with Fiasp®. Overall the frequency, type and severity of adverse reactions in the pediatric population do not indicate differences to the experience in the adult population. Lipodystrophy (including lipohypertrophy, lipoatrophy) at the injection site was reported more often in pediatric patients compared to adults. For lipodystrophy in the pediatric population."* [364]

[362] Cf. BGP Pharma ULC, Product Monograph Kirsty, p. 15ff.
[363] Cf. Novo Nordisk Canada Inc., Product Monograph Fiasp, p. 4.
[364] Cf. Novo Nordisk Canada Inc., Product Monograph Fiasp, p. 17.

	Novorapid	Diabetes mellitus	For children older than 2 years? No clear information	*"Pediatrics (2-17 years of age): Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness."* [365]
	Trurapi	Diabetes mellitus	Not specified	*"Trurapi: Pediatrics Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness."* [366]
Insulin degludec	**Xultophy**	Diabetes mellitus type 1	Only for adults	*"Xultophy: Pediatrics (< 18 years of age): Xultophy® is not indicated for use in children and adolescents below 18 years of age. No studies have been performed with Xultophy®in patients below 18 years of age."* [367]
	Tresiba	Diabetes mellitus type 1	Authorised for children older than 2? No clear information Approved not marketed	*"Tresiba: Pediatrics (>2 years old): TRESIBA® is also indicated for the treatment of pediatric patients (>2 years old) with Type 1 diabetes mellitus.* *TRESIBA® has not been investigated in pediatric patients with type 2 diabetes mellitus.* *The safety and efficacy of TRESIBA® has not been established in pediatric patients less than 2 years of age with type 1 diabetes mellitus."*[368]

[365] Cf. Novo Nordisk Canada Inc., Product Monograph NovoRapid, p. 4.
[366] Cf. Sanofi Aventis Canada Inc., Product Monograph Trurapi, p. 4.
[367] Cf. Novo Nordisk Canada Inc., Product Monograph Xultophy, p. 4.
[368] Cf. Novo Nordisk Canada Inc., Product Monograph Tresiba, p. 4.

Insulin detemir	**Levemir**	Diabetes mellitus type 1 (also authorised for type 2: treatment in adults)	For children 2 years and above	*"Pediatrics (<18 years of age): Evidence from clinical studies and experience suggests that use in the pediatric population is not associated with any differences in safety or effectiveness."* [369]
Insulin glargine	**Toujeo**	Diabetes mellitus type 1	Only adults	Toujeo (Sanofi): *"Safety and effictiveness have not been established in pediatric population."* [370]
	Basaglar	Diabetes mellitus type 1	For children older than 6	Basaglar (Eli Lilly): *"The indication for pediatric type 1 diabetes mellitus (age: >6 years old) has been granted on the basis of similarity, demonstrated between BASAGLAR and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and based on clinical experience with the reference products. BASAGLAR (insulin glargine (rDNA origin) injection) is a recombinant human insulin analogue indicated for once-daily subcutaneous administration in the treatment of patients over 17 years of age with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.* *BASAGLAR is also indicated in the treatment of pediatric patients (>6 years old) with type 1 diabetes mellitus who require basal (long-*

[369] Cf. Novo Nordisk Canada Inc., Product Monograph Levemir, p. 4.
[370] Cf. Sanofi Canada, Product Monograph Toujeo, p. 3.

				acting) insulin for the control of hyperglycemia. *Pediatrics (>6 years of age) BASAGLAR can be used in children over 6 years of age with type 1 diabetes mellitus, based on the established safety and effectiveness of the reference product (Lantus®) in children over 6 years of age with type 1 diabetes mellitus."*[371]
	Lantus	Diabetes mellitus type 1	For children older than 6? No clear information	*"Pediatrics (>6 years of age): Safety and effectiveness of LANTUS has been established in children over 6 years of age with Type 1 diabetes mellitus."* [372]
Insulin glulisine	**Apidra**	Diabetes mellitus type 1	For children older than 6	*"Pediatrics (<6 years of age): Based on the data submitted and reviewed by Health Canada, the safety and effectiveness of APIDRA have been investigated in pediatric patients (age 4 to 17 years) with Type 1 diabetes [9(1.6%) < 6 years, 32 (5.6%) between 6 and 8 years, 149 (26%) between 8 and 12 years, and382 (67%) above 12 years old]. Therefore, Health Canada has authorized an indication for pediatric use.* *-APIDRA has not been studied in pediatric patients younger than 4 years of age. There is insufficient clinical data on the use of APIDRA in children below the age of 6 years."*[373]

[371] Cf. Eli Lilly Canada Inc., Product Monograph Basaglar, p. 4.
[372] Cf. Sanofi-Aventis Canada Inc., Product Monograph Lantus, p. 4.
[373] Cf. Sanofi-Aventis Canada Inc., Product Monograph Apidra, p. 4.

Insulin human	**Novolin**	Diabetes mellitus type 1	Not specified	Insulin human Novonordisk: No data available
	Humulin	Diabetes mellitus type 1	Not specified	Humulin: *"Pediatrics (<18 years of age) HUMULIN may be used in children and adolescents, if clinically indicated."* [374]
Insulin lispro	**Lyumjev**	Diabetes mellitus type 1	For children Approved not marketed	Eli Lilly: *"Pediatrics (3 to 18 years of age): Clinical trials have been performed in children (61 patients aged 3 to 11) and children and adolescents (481 patients aged 9 to 18 years), comparing LIPRELOG 100 units/mL to regular human insulin. LIPRELOG 100 units/mL showed better postprandial blood glucose control, while maintaining a similar safety profile."* [375]
	Admelog	Diabetes mellitus type 1	For children	Admelog von Sanofi: *"Pediatrics (3 to 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ADMELOG in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use."* [376]
	Humalog	Diabetes mellitus type 1	For children	Humalog (Eli Lilly): *"Pediatrics (3 to 18 years of age): Clinical trials have been performed in children (61 patients aged 3 to 11) and children and adolescents (481 patients aged 9 to 18 years), comparing HUMALOG 100 units/mL to regular human insulin. HUMALOG 100 units/mL showed better*

[374] Cf. Eli Lilly Canada Inc., Product Monograph Humulin R, N and 30/70, p. 8.
[375] Cf. Eli Lilly Canada Inc., Product Monograph Liprelog, p. 8.
[376] Cf. Sanofi-Aventis Canada Inc., Product Monograph Admelog, p. 4.

				postprandial blood glucose control while maintaining a similar safety profile." [377]
Linagliptin	**Trajenta**	Diabetes mellitus type 2	Only for adults	*"Safety and effectiveness of TRAJENTA in pediatric patients have not been established. Therefore, TRAJENTA should not be used in this patient population. There are no data available on the use of TRAJENTA in patients younger than 18 years of age. Therefore, use of TRAJENTA in pediatric patients is not recommended. Studies characterizing the pharmacokinetics of linagliptin in pediatric patients have not yet been performed. Therefore, TRAJENTA should not be used in this patient population."* [378]
Linagliptin/ Metformin	**Jentadueto**	Diabetes mellitus type 2	Only for adults	*"Safety and effectiveness of JENTADUETO in pediatric patients have not been established. Therefore, JENTADUETO should not be used in this population. Studies characterizing the pharmacokinetics of linagliptin and metformin after administration of JENTADUETO in pediatric patients have not been performed."* [379]

[377] Cf. Eli Lilly Canada Inc., Product Monograph Humalog, p. 10.
[378] Cf. Boehringer Ingelheim Canada Inc., Product Monograph Trajenta, p. 3.
[379] Cf. Boerhinger Ingelheim Canada Inc., Product Monograph Jentadueto, p. 3.

Liraglutide	**Saxenda**	Diabetes mellitus type 2	Above 12 years	*"The safety and effectiveness of SAXENDA® in pediatric patients with type 2 diabetes have not been established.* *Pediatrics (aged 12 to less than 18 years): For pediatric patients aged 12 to less than 18 years, similar dose escalation schedule as for adults should be applied (see Table 2). The dose should be increased until 3.0 mg (maintenance dose) or maximum tolerated dose has been reached. Daily doses higher than 3.0 mg are not recommended. Pediatric patients who do not tolerate 3 mg daily may have their maintenance dose reduced to 2.4 mg daily. Discontinue SAXENDA® if the patient cannot tolerate the 2.4 mg dose. If pediatric patients do not tolerate an increased dose during dose escalation, the dose may also be lowered to the previous level. Dose escalation for pediatric patients may take up to 8 weeks.* *Evaluate the change in BMI after 12 weeks on the maintenance dose and discontinue SAXENDA® if the patient has not had a reduction in BMI of at least 1% from baseline, since it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment.* *Based on the data submitted and reviewed by Health Canada, the safety and efficacy of SAXENDA® in pediatric patients aged 12 to less than 18 Years has been established; therefore, Health Canada has authorized an indication for*

				pediatric use in pediatric patients aged 12 to less than 18 years. *The safety and efficacy of SAXENDA® in children and adolescents below 18 years of age with secondary causes of obesity has not been studied.* *In the pediatric clinical trial, patients did not have type 2 diabetes but were provided with blood glucose meters. Clinically significant hypoglycemia, defined as blood glucose <3 mmol/L, occurred in 1.6% of the SAXENDA®-treated patients compared to 0.8% of placebo-treated patients (see 8.2 Clinical Trial Adverse Reactions). Inform all pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.* *SAXENDA® can be used in pediatric patients aged 12 to less than 18 years, and with a body weight above or equal to 60 kg.* *The safety and efficacy of SAXENDA® have not been established in children under 12 years of age."* [380]

[380] Cf. Novo Nordisk Canada Inc., Product Monograph Saxenda, p. 4, 7.

	Victoza	Diabetes mellitus type 2	Above 10 years	Victoza: for children aged 10 years and above *"In adolescents and children aged 10 years and above with type 2 diabetes, Victoza® is indicated as an adjunct to metformin with or without basal insulin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.* *Victoza® should be initiated with a dose of 0.6 mg once daily for at least one week. The 0.6 mg dose is a starting dose intended to reduce gastrointestinal symptoms during initial titration. After one week at 0.6 mg per day, the dose may be increased to 1.2 mg once daily if additional glycemic control is required. Based on clinical response and after at least one week the dose may be increased to 1.8 mg once daily if additional glycemic control is required. (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests)* *No data are available for children below 10 years of age."* [381]
Liraglutide/ Insulin degludec	**Xultophy**	Diabetes mellitus type 2	Only adults	*"Pediatrics (< 18 years of age): Xultophy® is not indicated for use in children and adolescents below 18 years of age. No studies have been performed with Xultophy® in patients below 18 years of age."* [382]

[381] Cf. Novo Nordisk Canada Inc., Product Monograph Victoza, p. 12.
[382] Cf. Novo Nordisk Canada Inc., Product Monograph Xultophy, p. 4.

Lixisenatide	**Adlyxine**	Diabetes mellitus type 2	Only adults	*"The safety and efficacy of ADLYXINE have not been established in patients younger than 18 years of age, therefore ADLYXINE is not indicated in pediatric patients."* [383]
Lixisenatide/ Insulin glargine	**Soliqua**	Diabetes mellitus type 1	Only adults	Soliqua (Sanofi): *"The safety and efficacy of SOLIQUA in pediatric patients (<18 years of age) have not been established. Therefore, Health Canada has not authorized an indication for pediatric use."* [384]
Metformin (two examples)	**ACT Metformin**	Diabetes mellitus type 2	Only adults	*"The safety and effectiveness of metformin hydrochloride have not been studied in patients under 18 years of age. ACT METFORMIN should not be used in pediatric patients."* [385]
	Glucophage	Diabetes mellitus type 2	Only adults	*„Pediatrics (< 18 years of age): The safety and effectiveness of GLUCOPHAGE have not been studied in patients under 18 years of age. GLUCOPHAGE should not be used in pediatric patients (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)."* [386]

[383] Cf. Sanofi-Aventis Canada Inc., Product Monograph Adlyxine, p. 4.
[384] Cf. Sanofi-Aventis Canada Inc., Product Monograph Soliqua, p. 4.
[385] Cf. ACT Pharma, Product Monograph ACT Metformin, p. 3.
[386] Cf. Sanofi-Aventis Canada Inc., Product Monograph Glucophage, p. 3.

Pioglitazone (two examples)	**JAMP Pioglitazone**	Diabetes mellitus type 2	Only adults	*"Safety and effectiveness of pioglitazone hydrochloride in pediatric patients have not been established. Use in patients under 18 years of age is not recommended."* [387] *"Pediatrics: Pharmacokinetic data in the pediatric population are not available. JAMP Pioglitazone is not recommended for patients under 18 years of age."* [388]
Repaglinide	**Gluconorm**	Diabetes mellitus type 2	Only adults	*"Pediatrics (<18 years of age): Safety and effectiveness of GlucoNorm® has not been established in patients under 18 years of age. Use of GlucoNorm® is not recommended in pediatric patients."* [389] *"Pediatrics (<18 years of age): The use of GlucoNorm® is not recommended in pediatric patients. The safety and effectiveness in pediatrics has not been established. No studies of GlucoNorm®have been performed in pediatric patients."* [390]

[387] Cf. JAMP Pharma Corporation, Product Monograph JAMP Pioglitazone, p. 3.
[388] Cf. JAMP Pharma Corporation, Product Monograph JAMP Pioglitazone, p. 21.
[389] Cf. Novo Nordisk Canada Inc., Product Monograph Gluconorm, p. 3.
[390] Cf. Novo Nordisk Canada Inc., Product Monograph Gluconorm, p. 6.

Rosiglitazone	**Rosiglitazone AA Pharma (example)**	Diabetes mellitus type 2	Only adults	*"The safety and effectiveness of rosiglitazone have not been established in patients younger than 18 years of age. Furthermore, thiazoledinediones promote the maturation of preadipocytes and have been associated with weight gain. Therefore, ROSIGLITAZONE is not indicated in patients younger than 18 years of age."* [391]
Saxagliptine	**APO- Saxagliptin**	Diabetes mellitus type 2	Only adults	*„Safety and effectiveness of saxagliptin in pediatric patients have not been established. Therefore, APO SAXAGLIPTIN should not be used in this patient population."* [392] *"Pharmacokinetics in the pediatric population have not been studied. Therefore, APO-SAXAGLIPTIN should not be used in this patient population."* [393]
	Onglyza	Diabetes mellitus type 2	Only adults	*"Pediatrics (< 18 years of age): Safety and effectiveness of ONGLYZA in pediatric patients have not been established. Therefore, ONGLYZA should not be used in this patient population."*[394] *"Pediatrics (< 18 years of age): Pharmacokinetics in the pediatric population*

[391] Cf. AA Pharma Inc., Product Monograph Rosiglitazone, p. 4.
[392] Cf. APOTEXT Inc., Product Monograph Saxagliptin APO, p. 4.
[393] Cf. APOTEXT Inc., Product Monograph Saxagliptin APO, p. 23.
[394] Cf. AstraZeneca Canada Inc., Product Monograph Onglyza, p. 4.

				have not been studied. Therefore, ONGLYZA should not be used in this patient population." [395]
Saxagliptine/ Metformin	**Komboglyze**	Diabetes mellitus type 2	Only adults	*"Pediatrics (< 18 years of age): Safety and effectiveness of KOMBOGLYZE in pediatric patients have not been established. Therefore, KOMBOGLYZE should not be used in this patient population."* [396] *Saxagliptin:* *"Pharmacokinetics in the pediatric population have not been studied. Therefore, KOMBOGLYZE should not be used in this patient population."* [397]
Semaglutide	**Ozempic**	Diabetes mellitus type 2	Only adults	*"The safety and efficacy of OZEMPIC® have not been studied in pediatric populations. OZEMPIC® is not indicated for use in pediatric patients."* [398]
	Rybelsus	Diabetes mellitus type 2	Only adults	*"Pediatrics (< 18 years of age): The safety and efficacy of RYBELSUS® have not been studied in pediatric populations. RYBELSUS® is not indicated for use in pediatric patients."* [399]

[395] Cf. AstraZeneca Canada Inc., Product Monograph Onglyza, p. 25.
[396] Cf. AstraZeneca Canada Inc., Product Monograph Komboglyze, p. 4.
[397] Cf. AstraZeneca Canada Inc., Product Monograph Komboglyze, p. 33.
[398] Cf. NovoNordisk Canada, Product Monograph Ozempic, p. 4.
[399] Cf. Novo Nordisk Canada Inc., Product Monograph Rybelsus, p. 4.

Sitagliptin	**Januvia**	Diabetes mellitus type 2	Only adults	*"Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JANUVIA®in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use."* [400]
Sitagliptin/ Metformin	**Janumet**	Diabetes mellitus type 2	Only adults	*"Based on the data submitted and reviewed by Health Canada, the safety and efficacy of JANUMET® and JANUMET® XR in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use."* [401] *"Pediatrics:* *The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in pediatric patients (10 to 17 years of age) with type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18% lower compared to adult patients with type 2 diabetes for a 100 mg dose.* *-No studies with sitagliptin have been performed in pediatric patients < 10 years of age."*

[400] Cf Merck Canada Inc., Product Monograph Januvia, p. 4.
[401] Cf. Merck Canada Inc., Product Monograph Janumet, p. 18.

				"Health Canada has not authorized an indication for pediatric use." [402]

Note:

Source: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do
Key words:
1. ATC: A10A (Insulin and analogues), Status: approved à103 entries
2.ATC: A10B (Blood glucose lowering drugs, excluding insulin), Status: approved >474 entries (Stand 03. Dez. 2021)
Probleme: no filter for medicinal products which are authorised for children

[402] Cf. Merck Canada Inc., Product Monograph Janumet, p. 43.

Annex 3: Authorised antidiabetics in Japan

Active Ingredient	Name	Indication	Pediatric use	Review reports
Acarbose[403]	Glucobay, Acarbose Generics	For the treatment of diabetes mellitus	-Glucobay 50 and 100mg: For children no studies have been conducted	Not available
Anagliptin[404].[405]	Suiny, Beskoa, Swimny	For the treatment of type 2 diabetes mellitus	-Suiny 100mg: For children no studies have been conducted -Only dosage for adults available	No information available for children
Alogliptin[406] [407]	Nessina	It is usually used to treat type 2 diabetes. In general, for adults, take 2 tablets (25 mg of alogliptin) at a time, once a day. In patients with moderate or higher renal dysfunction, the dose may be reduced depending on the degree of renal function. Be sure to follow the instructions given.	9.7 For children no studies have been conducted	Not available

[403] Cf. PMDA, Product information Glucobay.
[404] Cf. PMDA, Review report Suiny.
[405] Cf. PMDA, Product information Suiny 100mg Tablets.
[406] Cf. Rad-Ar, Product information Nessina Tablets 12.5mg.
[407] Cf. PMDA, Product information Nessina.

Canagliflozin[408] [409] [410]	Canaglu	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet (100 mg of canagliflozin) at a time, once daily before or after breakfast. Be sure to follow the instructions given.	Canaglu 100mg: 9.7 For children no studies have been conducted.	Only available in Japanese language
Dapagliflozin[411] [412] [413]	Forxiga	For the treatment of type 2 diabetes mellitus Type 2 diabetes: In general, for adults, take 5 mg of dapagliflozin once daily. If the effect is insufficient, the dose may be increased to 1 tablet (10 mg as dapagliflozin) at a time, once a day. Type 1 diabetes: In general, for adults, take 5 mg of dapagliflozin once daily in combination with insulin preparations. If the effect is insufficient, the dose may be increased to 1 tablet (10 mg as dapagliflozin) at a time, once a day.	Forxiga 5 and 10mg:: No studies for safety or efficacy have been conducted in children	No information available for children
Dulaglutide[414]	Trulicity	Usually for the treatment of type 2 diabetes.The usual adult dosage is 0.75 mg subcutaneously once a week. Be sure to follow the instructions.	No information	Not available

[408] Cf. Rad-Ar, Product information Canaglu Tablets 100mg.
[409] Cf. PMDA, Product information Canaglu Tablets 100mg.
[410] Cf. PMDA, Review report Canaglu.
[411] Cf. PMDA, Report on the Deliberation Results of Forxiga.
[412] Cf. Rad-Ar, Product information Fossiga Tablets 10mg.
[413] Cf. PMDA, Product information Forxiga 5 and 10mg tablets.
[414] Cf. Rad-Ar, Product information Trulicity sub. Jinj. 0.075mg Ateos.

Empagliflozin [415] [416]	Jardiance	It is usually used to treat type 2 diabetes and chronic heart failure. Type 2 diabetes: In general, for adults, take 1 tablet (10 mg of the active ingredient) at a time, once daily before or after breakfast. If the effect is insufficient, the dose may be increased from 25 mg once a day. Chronic heart failure: In general, for adults, take 1 tablet (10 mg of the active ingredient) at a time, once daily before or after breakfast. This drug contains 10 mg of the main ingredient in one tablet. Be sure to follow the instructions given.	Jardiance 10 and 25mg: 9.7 For children no studies have been conducted, ohly dosage for adults is available.	Not available
Exenatide[417]	Byetta, Bydureon	It is usually used to treat type 2 diabetes. In general, for adults, 5 µg of the main ingredient is injected subcutaneously twice daily within 60 minutes before breakfast and supper. The dose may be increased up to 10 µg at a time depending on the condition, with a guideline of 1 month or more after the start of use, but the injection amount will be decided by the doctor. Be sure to follow the instructions.	No information available	Not available

[415] Cf. Rad-Ar, Product information Jardiance tablets 10mg.
[416] Cf. Boehringer Ingelheim, Product information Jardiance 10 and 25mg.
[417] Cf. Rad-Ar, Product information Byetta Pen.

Glimepirid[418] [419]	Amaryl,	It is usually used to treat type 2 diabetes.	Amaryl 0.5, 1 and 3mg: 7. 7. Administration to children, etc. Infants of low birth weight, newborns, infants, toddlers or infants under 9 years of age. Safety for children has not been established. (No experience in application) 2. Child Pediatric type 2 diabetics treated with diet and exercise therapy Non-glimepiride 0.5-6 mg/day for (9-16 years) In an uncontrolled study lasting 12 to 28 weeks in a blinded escalation method administered orally Four HbA1c (JDS) from start of dosing to last observation Ab 8.24% in untreated pediatric patients before study (10 patients) 7.61% with glimepiride 2 mg/day or less before study Treat study Among the pediatric patients (25 cases) who had, it decreased from 8.27% to 7.94%. A trend was observed. Also included were poor medication or maintenance dose injection 5 cases of insufficient duration (3 untreated cases, 2 treated cases). The maintenance dose at the end of administration was 0.5 mg/day for 4 patients, 1 mg/day 13 cases, 2 mg/day 6 cases, 4 mg/day 6 cases, 6 mg/day There were 6 cases (ITT population). → Approved for children?	Not available

[418] Cf. Rad-Ar, Product information Amaryl.
[419] Cf. Sanofi, Product information Amaryl 0.5, 1 and 3mg.

Ipragliflozin[420] [421] [422]	Suglat	For the treatment of type 1 diabetes mellitus and type 2 diabetes mellitus. Type 2 diabetes: In general, for adults, take 2 tablets (50 mg of ipragliflozin) once daily before or after breakfast. If the effect is inadequate, the dose may be increased to 4 tablets (100 mg) once daily while closely observing the course. Type 1 diabetes: In general, for adults, take 2 tablets (50 mg of ipragliflozin) at a time, once daily before or after breakfast, in combination with an insulin preparation. If the effect is inadequate, the dose may be increased to 4 tablets (100 mg) once daily while closely observing the course. In either case, low doses may be taken if there is severe liver dysfunction. Be sure to follow the instructions given.	Suglat 25 and 50mg: For children no studies have been conducted	No information available for children
Limeglimin[423]	Twymeeg	For the treatment of type 2 diabetes. In general, for adults, take 2 tablets (1,000 mg of the active ingredient) at a time, twice a day in the morning and evening. Be sure to follow the instructions given.	No information available	Not available

[420] Cf. PMDA, Report on the Deliberation Results, of Suglat.
[421] Cf. Rad-Ar, Product information Sugra tablets 25mg.
[422] Cf. Astellas, Product information Suglat 25 and 50mg.
[423] Cf. Rad-Ar, Product information Twimig Tablets 500mg.

Linagliptin[424] [425]	Trazenta	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet (5 mg of the active ingredient) at a time, once a day. Be sure to follow the instructions given.	Trazenta 5mg:: 9.7 For children no studies have been conducted	Not available
Liraglutide[426]	Victoza	For the treatment of type 2 diabetes mellitus	No information available	No information available for children
Lixisenatide[427] [428] [429]	Lyxumia	For the treatment of type 2 diabetes mellitus In general, for adults, 20 µg of the main ingredient is injected subcutaneously once a day before breakfast. However, start with 10 µg once daily, inject for at least 1 week and then increase to 15 µg once daily, then increase to 20 µg once daily after administration for at least 1 week. The injection volume may be adjusted according to the condition, but should not exceed 20 µg daily.	No study with children was conducted.	No information available for children
Luseogliflozin[430] [431]	Lusefi	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet (2.5 mg of luseogliflozin) once daily before or after breakfast, but depending on the symptoms,	9.7 For children no studies have been conducted	Not available

[424] Cf. Rad-Ar, Product information Trazenta Tablets 5mg.
[425] Cf. Bohringer Ingelheim, Product information Trazenta Tablets 5mg.
[426] Cf. PMDA, Report on the Deliberation Results Victoza.
[427] Cf. PMDA, Report on the Deliberation Results Lyxumia.
[428] Cf. Rad-Ar, Product information Liquismia.
[429] Cf. PMDA, Review report Lyxumia.
[430] Cf. Rad-Ar, Product information Lucefi tablets 2.5mg.
[431] Cf. PMDA, Product information Lusefi.

		increase the dose to 2 tablets (5 mg) once daily. Be sure to follow the instructions given.		
Metformin[432] [433] [434]	Melbin, Glycoran, Metgluco	Since 2014: Drugs with a new dosage indicated for the treatment of type 2 diabetes mellitus (for pediatric use). It is usually used to treat type 2 diabetes. In general, for adults, start by taking 2 tablets (500 mg of the active ingredient) daily in 2 to 3 divided doses immediately before or after meals. The maintenance dose is determined by looking at the effect, but usually 3 to 6 tablets (750 mg to 1,500 mg) are taken daily in 2 to 3 divided doses. For children over 10 years old, start by taking 2 tablets (500 mg of the active ingredient) daily in 2 to 3 divided doses immediately before or after meals. The maintenance dose is determined by looking at the effect, but usually 2 to 6 tablets (500 mg to 1,500 mg) are taken daily in 2 to 3 divided doses. The dose may be adjusted according to your symptoms, but the maximum daily dose is 9 tablets (2,250 mg) for adults and 8 tablets (2,000 mg) for children. Be sure to follow the instructions given.	Glycoran: 9.7 Children, etc. Clinical trials using efficacy and safety as indicators for children, etc. No test has been conducted. Metgluco 250 and 500mg: 9.7 Clinical trials for infants, newborn, low birth weight infants and young childre are currently not given --> is there a authorization for children older than 10 years?	Not available

[432] Cf. PMDA, New Drugs Approved in FY 2014.
[433] Cf. Rad-Ar, Product information Metformin Tablets 250mg.
[434] Cf. PMDA, Product information Metgluco Tablets 250 and 500mg.

Miglitol[435] [436] [437] [438]	Seibule Tablets, in US als Glyset auf dem Markt	It is usually used to improve postprandial hyperglycemia in diabetes. In general, for adults, take 2 tablets (50 mg of the active ingredient) at a time, 3 times a day just before meals. If the effect is inadequate, the dose may be increased to 3 tablets (75 mg). Be sure to follow the instructions given.	Only dosage for adults is mentioned Seibule 25, 50 and 75mg:9.7 studies have been conducted in children post- approval In addition, only data of adverse reactions is available, but no further information about the drug approval for children Miglitol JG: Safety has not been proven for children.	Not available
Mitiglinide calcium hydrat[439] [440]	Glufast	Usually for adults, for the treatment of type 2 diabetes. In general, for adults, take 1 tablet (10 mg of the active ingredient) at a time, 3 times a day immediately before each meal (within 5 minutes), but the dose may be adjusted according to the symptoms. Be sure to follow the instructions given.	Glufast 5 and 10mg: 9.7 No studies with children have been performed.	Not available
Nateglinide[441] [442]	Fastic, Starsis	It is usually used to improve postprandial blood glucose transition in type 2 diabetes. In general, for adults, take 3 tablets (90 mg of the active ingredient) at a time, 3 times a day immediately before each meal (within 10 minutes before meals). If the effect is	Starsis 30 and 90mg: 9.7No studies with children have been conducted. Fastic 30 and 90mg: 9.7No studies with children have been conducted.	Not available

[435] Cf. Rad-Ar, Product information Sable OD Tablets 25mg.
[436] Cf. PMDA, Products approved in FY 2008: New Drugs.
[437] Cf. PMDA, Product information Seibule Tablets 25, 50 and 75mg.
[438] Cf. PMDA, Product information Miglitol JG.
[439] Cf. Rad-Ar, Product information Glufast OD Tabelts 10mg.
[440] Cf. PMDA, Product information Glufast 5 and 10mg.
[441] Cf. Rad-Ar, Product information Fastic lock 30.
[442] Cf. PMDA, Product information Fastic 30 and 90mg.

		inadequate, the dose may be increased to 4 tablets (120 mg). Be sure to follow the instructions given.		
Omarigliptin[443]	Marzev	No information	Marizev 12.5 and 25mg: For children no studies have been conducted.	Not available
Pioglitazone[444] [445] [446]	Actos	It is usually used to treat type 2 diabetes. In general, for adults, take 1 to 2 tablets (15 to 30 mg of pioglitazone) once daily before or after breakfast. The dose may be adjusted according to your gender, age and symptoms, but the upper limit is 3 tablets (45 mg) daily. When used in combination with insulin preparations, for adults, take 1 tablet (15 mg of pioglitazone) at a time, once daily before or after breakfast. The dose may be adjusted according to your gender, age and symptoms, but the upper limit is 2 tablets (30 mg) daily. In either case, be sure to follow the instructions given.	Pioglitazone OD: Safety for children has not been proven. Actos 15 and 30mg: 9.7 For children no studies have been conducted	Not available

[443] Cf. MSD, Product information Marizv Tablets 12.5 and 25mg.
[444] Cf. Rad-Ar, Product information Actos OD lock 15.
[445] Cf. PMDA, Product information Pioglitazone OD Tablets 15 and 30mg.
[446] Cf. PMDA, Product information Actos Tabelts 15 and 30mg.

Repaglinide[447] [448]	Surepost	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet (0.25 mg of the active ingredient) at a time, 3 times a day just before meals (within 10 minutes). The maintenance dose is usually 1 to 2 tablets (0.25 to 0.5 mg) at a time, 3 times a day just before each meal (within 10 minutes). The dose may be adjusted according to need, and the dose may be increased up to 4 tablets (1 mg). Be sure to follow the instructions given.	Surepost: 9.7 For children no studies have been conducted	Not available
Saxagliptin[449] [450]	Onglyza	It is usually used to treat type 2 diabetes. In general, for adults, take 2 tablets (5 mg as saxagliptin) once a day. Depending on the symptoms, 1 tablet (2.5 mg) may be taken once a day. For patients with moderate or higher renal dysfunction, take 1 tablet (2.5 mg) at a time, once a day. Be sure to follow the instructions given.	Onglyza 2.5 and 5mg: No studies regarding safety and efficacy have been performed in children.	Not available
Semaglutide[451]	Ozempic, Rybelsus	For the treatment of type 2 diabetes mellitus	No information available	Not available

[447] Cf. Rad-Ar, Product information Surepost Tablets 0.25mg.
[448] Cf. PMDA, Product information Surepost.
[449] Cf. Rad-Ar, Product information Ongriza Tablets 2.5mg.
[450] Cf. PMDA, Product information Onglyza Tabelts 2.5 and 5mg.
[451] Cf. PMDA, New Drugs Approved in FY 2020.

Sitagliptin[452] [453] [454] [455]	Januvia, Glactiv	For the treatment of type 2 diabetes mellitus Those with normal or decreased renal function but mild (mild renal dysfunction): In general, for adults, take 50 mg of sitagliptin once a day, but if the effect is insufficient, follow the course. The dose may be increased to 1 tablet (100 mg) once a day while observing closely. Persons with impaired renal function (moderate renal dysfunction): In general, for adults, take 25 mg of sitagliptin once daily, but if the effect is insufficient, observe the course carefully. However, the dose may be increased up to 50 mg once a day. Those with impaired renal function (severe renal dysfunction, end-stage renal failure): In general, for adults, take 12.5 mg of sitagliptin once a day, but if the effect is insufficient, follow the course. The dose of 25 mg of the main ingredient may be increased up to once a day while carefully observing. This drug contains 100 mg of sitagliptin in one tablet. In either case, be sure to follow the instructions given.	Glactiv 12.5, 25, 50 and 100mg: 9.7 For children no studies have been conducted. Januvia 12.5, 25, 50 and 100mg: 9.7 For children no studies have been conducted.	No information available for children

[452] Cf. PMDA, Report on the Deliberation Results Januvia and Glactiv.
[453] Cf. Rad-Ar, Product information Januvia Tabelts 100mg.
[454] Cf. PMDA, Product information Glactiv 12.5, 25, 50 and 100mg.
[455] Cf. MSD, Product information Januvia.

Teneligliptine[456] [457]	Tenelia	For the treatment of type 2 diabetes mellitus In general, for adults, take 20 mg of teneligliptin once a day, but if the effect is insufficient, the dose may be increased to 40 mg once a day. This drug contains 20 mg of the main ingredient in one tablet. Be sure to follow the instructions given.	Tenelia 20 and 40mg: 9.7 For children no studies have been conducted	No information available for children
Tofogliflozin[458] [459] [460]	Deberza, Apleway	It is usually used to treat type 2 diabetes. In general, for adults, take 20 mg of tofogliflozin once daily before or after breakfast. Be sure to follow the instructions given.	Deberza 20mg: 9.7 No study for safety or efficacy have been conducted in children. Apleway 20mg: 9.7 No study for safety or efficacy have been conducted in children.	Not available
Trelagliptin[461] [462]	Zafatek	For the treatment of type 2 diabetes mellitus In general, for adults, take 1 tablet (100 mg as toleragliptin) once a week on the designated day of the week. In patients with moderate or higher renal dysfunction, the dose may be reduced depending on the degree of renal function. Be sure to follow the instructions given.	No information available	No information available for children

[456] Cf. PMDA, Report on the Deliberation Results Tenelia.
[457] Cf. Rad-Ar, Product Information Tenelia.
[458] Cf. Rad-Ar, Product information Develza Tablets 20mg.
[459] Cf. Kowa, Product information Deberza Tabelts 20mg.
[460] Cf. Kowa, Product information Apleway Tabelets 20mg.
[461] Cf. PMDA, Report on the Deliberation Results Zafatek Tabets 50 and 100mg.
[462] Cf. Rad-Ar, Product information Zafatek.

Vildagliptin[463] [464]	Equa	It is usually used for type 2 diabetes. In general, for adults, take 1 tablet (50 mg of the active ingredient) at a time, twice daily in the morning and evening. Depending on your symptoms, you may be taken 1 tablet (50 mg) once a day in the morning. Be sure to follow the instructions given. Patients with moderate or higher renal dysfunction or end-stage renal failure on dialysis: 1 tablet (50 mg) may be taken once daily in the morning. Be sure to follow the instructions given.	For children no studies have been conducted	Not available
Vogibose[465] [466]	Basen	It is usually used to treat diabetes and suppress the onset of type 2 diabetes in impaired glucose tolerance. Diabetes: In general, for adults, take 1 tablet (0.2 mg of the active ingredient) at a time, 3 times a day, just before each meal. If the effect is insufficient, increase the dose to 1.5 tablets (0.3 mg) at a time and take 3 times a day just before each meal. Suppression of type 2 diabetes in impaired glucose tolerance: In general, for adults, take 1 tablet (0.2 mg of the active ingredient) at a time, 3 times a day, just before each meal. Be	9.7: For children no studies have been conducted	Not available

[463] Cf. Rad-Ar, Product information Equa.
[464] Cf. PMDA, Product information Equa.
[465] Cf. Rad-Ar, Product information Basen.
[466] Cf. PMDA, Product information Basen.

		sure to follow the instructions for taking all of them.		
Alogliptin/ Metformin	Irisync	No information available	No information available	Not available
Alogliptin/ Pioglitazone[467]	Liovel, Riobel	It is usually to treat type 2 diabetes. In general, for adults, take 1 tablet at a time, once daily before or after breakfast. Be sure to follow the instructions given.	No information available	Not available
Anagliptin/ Metformin[468]	Metoana	It is usually to treat type 2 diabetes. In general, for adults, take 1 tablet twice daily in the morning and evening. Be sure to follow the instructions given.	No information available	Not available
Empagliflozin/ Linagliptin[469]	Tradiance Combination	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet at a time, once daily, before or after breakfast. Be sure to follow the instructions given.	No information available	Not available
Mitiglinide calcium hydrate/ Vogibose	No information	No information	No information available	Not available
Pioglitazone/ Glimepiride	No information	No information	No information available	Not available

[467] Cf. Rad-Ar, Product innformation Liovel.
[468] Cf. Rad-Ar, Product information Metoana.
[469] Cf. Rad-Ar, Product information Tradiance.

Pioglitazone/ Metformin[470]	Metact	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet at a time, once daily after breakfast. Be sure to follow the instructions given.	No information available	Not available
Sitagliptin/ Ipragliflozin	No information	No information	No information available	Not available
Teneligliptin/ Canagliflozin[471]	Canalia Combination	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet at a time, once daily before or after breakfast. Be sure to follow the instructions given.	No information available	Not available
Vildagliptine/ Metformin[472]	EquMet	It is usually used to treat type 2 diabetes. In general, for adults, take 1 tablet twice daily in the morning and evening. Be sure to follow the instructions given.	No information available	Not available
Insulin degludec/ Insulin aspart[473]	Ryzodeg	No information	No information available	Studies on children have been conducted. But it is not mentioned if the drug is authorised for this population.
Insulin degludec/ Liraglutide[474]	Xultophy	No information	No studies have been conducted with children <18 years of age.	Not available

[470] Cf. Rad-Ar, Product information Metact.
[471] Cf. Rad-Ar, Product information Canalia.
[472] Cf. Rad-Ar, Product Information EquMet.
[473] Cf. PMDA, Report on the Deliberation results Ryzodeg.
[474] Cf. PDMA, Product information Xultophy Combination injection FlexTouch.

Insulin glargin/ Lixisenatide[475] [476]	Soliqua	It is usually used to treat type 2 diabetes for which insulin therapy is indicated. In general, for adults, 5 to 20 doses are injected subcutaneously once daily before breakfast. However, start from 5 to 10 doses once a day. The injection volume may be adjusted according to the condition, but it should not exceed 20 doses per day. Be sure to follow the instructions.	9.7 Children: Clinical trials using efficacy and safety as indicators for children has not been implemented.	Not available
Diabetes Type 1				
Insulin aspart[477]	Novorapid, Fiasp, insulin aspart	It is usually used to treat diabetes for which insulin therapy is indicated. In general, for adults, 2 to 20 units of the main ingredient are injected subcutaneously immediately before each meal, but it may be used in combination with a long-acting insulin preparation. The injection volume may be adjusted according to the symptoms and laboratory findings, but the maintenance dose including the long-acting insulin preparation is usually 4 to 100 units per day. Intravenous or continuous subcutaneous infusion pumps are used as needed. Be sure to follow the instructions.	No information available	Not available

[475] Cf. Sanofi, Product information Soliqua.
[476] Cf. Rad-Ar, Product information Soliqua.
[477] Cf. Rad-Ar, Product information, Novorapid.

Insulin degludec[478]	Tresiba	For the treatment of diabetes mellitus in general, also for children.	No information available	Information about dosage available
Insulin detemir	Levemir	No information	No information available	Not available
Insulin glargine[479] [480]	Insulin Glargine, Lantus	For the treatment of diabetes mellitus in general, not not especially for children Post- marketing investigations for safety and efficacy will be assessed. It is usually used to treat diabetes for which insulin therapy is indicated. In general, adults are given subcutaneous injections of 4 to 20 units once daily initially, but sometimes with other insulin preparations. The injection time should be fixed daily, either before breakfast or before bedtime. The injection volume may be increased or decreased depending on the symptoms and laboratory findings, but the maintenance dose including the injection volume of other insulin preparations is usually 4 to 80 units per day. However, it may be used in excess of 80 units if necessary. Be sure to follow the instructions for injection.	No information available	No information available for children, only that there are post- marketing investigations, but when? Or already done?

[478] Cf. PMDA, Review Report Tresiba.
[479] Cf. PMDA, Review Report Insulin glargine.
[480] Cf. Rad-Ar, Product information Insulin glargine.

Insulin glulisine[481]	Apidra	It is usually used to treat diabetes for which insulin therapy is indicated. In general, for adults, 2 to 20 units are injected subcutaneously just before each meal, but it may be used in combination with an intermediate or long-acting dissolved insulin preparation. The injection volume may be adjusted according to the patient's symptoms and laboratory findings, but the maintenance dose including the injection volume of the intermediate or long-acting dissolved insulin preparation is usually 4 to 100 units. This medicine contains 300 units of the main ingredient in 1 kit (3 mL). Be sure to follow the instructions for injection.	Apidra: No information available about authorisation for treatment in children	Not available
Insulin human	Novolin	No information	No information available	Not available
Insulin lispro[482]	Humalog, Lymjev	It is usually used to treat diabetes for which insulin therapy is indicated. Normally, adults inject 2 to 20 units of the main ingredient subcutaneously immediately before each meal, but they may also use a long-acting insulin preparation and sometimes increase the number of injections. The injection volume may be adjusted according to the symptoms and laboratory findings, but the maintenance dose including	No information available	Not available

[481] Cf. Rad-Ar, Product information Apidra.
[482] Cf. Rad-Ar, Product information Humalog.

		the long-acting insulin preparation is usually 4 to 100 units per day. Be sure to follow the instructions.		

Annex 4: Authorised antidiabetics in Australia

Active Ingredient	Name	Indication	Pediatric use
Acarbose	GLARBOSE acarbose 100 mg tablet blister pack[483]	No information	Not specified
	ACARBOSE MYLAN acarbose 100 mg tablet blister pack and 50 mg[484]	No sufficient data on the safety and efficacy of acarbose in children available, therefore, acarbose should not be used in patients under 18 years of age.	No
	ACOBAY acarbose 50 mg tablet blister pack und 100 mg[485]	No information	Not specified
	ACARBOSE GPPL acarbose 50 mg tablet blister pack[486]	No information	Not specified
	GLYBOSAY acarbose 100 mg tablet blister pack[487]	No sufficient data on the safety and efficacy of acarbose in children availble, therefore, acarbose should not be used in patients under 18 years of age.	No
Alogliptin	NESINA alogliptin (as benzoate) 12.5 mg film-coated tablet blister pack, all strengths[488]	The safety and efficacy of NESINA in patients under 18 years of age have not yet been established.	No

[483] Cf. TGA, GLARBOSE acarbose 100 mg tablet blister pack.
[484] Cf. TGA, ACARBOSE MYLAN acarbose 100 mg tablet blister pack and 50 mg.
[485] Cf. TGA, ACOBAY acarbose 50 mg tablet blister pack und 100 mg.
[486] Cf. TGA, ACARBOSE GPPL acarbose 50 mg tablet blister pack.
[487] Cf. TGA, GLYBOSAY acarbose 100 mg tablet blister pack.
[488] Cf TGA, NESINA alogliptin (as benzoate) 12.5 mg film-coated tablet blister pack.

	VIPIDIA alogliptin (as benzoate) 25 mg film-coated tablet blister pack, all strengths[489]	Only for adults	No
Alogliptin/ Pioglitazone	OSENI 25/30 25 mg alogliptin (as benzoate) / 30 mg pioglitazone (as hydrochloride) film-coated tablet bottle, all strengths[490]	Only for adults	No
Empagliflozin	JARDIANCE empagliflozin 10 mg film-coated tablets blister pack, all strengths 10 and 25 mg[491]	Paediatric population: Safety and effectiveness of JARDIANCE in children below 18 years of age have not been established.	No
Empagliflozin/ Linagliptin	GLYXAMBI 25 mg/5 mg empagliflozin/linagliptin 25mg/5mg film coated tablet blister pack, all strengths 10mg/5g and 25/5mg[492]	Only for adults. The safety and effectiveness of GLYXAMBI in children under the age of 18 years have not been established. GLYXAMBI is not recommended for use in patients under 18 years of age.	No
Exenatide	BYDUREON exenatide 2 mg powder for injection pre-filled pen, pen and suspension for Injection[493]	Safety and efficacy of exenatide have not yet been established in children under 18 years of age.	No
Dapagliflozin/ Saxagliptin	QTERN 5/10 saxagliptin (as hydrochloride) / dapagliflozin	Only for adults. Safety and effectiveness of QTERN in paediatric and adolescent patients have not been established."	No

[489] Cf. TGA, VIPIDIA alogliptin (as benzoate) 25 mg film-coated tablet blister pack.
[490] Cf. TGA, OSENI 25/30, 25 mg alogliptin (as benzoate) / 30 mg pioglitazone (as hydrochloride) film-coated tablet bottle
[491] Cf. TGA, JARDIANCE empagliflozin 10 mg film-coated tablets blister pack, 10 and 25 mg.
[492] Cf. TGA, GLYXAMBI 25 mg/5 mg empagliflozin/linagliptin 25mg/5mg film coated tablet blister pack, 10mg/5g and 25/5mg.
[493] Cf. TGA, BYDUREON exenatide 2 mg powder for injection pre-filled pen, pen and suspension for Injection.

	(as propanediol monohydrate) 5 mg / 10 mg film-coated tablet blister pack[494]		
Dulaglutide	TRULICITY dulaglutide (rch) 1.5 mg/0.5 mL solution for injection prefilled pen[495]	Only for adults. Safety and effectiveness of TRULICITY have not been established in children and adolescents under 18 years of age.	No
Glipizide	GLIPIDIAB gipizide 5mg tablets blister pack[496]	No information	Not specified
Gliclazide	GLICLAZIDE-ARX gliclazide 80 mg tablet blister pack[497]	Not indicated for children.	Not specified
	GLICLAZIDE-STR gliclazide 80 mg tablet bottle[498]	Not indicated for children.	Not specified
	APX-GLICLAZIDE gliclazide 80 mg tablet bottle[499]	Not indicated for children.	Not specified
	PHARMACOR GLICLAZIDE gliclazide 30 mg modified release tablet blister pack, 30 und 60 mg[500]	Paediatric use: Not recommended for paediatric use. Dosage: For adult use only.	No

[494] Cf. TGA, QTERN 5/10 saxagliptin (as hydrochloride) / dapagliflozin 5 mg / 10 mg film-coated tablet blister pack.
[495] Cf. TGA, TRULICITY dulaglutide (rch) 1.5 mg/0.5 mL solution for injection prefilled pen.
[496] Cf. TGA, GLIPIDIAB gipizide 5mg tablets blister pack.
[497] Cf. TGA, GLICLAZIDE-ARX gliclazide 80 mg tablet blister pack.
[498] Cf. TGA, GLICLAZIDE-STR gliclazide 80 mg tablet bottle.
[499] Cf. TGA, APX-GLICLAZIDE gliclazide 80 mg tablet bottle.
[500] Cf. TGA, PHARMACOR GLICLAZIDE gliclazide 30 mg modified release tablet blister pack, 30 und 60 mg.

	ARDIX GLICLAZIDE 60 mg MR gliclazide 60 mg tablet blister pack[501]	Paediatric use: Not recommended for children use. Dosage: For adult use only.	No
Glimepiride	GLIMINTAS glimepiride 4mg tablet blister pack[502]	GLIMINTAS can be used as an adjunct to diet, exercise and weight loss to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type 2).	No
	GLIMEPIRIDE ASTRON glimepiride 4mg tablet blister pack[503]	No information available, only that GLIMEPIRIDE ASTRON can be used as an adjunct to diet, exercise and weight loss to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type 2).	No specified, if it only includes adults or also children
	GLIMEPIRIDE APOTEX Tablets[504]	Safety and efficacy of glimepiride in children have not been established. Glimepiride is not recommended for use in children.	No
	GLIMEPIRIDE INTAS glimepiride 4mg tablet blister pack[505]	No information, only that GLIMEPIRIDE INTAS can be used as an adjunct to diet, exercise and weight loss to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type 2).	No?
	NECARAL 1mg glimepiride tablet 1mg blister pack[506]	Safety and efficacy of glimepiride in children have not been established. Glimepiride is not recommended for use in children.	No
	GLIMEPIRIDE B&B 3mg glimepiride tablet 3mg blister pack[507]	The safety and efficacy of glimepiride in children have not been established. Glimepiride is not recommended for use in children.	No

[501] Cf. TGA, ARDIX GLICLAZIDE 60 mg MR gliclazide 60 mg tablet blister pack.
[502] Cf. TGA, GLIMINTAS glimepiride 4mg tablet blister pack.
[503] Cf. TGA, GLIMEPIRIDE ASTRON glimepiride 4mg tablet blister pack.
[504] Cf. TGA, GLIMEPIRIDE APOTEX Tablets.
[505] Cf. TGA, GLIMEPIRIDE INTAS glimepiride 4mg tablet blister pack.
[506] Cf. TGA, NECARAL 1mg glimepiride tablet 1mg blister pack.
[507] Cf. TGA, GLIMEPIRIDE B&B 3mg glimepiride tablet 3mg blister pack.

Insulin aspart	TRUVELOG insulin aspart 100 units/mL solution for injection vial[508]	Paediatric use: No data available.	Yes? Information is not really clear
	NOVORAPID FLEXTOUCH insulin aspart (rys) 300U / 3mL injection multidose cartridge and NOVOMIX Penfill and FlexPen[509]	Safety and effectiveness of NovoMix products in children and adolescents under the age of 18 have not been assessed due to limited clinical experience. Limited data suggest that when given to children NovoRapid showed similar glucose control compared to soluble human insulin. The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults. Long term data in children that include the effects on growth and development, are not available.”	Yes? Information is not really clear
Insulin aspart/ degludec	RYZODEG 70/30 PENFILL 70% insulin degludec (rys) / 30% insulin aspart (rys) 100 U/mL solution for injection cartridge und Flexpen[510]	RYZODEG 70/30 is indicated for use in children and adolescents from the age of 6 years.”	Yes

[508] Cf. TGA, TRUVELOG insulin aspart 100 units/mL solution for injection vial.
[509] Cf. TGA, NOVORAPID FLEXTOUCH insulin aspart (rys) 300U / 3mL injection multidose cartridge and NOVOMIX Penfill and FlexPen.
[510] Cf. TGA, RYZODEG 70/30 PENFILL 70% insulin degludec (rys) / 30% insulin aspart (rys) 100 U/mL solution for injection cartridge and Flexpen.

Insulin detemir	LEVEMIR FLEXPEN insulin detemir (rys) 100 U/mL injection cartridge and Penfill[511]	The efficacy and safety of Levemir were demonstrated in adolescents and children aged from 2 years' and older in studies up to 24 months in duration. Pharmacokinetic studies have been performed in children (6–12 years) and adolescents (13–17 years) with type 1 diabetes, and compared to adults with type 1 diabetes. A total of 16 males and 18 females were studied. No difference in pharmacokinetics was observed between the three age groups.	Yes
Insulin glargine	TOUJEO MAX SOLOSTAR insulin glargine 300 units/mL solution for injection injector pen[512]	Only for adults. Safety and effectiveness of Toujeo have not been established in children No clinical studies with Toujeo have been performed in the children. Therefore, no safety profile of Toujeo has been established.	No
	SEMGLEE insulin glargine (rDNA) 100 IU/mL, 3 mL solution for injection injector pen[513]	SEMGLEE can be used in children older than 6 years of age. In a study comparing insulin glargine to NPH insulin in children from 2-5 years, non-inferiority was not demonstrated in relation to the primary outcome of hypoglycaemia. The safety profile for patients ≤18 years of age is similar to the safety profile for patients >18 years.	Yes
	TOUJEO SOLOSTAR insulin glargine 300 units/mL solution for injection injector pen[514]	Toujeo can be used in paediatric patients from the age of 6 years. Safety and efficacy of Toujeo have been demonstrated in a 26-week trial in paediatric patients aged between 6 and 18 years of age.	Yes

[511] Cf. TGA, LEVEMIR FLEXPEN insulin detemir (rys) 100 U/mL injection cartridge and Penfill.
[512] Cf. TGA, TOUJEO MAX SOLOSTAR insulin glargine 300 units/mL solution for injection injector pen.
[513] Cf. TGA, SEMGLEE insulin glargine (rDNA) 100 IU/mL, 3 mL solution for injection injector pen.
[514] Cf. TGA, TOUJEO SOLOSTAR insulin glargine 300 units/mL solution for injection injector pen.

	BASAGLAR KwikPen insulin glargine (rbe) 100 IU/mL solution for injection cartridge[515]	Insulin glargine is indicated in the treatment of type 1 diabetes mellitus in adults and children and type 2 diabetes mellitus in adults who require insulin for the control of hypeglycaemia.	Yes
	OPTISULIN 100IU/mL insulin glargine (rbe) 3mL solution for injection cartridge[516]	Optisulin can be used for paediatric patients >6 years of age.	Yes
Insulin glargine/ Lixisenatide	SOLIQUA insulin glargine (rbe) 100 units/mL and lixisenatide 50 microgram/mL solution for injection injector pen[517]	Safety and effectiveness of Soliqua have not been established in paediatric patients. Only for adults.	No
Insulin human[518]	MIXTARD 50/50 PENFILL human insulin (rys) 100IU/mL injection multidose cartridge PROTAPHANE human insulin (rys) 100IU/mL injection multidose vial and additional Actrapid insulin and Penfill	Data in children were not assessed as part of this medicine registration. But dosage for children is available.	Yes? Information is not really clear
Insulin lispro	HUMALOG U200 KwikPen insulin lispro (rbe) 200 IU/mL	There have been no studies of HUMALOG U200 in children. HUMALOG U200 was shown to be bioequivalent to HUMALOG 100 units/mL in healthy adults in clinical studies	Yes

[515] Cf. TGA, BASAGLAR KwikPen insulin glargine (rbe) 100 IU/mL solution for injection cartridge.
[516] Cf. TGA, OPTISULIN 100IU/mL insulin glargine (rbe) 3mL solution for injection cartridge.
[517] Cf. TGA, SOLIQUA insulin glargine (rbe) 100 units/mL and lixisenatide 50 microgram/mL solution for injection injector pen.
[518] Cf. TGA, Actrapid, Mixtard and Protaphane.

	solution for injection multidose syringe[519]	involving children and adolescents aged 3 –19 years, HUMALOG 100 units/mL has been shown to be safe, effective and well-tolerated.	
Linagliptin	TRAJENTA linagliptin 5 mg film-coated tablet blister pack[520]	TRAJENTA is not recommended for the use in children under 18 years due to lack of data on safety and efficacy.	No
Liraglutide	VICTOZA liraglutide (rys) 6mg/mL solution for injection, pre-filled pen[521]	Liraglutide has not been studied in paediatric subjects. Only for adults.	No
	SAXENDA liraglutide (rys) 6mg/mL solution for injection, pre-filled pen[522]	Safety and efficacy of SAXENDA in children and adolescents under the age of 18 have not been established. No data are available. SAXENDA is not indicated for use in paediatric patients.	No
Metformin	METFORMIN-STR metformin hydrochloride 1000 mg tablet blister pack[523] METFORMIN-STR metformin hydrochloride 1000 mg tablet bottle METFORMIN-STR metformin hydrochloride 850 mg tablet blister pack METFORMIN-STR metformin hydrochloride 850 mg tablet	There is no exact information. It is only generally stated in the product information that the medicinal products can be used for the treatement of diabetes mellitus type 2 Metformin can be used in the treatment of type 2 diabetes mellitus not satisfactorily controlled by diet, where the risk of lactic acidosis is minimised by excluding predisposing factors, especially impaired renal, hepatic or cardiovascular function. Metformin is indicated as initial therapy or in sulfonylurea failure, either alone or in combination with a sulfonylurea or as adjuvant therapy in insulin-dependent diabetes.	Not specified

[519] Cf. TGA, HUMALOG U200 KwikPen insulin lispro (rbe) 200 IU/mL solution for injection multidose syringe.
[520] Cf. TGA, TRAJENTA linagliptin 5 mg film-coated tablet blister pack.
[521] Cf. TGA, VICTOZA liraglutide (rys) 6mg/mL solution for injection, pre-filled pen.
[522] Cf. TGA, SAXENDA liraglutide (rys) 6mg/mL solution for injection, pre-filled pen.
[523] Cf. TGA, Metformin STR HCl 100mg tablet blister pack.

	bottle METFORMIN-STR metformin hydrochloride 500 mg tablet blister pack METFORMIN-STR metformin hydrochloride 500 mg tablet bottle METFORMIN-ARX metformin hydrochloride 1000 mg tablet blister pack METFORMIN-ARX metformin hydrochloride 850 mg tablet blister pack METFORMIN-ARX metformin hydrochloride 850 mg tablet bottle METFORMIN-ARX metformin hydrochloride 500 mg tablet bottle and 500 ml tablet blister pack		
	APX-METFORMIN (METFORMIN HYDROCHLORIDE) TABLETS 500 mg, 850 mg, 1000 mg[524]	It is only stated that the drug is for use in adults, no more specification: APX-METFORMIN is not recommended for use in children, except those with insulin resistant diabetes that are being treated in hospital. The diagnosis of type 2 diabetes mellitus should be confirmed before treatment with metformin is started. There have been controlled studies. Results: No effect of metformin on growth and puberty has been detected during controlled clinical studies of one-year duration but clinical data in relation to the long-term effect of	Not specified

[524] Cf. TGA, APX- Metformin tablets.

		metformin on the development of skeletal and reproductive system in children and adolescents are not available. Therefore, a careful follow-up of the effect of metformin on these parameters in metformin-treated children, especially pre-pubescent children, is recommended.	
	PHARMACOR METFORMIN XR 500 metformin hydrochloride 500 mg extended release tablet blister pack à for 500, 750 and 1000 mg[525]	Recommended for adults. Due to the lack of data, Metformin extended release tablet should not be used in children.	No
	Diaxemet XR 500, 750, 100mg[526]	Due to the lack of data, DIAXEMET XR 500, DIAXEMET XR 750 or DIAXEMET XR 1000 should not be used in children.	No
	Pharmacor Metformin XR 500, 750, 1000mg[527]	Due to the lack of date, PHARMACOR METFORMIN XR 500, PHARMACOR METFORMIN XR 750 or PHARMACOR METFORMIN XR 1000 should not be used in children.	No
	Diabex XR 500, 750, 1000mg[528]	For the treatment in adults. Due to the lack of data, Diabex XR 500, Diabex XR 750 or Diabex XR 1000 should not be used in children.	No
	METCIP metformin hydrochloride 1000 mg tablet blister pack[529] and includes all other strengths	Metformin can be used in the treatment of type 2 diabetes mellitus in adults, children from 10 years of age and adolescents, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.,	Yes

[525] Cf. TGA, PHARMACOR METFORMIN XR 500 metformin hydrochloride 500 mg extended release tablet blister pack à for 500, 750 and 1000 mg.
[526] Cf. TGA, Diaxemet XR 500, 750, 100mg.
[527] Cf. TGA, Pharmacor Metformin XR 500, 750, 1000mg.
[528] Cf. TGA, Diabex XR 500, 750, 1000mg.
[529] Cf. TGA, METCIP metformin hydrochloride 1000 mg tablet blister pack.

	APO-METFORMIN 1000 metformin hydrochloride 1000 mg tablet blister pack CIP-METFORMIN metformin hydrochloride 500 mg tablet blister pack, and all strengths[530] CIPLA-METFORMIN metformin hydrochloride 500 mg tablet blister pack, and all strengths DIAFORMIN 1000 metformin 1000mg (as hydrochloride) tablet blister bulk pack and all strengths EMNORM metformin hydrochloride 850 mg tablet blister pack and all strengths, also 500, 850 and 1000 mg METMIN metformin hydrochloride 850 mg tablet blister pack and all strengths GTA-METFORMIN metformin hydrochloride 500 mg tablet bottle and all strengths	It is authorised for children >10 years of age and adults: Metformin can be used in the treatment of type 2 diabetes mellitus in adults, children from 10 years of age and adolescents, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.	Yes

[530] Cf. TGA, CIP-Metformin 500mg tablet blister pack.

	METFORMIN SANDOZ metformin hydrochloride 1000 mg tablet blister pack[531]	Metformin is not recommended for use in children, except those with insulin resistant diabetes who are being treated in hospital.	No
Metformin/ Alogliptin	VIPDOMET 12.5/1000; 12.5 mg alogliptin (as benzoate) / 1000 mg metformin hydrochloride film-coated tablets blister pack Also 500 mg[532]	Information is not specified, it is only stated that the drug is for use in adults.	No
	NESINA MET 12.5/1000; 12.5 mg alogliptin (as benzoate) / 1000 mg metformin hydrochloride film-coated tablets blister pack[533]	The safety and efficacy of NESINA MET in children have not been established.	No
	VIPDOMET 12.5/850; 12.5 mg alogliptin (as benzoate) / 850 mg metformin hydrochloride film-coated tablets blister pack[534]	VIPDOMET can be used to improve glycaemic control in adult patients with type 2 diabetes mellitus.	No

[531] Cf. TGA, METFORMIN SANDOZ metformin hydrochloride 1000 mg tablet blister pack.
[532] Cf. TGA, VIPDOMET 12.5/1000; 12.5 mg alogliptin (as benzoate) / 1000 mg metformin hydrochloride film-coated tablets blister pack.
[533] Cf. TGA, NESINA MET 12.5/1000; 12.5 mg alogliptin (as benzoate) / 1000 mg metformin hydrochloride film-coated tablets blister pack.
[534] Cf. TGA, VIPDOMET 12.5/850; 12.5 mg alogliptin (as benzoate) / 850 mg metformin hydrochloride film-coated tablets blister pack.

Metformin/ Linagliptin	TRAJENTAMET 2.5 mg/1000 mg linagliptin 2.5 mg / metformin hydrochloride 1000 mg film-coated tablet blister pack[535]	Safety and effectiveness of TRAJENTAMET in children have not been established." Linagliptin Pharmacokinetics studies of linagliptin in paediatric patients have not been performed. Metformin hydrochloride Single dose study: After single doses of metformin 500 mg, children have shown a similar pharmacokinetic profile to that observed in healthy adults.	No
Metformin/ Sitagliptin	Sitagliptin/Metformin Sandoz 50/500 sitagliptin (as hydrochloride monohydrate)/metformin hydrochloride 50 mg/500 mg film coated tablet blister pack[536]	Only for adults. Sitagliptin/Metformin Sandoz can be used as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate."	No
	VELMETIA XR 100/1000 sitagliptin (as phosphate monohydrate) 100 mg and metformin hydrochloride 1000 mg modified[537]	Only in adults. VELMETIA XR can be used as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both sitagliptin and metformin is appropriate.	No

[535] Cf. TGA, TRAJENTAMET 2.5 mg/1000 mg linagliptin 2.5 mg / metformin hydrochloride 1000 mg film-coated tablet blister pack.
[536] Cf. TGA, Sitagliptin/Metformin Sandoz 50/500 sitagliptin (as hydrochloride monohydrate)/metformin hydrochloride 50 mg/500 mg film coated tablet blister pack.
[537] Cf. TGA, VELMETIA XR 100/1000 sitagliptin (as phosphate monohydrate) 100 mg and metformin hydrochloride 1000 mg modified.

	JANUMET XR 100/1000 sitagliptin (as phosphate monohydrate)/metformin hydrochloride 100 mg/1000 mg extended release tablet bottle[538] And also all other strengths with are available on the market	JANUMET or JANUMET XR should not be used in children and adolescents between 10 to 17 years of age because of insufficient efficacy. JANUMET and JANUMET XR have not been studied in children younger than 10 years of age.	No
Metformin/ Empagliflozin	JARDIAMET 12.5 mg / 1000 mg empagliflozin/metformin hydrochloride 12.5mg/1000mg film coated tablet blister pack[539] and all other strengths which are available on the market	JARDIAMET is not recommended for use in children under 18 years because there is a lack of data on safety and efficacy. Empagliflozin No pharmacokinetics studies of empagliflozin in children have not been performed." Metformin hydrochloride: "Single dose study: After single doses of metformin 500 mg, children have shown a similar pharmacokinetic profile to that observed in healthy adults."	No
Metformin/ Dapagliflozin	XIGDUO XR 5/1000 dapagliflozin 5 mg (as propanediol monohydrate) / metformin hydrochloride 1000 mg modified release tablets blister pack[540]	Safety and effectiveness of XIGDUO XR in children have not been established. Dapagliflozin: Pharmacokinetics in children have not been studied. Only for adults.	No

[538] Cf. TGA, JANUMET XR 100/1000 sitagliptin (as phosphate monohydrate)/metformin hydrochloride 100 mg/1000 mg extended release tablet bottle.
[539] Cf. TGA, JARDIAMET 12.5 mg / 1000 mg empagliflozin/metformin hydrochloride 12.5mg/1000mg film coated tablet blister pack.
[540] Cf. TGA, XIGDUO XR 5/1000 dapagliflozin 5 mg (as propanediol monohydrate) / metformin hydrochloride 1000 mg modified release tablets blister pack.

Metformin/ Saxagliptin	KOMBIGLYZE XR 5/500 tablets 5 mg saxagliptin (as hydrochloride) immediate release and 500 mg metformin hydrochloride[541]	Safety and effectiveness of KOMBIGLYZE XR in children have not been established.	No
Metformin/ Vildagliptin	GALVUMET 50/500 vildagliptin 50 mg/metformin hydrochloride 500 mg film coated tablet blister pack[542]	The safety and effectiveness of GALVUMET in children have not been established. Therefore, GALVUMET is not recommended for use in children under 18 years of age.	No
Pioglitazone	NOUMED PIOGLITAZONE 15mg tablets, 30 mg and 45 mg[543]	Safety and effectiveness in children have not been established." It is not stated that the drug is only authorised for adults.	No? Information is not really clear
	ACTAZE (pioglitazone (as hydrochloride)) tablets[544]	Safety and effectiveness in children have not been established."	No? Information is not really clear
	AURO-PIOGLITAZONE 30 pioglitazone (as hydrochloride) 30 mg tablet blister pack[545] And all other strengths which are available on the market	Safety and effectiveness in children have not been established.	No? Information is not really clear

[541] Cf. TGA, KOMBIGLYZE XR 5/500 tablets 5 mg saxagliptin (as hydrochloride) immediate release and 500 mg metformin hydrochloride.
[542] Cf. TGA, GALVUMET 50/500 vildagliptin 50 mg/metformin hydrochloride 500 mg film coated tablet blister pack.
[543] Cf. TGA, NOUMED PIOGLITAZONE 15mg tablets, 30 mg and 45 mg.
[544] Cf. TGA, ACTAZE (pioglitazone (as hydrochloride)) tablets.
[545] Cf. TGA, AURO-PIOGLITAZONE 30 pioglitazone (as hydrochloride) 30 mg tablet blister pack.

	GLITOS 15 pioglitazone (as hydrochloride) 15mg tablet blister pack[546]	No information available.	No? Information is not really clear
	APOTEX-PIOGLITAZONE pioglitazone 30 mg (as hydrochloride) tablet blister pack[547]	Safety and effectiveness in children have not been established.	No? Information is not really clear
	ACPIO 30 pioglitazone (as hydrochloride) 30 mg tablet blister pack[548] VEXAZONE pioglitazone (as hydrochloride) 45mg tablet blister pack[549] PIOGLITAZONE SANDOZ pioglitazone (as hydrochloride) 30mg tablet blister pack[550]	Safety and effectiveness in paediatric patients have not been established.	No? Information is not really clear
Saxagliptin	ONGLYZA saxagliptin (as hydrochloride) 2.5 mg film-coated tablet blister pack[551]	Safety and effectiveness of ONGLYZA in paediatric and adolescent patients have not been established. “	No

[546] Cf. TGA, GLITOS 15 pioglitazone (as hydrochloride) 15mg tablet blister pack.
[547] Cf. TGA, APOTEX-PIOGLITAZONE pioglitazone 30 mg (as hydrochloride) tablet blister pack.
[548] Cf. TGA, ACPIO 30 pioglitazone (as hydrochloride) 30 mg tablet blister pack.
[549] Cf. TGA, VEXAZONE pioglitazone (as hydrochloride) 45mg tablet blister pack.
[550] Cf. TGA, PIOGLITAZONE SANDOZ pioglitazone (as hydrochloride) 30mg tablet blister pack.
[551] Cf. TGA, ONGLYZA saxagliptin (as hydrochloride) 2.5 mg film-coated tablet blister pack.

Sitagliptin	SITAGLIPTIN SANDOZ PHARMA sitagliptin (as hydrochloride monohydrate) 100 mg tablet blister pack[552]	Only for adults	No
Vildagliptin	GALVUS vildagliptin 50 mg tablets blister pack[553]	No studies have been performed patients under 18 years of age. Therefore, the use of vildagliptin in paediatric patients is not recommended. Only for adults.	No

[552] Cf. TGA, SITAGLIPTIN SANDOZ PHARMA sitagliptin (as hydrochloride monohydrate) 100 mg tablet blister pack.
[553] Cf. TGA, SITAGLIPTIN SANDOZ PHARMA sitagliptin (as hydrochloride monohydrate) 100 mg tablet blister pack.

Annex 5: Authorised antidiabetics in the European Union

Active Ingredient	Name	Indication	Pediatric use (Source: Product information, EPAR)	PIP
Albiglutide	Eperzan	Diabetes mellitus type 2, only for adults	No data available	Treatment of type 2 diabetes mellitus The request for the waiver applies to: all subsets of the paediatric population from birth to less than 10 years of age; • for powder and solvent for solution for injection, subcutaneous use; • on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s). No studies have been performed between 10 and 18 years of age.[554]

[554] Cf. EMA, European Medicines Agency decision P/0272/2016 of 7 October 2016 on the acceptance of a modification of an agreed paediatric investigation plan for albiglutide (Eperzan), (EMEA-001175-PIP01-11-M04) in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

Alogliptin	Vipidia	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Vipidia in children and adolescents under 18 years old have not been established. No data are available. -There is a deferral for the obligation to submit the results of studies with Vipidia in one or more subsets of the paediatric population in the treatment of type 2 diabetes mellitus. -The pharmacokinetics of alogliptin in children and adolescents below 18 years old has not been established. No data are available.[555]	Treatment of type 2 diabetes mellitus The waiver applies to: • all subsets of the paediatric population from birth to less than 10 years of age; • film-coated tablet, oral use; • on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset.
Alogliptin/ Pioglitazone	Incresync	Diabetes Type-2, for adults aged 18 or older	-Safety and efficacy of Incresync in children and adolescents under 18 years old have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Incresync in all subsets of the paediatric population in the treatment of type 2 diabetes mellitus. -Pharmacokinetics of pioglitazone in children and adolescents under 18 years old has not been established. No data are available.[556]	Date of authorisation: 19/09/2013, but no PIP available on the EMA website Safety information are missing for children and adolescents[557] → For fixed-dose combination products a PIP is not needed[558]

[555] Cf. EMA, Annex 1 Summary of Product Characteristics Vipidia.
[556] Cf. EMA, Annex 1 Summary of Product Characteristics Incresy.
[557] Cf. EMA, CHMP assessment report.
[558] Cf. EMA, PIP: questions and answers.

Canagliflozin	Invokana	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of canagliflozin in children under 18 years of age have not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with canagliflozin in one or more subsets of the paediatric population in type 2 diabetes. -A paediatric phase 1 study have been performed examining the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents ≥ 10 to < 18 years of age with type 2 diabetes mellitus. The observed pharmacokinetic and pharmacodynamic responses were consistent with those found in adults.[559]	The waiver applies to: • the paediatric population from birth to less than 10 years of age; • tablet, oral use; • on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s). Studies must be done with children from 10 years to less than 18 years of age[560]

[559] Cf. EMA, Annex 1 Summary of Product Characteristics Invokana.
[560] Cf. EMA, PIP decision, EMA December 2020.

Canagliflozin/ Metformin	Vokana met	Diabetes Mellitus, Type-2, for adults only	-Safety and efficacy of Vokanamet in children under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Vokanamet in all subsets of the paediatric population in type 2 diabetes. -a paediatric phase 1 study have been performed that examined the pharmacokinetics and pharmacodynamics of canagliflozin in children and adolescents between 10 to under 18 years of age with type 2 diabetes mellitus. Results: Pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. -There have been performed a single dose study: Results: similar pharmacokinetic profile to that observed in healthy adults.[561]	Date of authorisation 23/04/2014, but no PIP available Acc. EPAR: Safety and efficacy in children under 18 years of age have not been established. No date available.[562] → For fixed-dose combination products a PIP is not needed[563]
Dapagliflozin	Edistride	Diabetes mellitus type 2 For children aged 10 years and older	-Edistride is recommended for the use in children aged 10 years and older for the treatment of type 2 diabetes. No data are available in children below 10 years of age. -Edistride is not recommended for children and adolescents under 18 years of age for the treatment of heart failure or for the treatment of chronic kidney disease, because it has not been studied in these patients. -Edistride is indicated in adults and children aged 10 years and above for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise.[564]	No PIP available for children under 10 years of age Date of authorisation: 09/11/2015 No comment what happens with children under 10 years, no PIP have been done --> PIP of Forxiga, because it is the same marketing authorisation and holder, so only one PIP is necessary[565]

[561] Cf. EMA, Annex 1 Summary of Product Characteristics Vokanamet.
[562] Cf. EMA, EPAR Vokanamet.
[563] Cf. EMA, PIP: questions and answers.
[564] Cf. EMA, Annex 1 Summary of Product Characteristics Edistrid.
[565] Cf. EMA, Post-authorisation Summary positive opinion Estride.

	Forxiga	Diabetes mellitus type 2, For children aged 10 years and older	-Forxiga is indicated in adults and children aged 10 and above for the treatment of type 2 diabetes mellitus. -No dose adjustment is required for the treatment of type 2 diabetes mellitus in children aged 10 years and above. No data are available for children below 10 years of age. -Safety profile that could be observed in a clinical study in children aged 10 years and above with type 2 diabetes mellitus was similar to that observed in the studies in adults.[566]	Waiver for indication prevention of cardiovascular events in patients with chronic heart failure- waiver for age from birth to less than 18 years of age.[567] Waiver for indication Treatment of ischaemic heart disease- waiver for all ages from birth to less than 18 years of age[568] Waiver for indication Treatment of chronic kidney disease- waiver for age from birth to less than 2 years of age (grounds: unsafety) and from 2 years to less than 18 years of age (grounds: no therapeutic benefit)[569] Waiver for treatment of type 1 diabetes mellitus- waiver for age from birth to less than 2 years of age[570]

[566] Cf. EMA, Annex 1 Summary of Product Characteristics Forxiga.
[567] Cf. EMA, EMA decision Forxiga July 2018.
[568] Cf. EMA, PIP decision Forxiga December 2020.
[569] Cf. EMA, EMA decision Forxiga December 2018.
[570] Cf. EMA, PIP decision Forxiga October 2017.

				Waiver for indication type 2 diabetes mellitus for age birth to less than 10 years of age (grounds: disease does not occur this age)[571]
Dulaglutide	Trulicity	Diabetes Mellitus, Type-2, only for adults	-Pharmacokinetics studies of dulaglutide in paediatric patients have not been performed. -Safety and efficacy of dulaglutide in children aged less than 18 years have not yet been established. No data are available. -There is a deferral the obligation to submit the results of studies with Trulicity in one or more subsets of children for the treatment of type 2 diabetes mellitus.[572]	Waiver for indication type 2 diabetes mellitus- waiver for age from birth to less than 10 years of age Studies must be done with children from 10 to less than 18 years of age[573]

[571] Cf. EMA, PIP decision Forxiga March 2020.
[572] Cf. EMA, Annex 1 Summary of Product Characteristics Trulicity.
[573] Cf. EMA, EMA decision Trulicity May 2020.

Empagliflozin	Jardiance	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of empagliflozin in children and adolescents has not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with Jardiance in one or more subsets of the paediatric population in type 2 diabetes mellitus). -There is a waiver for the obligation to submit the results of studies with Jardiance in all subsets of the paediatric population in heart failure. -A paediatric Phase 1 study have been performed examining the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescentsbetween 10 and under 18 years of age with type 2 diabetes mellitus. Results: Pharmacokinetic and pharmacodynamic responses were consistent with those found in adults.[574]	Waiver for the indication Treatment of type 2 diabetes mellitus for age from birth to less than 10 years of age (grounds: disease does not occur age), studies from 10 to less than 18 years of age must be done[575] Waiver for indication Treatment of type 1 diabetes mellitus waiver for age from birth to less than 2 years of age, from 2 to 18 years studies must be done (grounds: drug is unsafe)[576] Waiver for indication Prevention of cardiovascular events for all children ages[577] Waiver also for indication "chronic kidney disease"[578]

[574] Cf. EMA, Annex 1 Summary of Product Characteristics Jardiance.
[575] Cf. EMA, EMA decision Jardiance March 2021.
[576] Cf. EMA, EMA decision, Jardiance September 2019.
[577] Cf. EMA, EMA decision August 2017 Jardiance.
[578] Cf. EMA, EMA decision March 2019 Jardiance.

Empagliflozin/ Linagliptin	Glyxambi	Diabetes Type-2, only for adults aged 18 and older	-Safety and efficacy of Glyxambi in chidlren under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of trials with Glyxambi in all subsets of the paediatric population in type 2 diabetes mellitus -A paediatric Phase 1 trial have been performed examining the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to younger than 18 years of age with type 2 diabetes mellitus. Results: Pharmacokinetic and pharmacodynamic responses were consistent with those found in adult. -A paediatric Phase 2 trial have been performed for the examination of the pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents from 10 to younger than 18 years of age with type 2 diabetes mellitus. Results: Pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition. But because of the limited nature of the data set the results should be interpreted cautiously. -Pharmacokinetics studies of empagliflozin and linagliptin in paediatric patients have not been performed.[579]	Date of authorisation: 11/11/2016, but no PIP available But in the EPAR there is a statement: There is a waiver for the obligation to submit the results of trials with Glyxambi in all subsets of the paediatric population in type 2 diabetes mellitus[580] → For fixed-dose cimbination products a PIP is not needed[581]

[579] Cf. EMA, Annex 1 Summary of Product Characteristics Glyxambi.
[580] Cf. EMA, EPAR Glyxambi.
[581] Cf. EMA, PIP: questions and answers.

Empagliflozin/ Metformin	Synjardy	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Synjardy in children and adolescents aged 0 to 18 years has not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Synjardy in all subsets of the paediatric population in type 2 diabetes. -A paediatric Phase 1 study examined the pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents between 10 and under 18 years of age with type 2 diabetes mellitus. Results: Pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. -Single dose study in children. Results: Similar pharmacokinetic profile to that observed in healthy adults. -Multiple-dose study: Peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were approximately 33% and 40% lower, respectively, compared to diabetic adults.[582]	Date of authorisation: 27/05/2015, but no PIP available[583] → For fixed- dose combination products a PIP is not needed[584]
Ertugliflozin	Steglatro	Diabetes Mellitus, Type-2, only for adults	-It is indicated for the treatment of adults aged 18 years and older with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control. -For children and adolescents below 18 years Steglatro is not recommended. Safety and efficacy are not known.[585]	Waiver for indication treatment of type 2 diabetes mellitus age from birth to less than 10 years of age, for 10 to less than 18 years of age studies must be done[586]

[582] Cf. EMA, Annex 1 Summary of Product Characteristics Synjardy.
[583] Cf. EMA, EPAR Synjardy.
[584] Cf. EMA, PIP: questions and answers.
[585] Cf. EMA, Annex 1 Summary of Product Characteristics Steglatro.
[586] Cf. EMA, EPAR Steglatro.

Exenatide	Byetta	Diabetes, Type-2, only for adults	-The efficacy of exenatide in children and adolescents under 18 years of age was not demonstrated. -Interaction studies have only been performed in adults. "The efficacy and safety of immediate release exenatide was evaluated in a 28-week randomized, double-blind, placebo controlled study conducted in 120 patients aged 10 to 17 years with type 2 diabetes. No new safety findings were identified in this paediatric study. -A single-dose pharmacokinetic study has been performed in 13 patients with type 2 diabetes and between the ages of 12 and 16 years. Results: administration of exenatide (5 mcg) resulted in slightly lower mean AUC (16% lower) and Cmax (25% lower) compared to those observed in adults.[587]	Waiver for indication Treatment of type 2 diabetes mellitus, age from birth to less than 10 years , for children from 10 to less than 18 years of age studies must be done[588]

[587] Cf. EMA, Annex 1 Summary of Product Characteristics Byetta.
[588] Cf. EMA, EMA decision Byetta.

	Bydureon	Diabetes Mellitus, Type-2, only for adults	-Interaction studies with exenatide have only been performed in adults. -There is a deferral for the obligation to submit the results of studies with prolonged-release exenatide in one or more subsets of the paediatric population in type 2 diabetes mellitus. -A single-dose pharmacokinetic study of immediate-release exenatide in 13 patients with type 2 diabetes and between the ages of 12 and 16 years have been performed. Results: Administration of exenatide (5 mcg) resulted in slightly lower mean AUC (16% lower) and Cmax (25% lower) compared to those observed in adults. No pharmacokinetics study of prolonged-release exenatide has been conducted in the paediatric population. -safety and efficacy of prolonged-release exenatide in children and adolescents aged under 18 years have not yet been established.[589]	Waiver for indication Treatment of type 2 diabetes mellitus, age from birth to less than 10 years , for children from 10 to less than 18 years of age studies must be done[590]

[589] Cf. EMA, Annex 1 Summary of Product Characteristics Bydureon.
[590] Cf. EMA, EMA decision Bydureon.

Glibenclamide	Amglidia	Diabetes mellitus, for the treatment of neonatal diabetes mellitus, for use in newborns, infants and children	-Safety and efficacy of Amglidia in elderly patients has not been established since the medicinal product is indicated in children. -Amglidia is to be used in newborns, infants and children.[591]	Receives orphan designation status[592]
Glimepiride/ Pioglitazone	Tandemact	Diabetes Mellitus, Type-2, only for adults	-The safety and efficacy of Tandemact in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Tandemact in all subsets of the paediatric population in type 2 diabetes mellitus.[593]	Date of authorisation: 08/01/2007, No PIP data available → no PIP needed because not scope of Art. 7 (valid up from 26/07/2008
Glucagon	Baqsimi	Diabetes mellitus, for adults, adolescents and children aged 4	-Safety and efficacy of Baqsimi in infants and children aged from 0 to younger than 4 years have not yet been established. No data are available. -Same adverse reactions have been observed in children as observed in adults. -There is a deferral for the obligation to submit the results of studies with Baqsimi in one or more subsets of the paediatric population in the treatment of severe hypoglycaemia.[594]	Waiver for the indication Treatment of hypoglycaemia, for the age from birth to less than 1 year og age, from 1 to 18 years studies must be done.[595]

[591] Cf. EMA, Annex 1 Summary of Product Characteristics Amglidia.
[592] Cf. EMA, Orphan designation Amglidia.
[593] Cf. EMA, Annex 1 Summary of Product Characteristics Tandemact.
[594] Cf. EMA, Annex 1 Summary of Product Characteristics Baqsimi.
[595] Cf. EMA, EMA decision Baqsimi.

		years and over		
	Ogluo	Diabetes mellitus, adults, adolescents, and children aged 2 years and over with diabetes mellitus.	-Safety and efficacy of Ogluo in children aged less than 2 years have not been established. No data are available.[596]	Date of authorisation: 11/02/2021, but no PIP data available PIP for children under 2 is missing, no information available[597] → Is a Hybrid due to that it does not need a PIP
Insulin aspart	Fiasp	For children from one year of age and adults with diabetes, Type-1 and -2	The efficacy and safety of Fiasp have been studied in a 1:1:1 randomised active controlled clinical trial in children and adolescents with type 1 diabetes, aged 1 to 18 years, for a period of 26 weeks (N=777).The observed effects and the safety profiles were comparable between all age groups.[598]	No PIP data available Date of authorisation: 09/01/2017 PIP is missing for children under 1 year of age, no information available[599] → Generic → Does not need a PIP

[596] Cf. EMA, Annex 1 Summary of Product Characteristics Ogluo.
[597] Cf. EMA, EPAR Ogluo.
[598] Cf. EMA, Annex 1 Summary of Product Characteristics Fiasp.
[599] Cf. EMA, EPAR Fiasp.

	Kirsty, prev. Kixelle	Diabetes mellitus, children aged 1 year or older and adults	-Kirsty can be used in children and adolescents aged 1 year and above -The safety and efficacy of Kirsty in children below 1 year of age have not been established. No data are available." -Same advser reactions are observed as in the general population. -A clinical trial have been performed. Results: The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults. "The efficacy and safety have been investigated. Results: safety profiles were comparable between all age groups. The pharmacokinetic and pharmacodynamic properties of insulin aspart were investigated in children (6-12 years) and adolescents (13-17 years) with type 1 diabetes. Insulin aspart was rapidly absorbed in both age groups, with similar tmax as in adults. However, Cmax differed between the age groups, stressing the importance of the individual titration of insulin aspart.[600]	Date of authorisation: 05/02/2021, No PIP available for children under 1 year of age Information or PIP is missing for children under 1 year No PIP needed, because Kirsty is a generic product

[600] Cf. EMA, Annex 1 Summary of Product Characteristics Kirsty.

	I. aspart Sanofi	Diabetes mellitus, for adults, adolescents and children aged 1 year and above	-Insulin aspart Sanofi can be used in adolescents and children aged 1 year -Same adverse reactions have been observed in the paediatric population do as in the general population. -Pharmacokinetic and pharmacodynamic studies of insulin aspart have been performed in children (6–12 years) and adolescents (13–17 years) with type 1 diabetes. Insulin aspart was rapidly absorbed in both age groups, with similar tmax as in adults. However, Cmax differed between the age groups, stressing the importance of the individual titration of insulin aspart.[601]	Date of authorisation: 07/07/2020, No PIP available No information or PIP available for children under 1 year[602] No PIP needed, because I. aspart Sanofi is a generic product
	Novorapid	Diabetes mellitus, for treatment of diabetes mellitus in adults, adolescents and children aged 1 year and above	-NovoRapid can be used in children and adolescents aged 1 year and above -The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults. -The efficacy and safety of NovoRapid: in studies safety profiles were comparable between all age groups. -Pharmacokinetic and pharmacodynamic studies of NovoRapid have been performed in children (6–12 years) and adolescents (13–17 years) with type 1 diabetes. Insulin aspart was rapidly absorbed in both age groups, with similar tmax as in adults. However, Cmax differed between the age groups, stressing the importance of the individual titration of NovoRapid.[603]	Date of authorisation: 07/09/1999, no PIP needed It the reference product of insulin aspart

[601] Cf. EMA, Annex 1 Summary of Product Characteristics Insulin aspart Sanofi.
[602] Cf. EMA, EPAR Insulin aspart Sanofi.
[603] Cf. EMA, Annex 1 Summary of Product Characteristics Novorapid.

Insulin aspart/ degludec	Ryzodeg	For adults, adolescents and children from 2 years of age, for diabetes Type-1 and -2	-No clinical experience with the use of this medicinal product in children below the age of 2 years. This medicinal product can be used in adolescents and children from the age of 2 years -Ryzodeg should be used with special caution in children 2 to 5 years old because data from the clinical trial indicate that there may be a higher risk for severe hypoglycaemia in children in this age group. -There is a waiver for the obligation to submit the results of trials with Ryzodeg in: Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and in all subsets of the paediatric population in type 2 diabetes mellitus -The efficacy and safety of Ryzodeg have been studied in a randomised controlled clinical trial in children and adolescents with diabetes mellitus type 1 An efficacy and safety evaluation for adolescent patients with type 2 diabetes mellitus has been made using data from adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. This assessment supports the use of Ryzodeg in adolescent patients with type 2 diabetes mellitus. -Pharmacokinetic studies were investigated in children (6–11 years) and adolescents (12–18 years) that suffers from type 1 diabetes mellitus. Comparision to adults after single dose administration. Results: Total exposure and peak concentration of insulin aspart were higher in children than in adults and were similar for adolescents and adults. The pharmacokinetic properties of insulin degludec in children (1–11 years) and adolescents (12– 18 years) were at steady state comparable to those observed in adults with type 1 diabetes mellitus. Total exposure of insulin degludec after single dose administration was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.[604]	Waiver for indication Treatment of type 1 diabetes mellitus for the age from birth to less than 12 months of age. And waiver for indication treatment of type 2 diabetes mellitus for the age from birth to less than 10 years of age (grounds disease does not occur this population) and from 10 to 18 (grounds: no therapeutic benefit)[605]

[604] Cf. EMA, Annex 1 Summary of Product Characteristics Ryzodeg.
[605] Cf. EMA, EMA decision Ryzodeg.

Insulin degludec	Tresiba	Treatment of diabetes mellitus in adults, adolescents and children from the age of 1 year for type 1 and for children aged 10 and above for treatment of type 2 diabetes mellitus	-There is no clinical experience with the use of this medicinal product in children below the age of 1 year. This medicinal product can be used in adolescents and children from the age of 1 year (see section 5.1). When changing basal insulin to Tresiba, dose reduction of basal and bolus insulin needs to be considered on an individual basis in order to minimise the risk of hypoglycaemia (see section 4.4) -Pharmakokinetic studies have been performed in children and adolescents up to 18 years of age. Safety and efficacy have been demonstrated in a long term trial in children aged 1 to less than 18 years. Saome adverse reactions have been observed as in the general diabetes population. -There is waiver for the obligation to submit the results of trials with Tresiba in: Neonates and infants from birth to less than 12 months of age with type 1 diabetes mellitus and children from birth to less than 10 years of age with type 2 diabetes mellitus. Grounds: the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset The efficacy and safety of Tresiba have been studied in a 1:1 randomised controlled clinical trial in children and adolescents with type 1 diabetes mellitus for a period of 26 weeks (n=350), followed by a 26-week extension period (n=280). Results: No safety issues were identified with Tresiba with respect to adverse events and standard safety parameters. Antibody development was sparse and had no clinical impact. Efficacy and safety data for adolescent patients with type 2 diabetes mellitus have been extrapolated from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus.	Waiver for indication treatment of type 1 diabetes mellitus for the age from birth to less than 12 months of age (grounds: disease does not occur population) And waiver for indication treatment of type 2 diabetes mellitus for age from birth to lass than 10 years of age (grounds disease does not occur this population) Studies must be done with children for type 1 from 1 to 18 years of age[607]

[607] Cf. EMA, EMA decision Tresiba.

			Results support the use of Tresiba in adolescent patients with type 2 diabetes mellitus. -Pharmacokinetic studies have been performed in children (1-11 years) and adolescents (12-18 years): Comparison to adults. Total exposure after a single dose was, however, higher in children and adolescents than in adults with type 1 diabetes mellitus.[606]	
Insulin degludec/ Liraglutide	Xultophy	Diabetes mellitus Type-2, only for adults	-There is no relevant use of Xultophy in children. -There is a waiver for the obligation to submit the results of studies with Xultophy in all subsets of the paediatric population for treatment of type 2 diabetes mellitus -No studies have been performed with Xultophy in children and adolescents below 18 years of age.[608]	Date of authorisation: 18/09/2014, but no PIP available PIP is missing[609] -->For fixed- dose combination products a PIP is not needed[610]

[606] Cf. EMA, Annex 1 Summary of Product Characteristics Tresiba.
[608] Cf. EMA, Annex 1 Summary of Product Characteristics Xultophy.
[609] Cf. EMA, EPAR Xultphy.
[610] Cf. EMA, PIP: questions and answers.

Insulin detemir	Levemir	Diabetes Mellitus, Type-1 and -2, for adults, adolescents and children aged 1 year and above	-Levemir can be used in adolescents and children from the age of 1 year -The safety and efficacy of Levemir in children below the age of 1 year have not been established. No data are available. -Same adverse reactions observed in the paediatric population as in the general diabetes population. -Efficacy and safety of Levemir has been studied for up to 12 months, in three randomised controlled clinical trials in adolescents and children (n=1,045 in total); the trials included in total 167 children aged 1–5 years. Results support the use of Levemir in adolescent patients with type 2 diabetes mellitus." -pharmacokinetic studiesin children from 1 year to 17 years: comparison to adults with type 1 diabetes. Results: There were no clinically relevant differences in pharmacokinetic properties between young children, children, adolescents and adults.[611]	Waiver for indication Treatment of type 1 diabetes mellitus, children from birth to less than year of age (grounds: no therapeutic benefit) And waiver for indication treatment of type 2 diabetes mellitus children from birth to less than 10 years of age (grounds: disease does not occur this population) Studies must be done for type 1 diabetes mellitus for children aged 1 to 18 years of age.[612]

[611] Cf. EMA, Annex 1 Summary of Product Characteristics Levemir.
[612] Cf. EMA, European Medicines Agency decision Levemir.

Insulin glargine	Abasaglar, prev. Abasria	For children over the age of two and adults, for treatment of diabetes Type-1 and -2	-The safety and efficacy of insulin glargine have been established in adolescents and children aged 2 years and older. -The safety and efficacy of insulin glargine have not been established in children younger than 2 years of age. No data are available. -safety profile for children and adolescents below 18 years of age is similar to the safety profile for adults. More adverse reaction are observed, e.g.more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in children and adolescents under 18 years of age than in adults. -Clinical study safety data are not available for children under 2 years. -a randomised, controlled clinical study, paediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) has been performed. -Pharmacokinetics studies in children aged 2 to less than 6 years with type 1 diabetes mellitus have been performed. Results: plasma concentration patterns are similar to adults, providing no evidence for accumulation of insulin glargine or its metabolites with chronic dosing.[613]	Date of authorisation: 09/09/2014, but no PIP available PIP is missing for children under 2 years[614] No PIP needed, because Basaglar is a generic product

[613] Cf. EMA, Annex 1 Summary of Product Characteristics Abasaglar.
[614] Cf. EMA, EPAR Abasaglar.

	Lantus	Diabetes mellitus, Treatment of diabetes mellitus in adults, adolescents and children aged 2 years and above.	-Can be used in adolescents and children aged 2 years and older patients -Safety and efficacy of Lantus have been established in adolescents and children aged 2 years and older. -Children below 2 years of age The safety and efficacy of Lantus have not been established. No data are available. -safety profile for children and adolescents under 18 years of age is similar to the safety profile for adults. -More adverse reactions are observed e.g. injection site reactions and skin reactions (rash, urticaria) in children and adolescents (≤18 years of age) than in adults. -Clinical study safety data are not available for children under 2 years. -Clinical trials have been performed in children aged older than 2 years. -Pharmacokinetics studies in children aged 2 to less than 6 years with type 1 diabetes mellitus have been performed. Results: plasma concentration patterns are similar to adults.[615]	Waiver for indication treatment of type 1 diabetes mellitus for children less than 1 year of age (grounds: no therapeutic benefit) and children from 6 to less than 18 years of age (grounds: no therapeutic benefit) And waiver for indication treatment of type 2 diabetes mellitus for children less than 10 years of age (grounds: disease does not occur this population) and for children from 10 to less than 18 years of age (grounds: no therapeutic benefit) Studies must be done for type 1 for children from 1 to less than 6 years of age.[616]

[615] Cf. EMA, Annex 1 Summary of Product Characteristics Lantus.
[616] Cf. EMA, European Medicines Agency decision Lantus.

	Toujeo	Diabetes mellitus, in adults, adolescents and children from the age of 6 years	-Toujeo is recommended for the use in adolescents and children from the age of 6 years. -Safety and efficacy of Toujeo have been demonstrated in a study in children aged 6 to less than 18 years. -Adverse reaction in children are the same as in the general diabetes population -Clinical study safety data are not available for children under 6 years.But extrapolation of efficacy and safety data for paediatric patients with type 2 diabetes mellitus have been has been done from data for adolescent and adult patients with type 1 diabetes mellitus and adult patients with type 2 diabetes mellitus. Results: Toujeo can be used for children with type 2 diabetes mellitus.[617]	Waiver for indication treatment of type 1 diabetes mellitus for children less than 1 year of age (grounds: no therapeutic benefit) and children from 6 to less than 18 years of age (grounds: no therapeutic benefit) And waiver for indication treatment of type 2 diabetes mellitus for children less than 10 years of age (grounds: disease does not occur this population) and for children from 10 to less than 18 years of age (grounds: no therapeutic benefit) Studies must be done for type 1 for children from 1 to less than 6 years of age.[618]
Insulin glargine/ Lixisenatide	Suliqua	Diabetes Mellitus, Type-2, only for adults	-No experience with Suliqua in children and adolescents aged less than 18 years; therefore, the use of Suliqua is not recommended in this age group. -There is a waiver for the obligation to submit the results of studies with Suliqua in all subsets of the paediatric population for treatment of type 2 diabetes mellitus.[619]	Date of authorisation: 30/03/2017,but no PIP available PIP is missing[620]

[617] Cf. EMA, Annex 1 Summary of Product Characteristics Toujeo.
[618] Cf. EMA, European Medicines Agency decision Toujeo.
[619] Cf. EMA, Annex 1 Summary of Product Characteristics Suliqua.
[620] Cf. EMA, EPAR Suliqua.

Insulin glulisine	Apidra	Diabetes mellitus, Treatment of adults, adolescents and children 6 years or older, with diabetes mellitus, where treatment with insulin is required	-insufficient clinical information on the use of Apidra in children younger than the age of 6 years are available. -Type 1 diabetes mellitus–Paediatric study: A 26-week phase III clinical study have been performed to compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus.Insulin glargine or NPH as basal insulin have been used. Results: Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA1c equivalent) from baseline to endpoint and by self-monitored blood glucose values. -Type 2 diabetes mellitus studies: Only studies with adults have been performed.[621]	Date of authorisation: 27/09/2004, no PIP needed[622]
Insulin human	Insuman	Diabetes mellitus type 1 Authorised for children?	-No data are available. Because of that, the safety and efficacy of Insuman Implantable have not been established in children.[623]	Date of authorisation: 21/02/1997, no PIP needed[624]

[621] Cf. EMA, Annex 1 Summary of Product Characteristics Apidra.
[622] Cf. EMA, EPAR Apidra.
[623] Cf. EMA, Annex 1 Summary of Product Characteristics Insuman.
[624] Cf. EMA, EPAR Insuman.

	Insulatard	Diabetes mellitus Insulatard is indicated for treatment of diabetes mellitus	-Insulatard can be used in children and adolescents. -adverse reactions that could been observed in the children do not indicate any differences to the broader experience in the general population.[625]	Date of authorisation: 07/10/2002, no PIP needed[626]
	Protaphane	Diabetes mellitus	-Protaphane can be used in children and adolescents. -adverse reactions that could been observed in the children do not indicate any differences to the broader experience in the general population.[627]	Date of authorisation: 07/10/2002, no PIP needed[628]
	Actrapid	Diabetes mellitus	-Actrapid can be used in children and adolescents. -adverse reactions that could been observed in the children do not indicate any differences to the broader experience in the general population. -The pharmacokinetic profile of Actrapid has been studied in a small number (n=18) of diabetic children (aged 6–12 years) and adolescents (aged 13–17 years). Results: limited data, but they suggest that the pharmacokinetic profile in children and adolescents may be similar to that in adults. However, there differences between age groups in Cmax have been observed.[629]	Date of authorisation: 07/10/2002, no PIP needed[630]

[625] Cf. EMA, Annex 1 Summary of Product Characteristics Insultard.
[626] Cf. EMA, EPAR Insultard.
[627] Cf. EMA, Annex 1 Summary of Product Characteristics Protaphane.
[628] Cf. EMA, EPAR Protaphane.
[629] Cf. EMA, Annex 1 Summary of Product Characteristics Actrapid.
[630] Cf. EMA, EPAR Actrapid.

	Actraphane	Diabetes mellitus	-Actraphane can be used in children and adolescents. -adverse reactions that could been observed in the children do not indicate any differences to the broader experience in the general population[631].	Date of authorisation: 07/10/2002, no PIP needed[632]
	Mixtard	Diabetes mellitus	-Mixtard can be used in children and adolescents. -adverse reactions that could been observed in the children do not indicate any differences to the broader experience in the general population.[633]	Date of authorisation: 07/10/2002, no PIP needed[634]
Insulin lispro	Humalog	Diabetes mellitus, for adults and children	-Humalog is recommended for use in adolescents and children. -Use of Humalog Mix25 to children below 12 years of age should be considered only in case of an expected benefit when compared to soluble insulin. - There have been clinical trials performed in children (61 patients aged 2 to 11) and children and adolescents (481 patients aged 9 to 19 years). The studies compared insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is similar to that observed in adults.[635]	Date of authorisation: 30/04/1996, no PIP needed[636] Is the reference product
	Lyumjev	Treatment of diabetes mellitus in adults. (other excipients than	-Safety and efficacy of Lyumjev in children and adolescents below 18 years of age have not yet been established. -pharmacokinetics and pharmacodynamics studies: to assess pharmacokinetic differences between Lyumjev and Humalog. Results similar in children and adolescents as observed in adults.	Date of authorisation: 24/03/2020, but no PIP available[638] → Same company (Eli Lilly) than Humalog. Refers to PIP of Humalog? But L. is authorised only for adults

631 Cf. EMA, Annex 1 Summary of Product Characteristics Actraphane.
632 Cf. EMA, EPAR Actraphane.
633 Cf. EMA, Annex 1 Summary of Product Characteristics Mixtard.
634 Cf. EMA, EPAR Mixtard.
635 Cf. EMA, Annex 1 Summary of Product Characteristics Humalog.
636 Cf. EMA, EPAR Humalog.
638 Cf. EMA, EPAR Lyumjev.

		Humalog, faster)	Following a subcutaneous injection, it can be observed that Lyumjev has an accelerated absorption with a higher early insulin lispro exposure in children (6–11 years) and adolescents (12–17 years) while it maintains a similar total exposure, maximum concentration and time to maximum concentration compared to Humalog. Following a subcutaneous bolus infusion with CSII therapy, a trend towards an accelerated absorption in children and adolescents can be observed whilst total exposure, maximum concentration and time to maximum concentration were similar compared to Humalog. -Safety and efficacy of Lyumjev in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made. -The pharmacokinetic differences between Lyumjev and Humalog were, overall, similar in children and adolescents as observed in adults. Following a subcutaneous injection, Lyumjev showed an accelerated absorption with a higher early insulin lispro exposure in children from 6 to 11 years of age and adolescents aged from 12 to 17 years. The total exposure have been the same, maximum concentration and time to maximum concentration compared to Humalog.[637]	→ Biosimilar, due to that it does not need a PIP
	I lispro Sanofi	Diabetes mellitus, for children and adults	-it is recommended for the use in adolescents and children. -Clinical trials have been performed in children (61 patients aged 2 to 11) and children and adolescents (481 patients aged 9 to 19 years). It compared insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is similar to that seen in adults.[639]	No PIP needed, for all children, although there are only studies in children above 2 years of age No PIP needed, because Insulin lispro Sanofi is a generic product

[637] Cf. EMA, Annex 1 Summary of Product Characteristics Lymjev.
[639] Cf. EMA, Annex 1 Summary of Product Characteristics Insulin lispro Sanofi.

	Liprolog	Diabetes mellits, for children and adults	-it is recommended for the use in adolescents and children. -Clinical trials have been performed in children (61 patients aged 2 to 11) and children and adolescents (481 patients aged 9 to 19 years). It compared insulin lispro to human soluble insulin. The pharmacodynamic profile of insulin lispro in children is similar to that seen in adults.[640]	Date of authorisation: 01/08/2001, no PIP needed[641]
Linagliptin	Trajenta	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with linagliptin in one or more subsets of the paediatric population in Type 2 diabetes- -A paediatric pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents ≥10 to <18 years of age with type 2 diabetes mellitus have been performed. Results: pharmacokinetic and pharmacodynamic responses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.). Because of the limited nature of the data set the results should be interpreted cautiously.[642]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 10 years of age (grounds: disease does not occur this population), studies must be done with children from 10 to less than 18 years of age.[643]

[640] Cf. EMA, Annex 1 Summary of Product Characteristics Liprolog.
[641] Cf. EMA, EPAR Liprolog, EPAR Liprolog.
[642] Cf. EMA, Annex 1 Summary of Product Characteristics Trajenta.
[643] Cf. EMA, European Medicines Agency decision Trajenta.

Linagliptin/ Metformin	Jentadueto	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Jentadueto in children and adolescents aged between 0 to 18 years have not been established. No data are available. -There is a waiver for the obligation to submit the results of the studies with Jentadueto in all subsets of the paediatric population in type 2 diabetes. -Paediatric pharmacokinetics and pharmacodynamics of 1 mg and 5 mg linagliptin in children and adolescents aged 10 to younger than 18 year of age with type 2 diabetes mellitus have been performed. Results: The observed pharmacokinetic and pharmacodynamic reponses were consistent with those found in adult subjects. Linagliptin 5 mg showed superiority over 1 mg with regard to trough DPP-4 inhibition (72% vs 32%, p=0.0050) and a numerically larger reduction with regard to adjusted mean change from baseline in HbA1c (-0.63% vs -0.48%, n.s.). Because of the limited nature of the data set the results should be interpreted cautiously. -Single dose study: after single doses of metformin hydrochloride 500 mg, paediatric patients have demonstrated a similar pharmacokinetic profile to that observed in healthy adults. -Multiple-dose study: data are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (Cmax) and systemic exposure (AUC0-t) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.[644]	Date of authorisation: 19/07/2012, but no PIP available[645] → For fixed-dose combination products a PIP is not needed[646]

[644] Cf. EMA, Annex 1 Summary of Product Characteristics Jentadueto.
[645] Cf. EMA, EPAR Jentadueto.
[646] Cf. EMA, PIP: questions and answers.

Liraglutide	Victoza	Diabetes mellitus Type-2, adults and children from 10 years of age who have type 2 diabetes	-Interaction studies have not been performed in children -Overall, frequency, type and severity of adverse reactions in adolescents and children aged 10 years and above show a comparability to that observed in the adults. Rate of confirmed hypoglycaemic episodes was higher with liraglutide (0.58 events/patient year) compared to placebo (0.29 events/patient year). In patients that have been treated with insulin prior to a confirmed hypoglycaemic episode the rate was higher with liraglutide (1.82 events/patient year) compared to placebo (0.91 events/patient years). No severe hypoglycaemic episodes occurred in the liraglutide treatment group. -In a double-blind study that had the aim to compare the efficacy and safety of Victoza 1.8 mg versus placebo as add-on to metformin ± insulin in adolescents and children aged 10 years and above with type 2 diabetes, Victoza was superior to placebo treatment in reducing HbA1c after 26 weeks (-1.06, [-1.65, 0.46]). The treatment difference in HbA1c was 1.3% after additional 26 weeks of open label extension that confirms the sustained glycaemic control with Victoza. Th efficacy and safety profile of Victoza was comparable to that observed in the adult population treated with Victoza. Based on adequate glycaemic control or tolerability, 30% of trial subjects remained on a dose of 0.6 mg, 17% escalated to a dose of 1.2 mg and 53% escalated to a dose of 1.8 mg. -Pharmacokinetic studies have been performed in children with type 2 diabetes aged 10 years and older. The liraglutide exposure in adolescents and children was comparable to that observed in the adult population.[647]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 10 years of age (grounds: disease does not occur this population), studies must be done with children from 10 to less than 18 years of age.[648]

[647] Cf. EMA, Annex 1 Summary of Product Characteristics Victoza.
[648] Cf. EMA, European Medicines Agency decision Victoza.

Lixisenatide	Lyxumia	Diabetes Mellitus, Type-2, for adults only	-Safety and efficacy of lixisenatide in children and adolescents less than 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Lyxumia in all subsets of children with type 2 diabetes mellitus.[649]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 10 years of age (grounds: disease does not occur this population), And waiver for children from 10 to less than 18 years of age (grounds: no significant therapeutic benefit).[650]
Metformin/ Dapagliflozin	Xigduo	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Xigduo in children and adolescents aged between 0 to 18 years have not yet been established. No data are available. -Interaction studies have not been performed in children. -There is wa waiver for the obligation to submit the results of studies with Xigduo in all subsets of the paediatric population in the treatment of type 2 diabetes -Pharmacokinetic studies in children have not been studied.[651]	Date of authorisation: 16/01/2014, but no PIP available[652] → For fixed-dose combination products a PIP is not needed[653]
Metformin/ Pioglitazone	Glubrava	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Glubrava in children and adolescents under 18 years of age have not been established. No data are available.	Date of authorisation: 11/12/2007, but no PIP available[655]

[649] Cf. EMA, Annex 1 Summary of Product Characteristics Lyxumia.
[650] Cf. EMA, European Medicines Agency decision Lyxumia.
[651] Cf. EMA, Annex 1 Summary of Product Characteristics Xigduo.
[652] Cf. EMA, EPAR Xigduo.
[653] Cf. EMA, PIP: questions and answers.
[655] Cf. EMA, EPAR Glubrav.

			-There is a waiver for the obligation to submit the results of studies with Competact in all subsets of children with type 2 diabetes mellitus.[654]	→ For fixed- dose combination products a PIP is not needed[656]
Metformin/ Saxagliptine	Kombogl yze	Diabetes Mellitus, Type-2, for adults only	-Safety and efficacy in children and adolescents from birth to younger than 18 years of age have not been established. No data are available. -There is waiver for the obligation to submit the results of studies with Komboglyze in all subsets of the paediatric population in type 2 diabetes mellitus.[657]	Date of authorisation: 24/11/2011, but no PIP available[658] → For fixed- dose combination products a PIP is not needed[659]
Nateglinide	Starlix	Diabetes mellitus type 2, no further information	-No data available on the use of nateglinide in patients under 18 years of age, and therefore the use in this age group is not recommended. -No clinical studies have been performed in children and adolescents. Use is therefore not recommended in these patient groups[660]	Date of authorisation: 03/04/2001, no PIP needed
Pioglitazone	Actos	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Competact in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with Competact in all subsets of children with type 2 diabetes mellitus.[661]	Date of authorisation: 13/10/2000, no PIP needed
	Competa ct	Diabetes Mellitus,	-Safety and efficacy of Competact in children and adolescents under 18 years of age have not been established. No data are available.	Date of authorisation: 28/07/2006, no PIP needed

[654] Cf. EMA, Annex 1 Summary of Product Characteristics Glubrav.
[656] Cf. EMA, PIP: questions and answers.
[657] Cf. EMA, Annex 1 Summary of Product Characteristics Komboglyze.
[658] Cf. EMA, EPAR Komboglyze.
[659] Cf. EMA, PIP: questions and answers.
[660] Cf. EMA, Annex 1 Summary of Product Characteristics Starlix.
[661] Cf. EMA, Annex 1 Summary of Product Characteristics Actos.

		Type-2, only for adults	-There is a waiver for the obligation to submit the results of studies with Competact in all subsets of children with type 2 diabetes mellitus.[662]	
	P Actavis	Diabetes Mellitus, Type-2, only for adults	Safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with pioglitazone in all subsets of children suffering of Type 2 Diabetes Mellitus.[663]	Date of authorisation: 15/03/2012, but no PIP available[664] No PIP needed, because this is a generic product
	Glustin	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with pioglitazone in all subsets of children suffering of Type 2 Diabetes Mellitus.[665]	Date of authorisation: 11/10/2000, no PIP needed
	P accord	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with pioglitazone in all subsets of children suffering of Type 2 Diabetes Mellitus.[666]	Date of authorisation: 21/03/2012, but no PIP available[667] No PIP needed, this is a generic product

[662] Cf. EMA, Annex 1 Summary of Product Characteristics Competact.
[663] Cf. EMA, Annex 1 Summary of Product Characteristics Pioglitazone Actavis.
[664] Cf. EMA, EPAR Pioglitazone Actavis.
[665] Cf. EMA, Annex 1 Summary of Product Characteristics Glustin.
[666] Cf. EMA, Annex 1 Summary of Product Characteristics Pioglitazone Accord.
[667] Cf. EMA, EPAR Pioglitazone Accord.

	Glidipion	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of pioglitazone in children and adolescents under 18 years of age have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with pioglitazone in all subsets of children suffering of Type 2 Diabetes Mellitus.[668]	Date of authorisation: 15/03/2012, not no PIP available[669] No PIP needed, this is a generic product
Repaglinide	R Teva	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of repaglinide in children younger than 18 years have not been established. No data are available. -No interaction studies have been performed in children and adolescents. -Pharmakokinetic: No data are available.[670]	Date of authorisation: 28/09/2009, but no PIP available[671] No PIP needed, this is a generic product
	R Accord	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of repaglinide in children younger than 18 years have not been established. No data are available. -No interaction studies have been performed in children and adolescents.[672]	Date of authorisation: 22/12/2011, but no PIP available[673] No PIP needed, this is a generic product
	Prandin	Diabetes mellitus Type-2, only for adults	-Safety and efficacy of repaglinide in children younger than 18 years have not been established. No data are available. -No interaction studies have been performed in children and adolescents.[674]	Date of authorisation: 29/01/2001, no PIP needed

[668] Cf. EMA, Annex 1 Summary of Product Characteristics Glidipion.
[669] Cf. EMA, EPAR Glipidion.
[670] Cf. EMA, Annex 1 Summary of Product Characteristics Repaglinide.
[671] Cf. EMA, EPAR Repalinide, Teva.
[672] Cf. EMA, Annex 1 Summary of Product Characteristics Repaglinide Accord.
[673] Cf. EMA, EPAR Repaglinide Accord.
[674] Cf. EMA, Annex 1 Summary of Product Characteristics Prandin.

	Novonorm	Diabetes mellitus Type-2, only for adults	Safety and efficacy of repaglinide in children younger than 18 years have not been established. No data are available. -No interaction studies have been performed in children and adolescents.[675]	Date of authorisation: 16/08/1998, no PIP needed
Saxagliptin	Onglyza	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Onglyza in children and adolescents has not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with Onglyza in one or more subsets of children in type 2 diabetes mellitus.[676]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 10 years og age (grounds: disease does not occur this population), studies with children from 10 to less than 18 years of age must be done.[677]
Sotagliflozin	Zynquista	Diabetes mellitus Type-1, for adults only	-Safety and efficacy of sotagliflozin in children and adolescents has not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with Zynquista in one or more subsets of children in type 1 diabetes mellitus.[678]	Date of authorisation: 26/04/2019[679] Waiver applies to: • the paediatric population from birth to less than 6 months of age; • granules, tablets, oral use; • on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

[675] Cf. EMA, Annex 1 Summary of Product Characteristics Novonorm.
[676] Cf. EMA, Annex 1 Summary of Product Characteristics Onglyza.
[677] Cf. EMA, European Medicines Agency decision Onglyza.
[678] Cf. EMA, Annex 1 Summary of Product Characteristics Zynquista.
[679] Cf. EMA, EPAR Zynquista.

				The waiver applies to: • infants and toddlers from 6 months to less than 24 months of age; • granules, tablets, oral use; • on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments. → Studies must be done with children from 2 to 18 years of age.[680]
Sitagliptin	Tesavel	Diabetes type-2, only for adults	-Sitagliptin is not recommended for the use in children and adolescents from 10 to 17 years of age because of insufficient efficacy. -Sitagliptin has not been studied in childrenunder 10 years of age. -Clinical trials with sitagliptin showed in paediatric patients with type 2 diabetes mellitus aged from 10 to17 years that the profile of adverse reactions was comparable to that observed in adults. -The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 to 17 years of age that suffer of type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and	PIP is superseded by the PIP of Januvia[682]

[680] Cf. EMA, European Medicines Agency decision Zynquista.
[682] Cf. EMA, European Medicines Agency decision Tesavel.

			100 mg. No studies with sitagliptin have been investigated in paediatric patients with age under 10 years.[681]	
	Januvia	Diabetes Type-2, only for adults	-Sitagliptin is not recommended for the use in children and adolescents from 10 to 17 years of age because of insufficient efficacy. -Sitagliptin has not been studied in childrenunder 10 years of age. -Clinical trials with sitagliptin showed in paediatric patients with type 2 diabetes mellitus aged from 10 to17 years that the profile of adverse reactions was comparable to that observed in adults. -The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 to 17 years of age that suffer of type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been investigated in paediatric patients with age under 10 years.[683]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 10 years og age (grounds: disease does not occur this population), studies with children from 10 to less than 18 years of age must be done.[684]

[681] Cf. EMA, Annex 1 Summary of Product Characteristics Tesavel.
[683] Cf. EMA, Annex 1 Summary of Product Characteristics Januvia.
[684] Cf. EMA, European Medicines Agency decision Januvia.

	Ristaben	Diabetes Mellitus, Type-2, only for adults	-Sitagliptin is not recommended for the use in children and adolescents from 10 to 17 years of age because of insufficient efficacy. -Sitagliptin has not been studied in childrenunder 10 years of age. -Clinical trials with sitagliptin showed in paediatric patients with type 2 diabetes mellitus aged from 10 to17 years that the profile of adverse reactions was comparable to that observed in adults. -A 54-week, double-blind study was performed to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on antihyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks. Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3). -The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 to 17 years of age that suffer of type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been investigated in paediatric patients with age under 10 years.[685]	Date of authorisation: 15/03/2010, but no PIP available[686]

[685] Cf. EMA, Annex 1 Summary of Product Characteristics Ristaben.
[686] Cf. EMA, EPAR Ristaben.

	Xelevia	Diabetes Mellitus, Type-2, only for adults	-Sitagliptin is not recommended for the use in children and adolescents from 10 to 17 years of age because of insufficient efficacy. -Sitagliptin has not been studied in childrenunder 10 years of age. Clinical trials with sitagliptin showed in paediatric patients with type 2 diabetes mellitus aged from 10 to17 years that the profile of adverse reactions was comparable to that observed in adults." -A 54-week, double-blind study was performed to evaluate the efficacy and safety of sitagliptin 100 mg once daily in paediatric patients (10 to 17 years of age) with type 2 diabetes who were not on antihyperglycaemic therapy for at least 12 weeks (with HbA1c 6.5% to 10%) or were on a stable dose of insulin for at least 12 weeks (with HbA1c 7% to 10%). Patients were randomised to sitagliptin 100 mg once daily or placebo for 20 weeks. Mean baseline HbA1c was 7.5%. Treatment with sitagliptin 100 mg did not provide significant improvement in HbA1c at 20 weeks. The reduction in HbA1c in patients treated with sitagliptin (N=95) was 0.0% compared to 0.2% in patients treated with placebo (N=95), a difference of -0.2% (95% CI: -0.7, 0.3). -The pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 to 17 years of age that suffer of type 2 diabetes. In this population, the dose-adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. This is not considered to be a clinically meaningful difference compared to adult patients based on the flat PK/PD relationship between the dose of 50 mg and 100 mg. No studies with sitagliptin have been investigated in paediatric patients with age under 10 years.[687]	PIP superseded by the PIP of Januvia[688]

[687] Cf. EMA, Annex 1 Summary of Product Characteristics Xelevia.
[688] Cf. EMA, EMA decision Xelevia.

Sitagliptin/ Ertugliflozin	Stegluja n	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Steglujan in children under 18 years of age have not been performed. No data are available. -There is a waiver for the obligation to submit the results of studies with Steglujan in all subsets of the paediatric population in the treatment of type 2 diabetes -No studies with ertugliflozin have been performed in children.[689]	Date of authorisation: 23/03/2018, but no PIP available[690] → For fixed- dose combination products a PIP is not needed[691]

[689] Cf. EMA, Annex 1 Summary of Product Characteristics Stegluja.
[690] Cf. EMA, EPAR Steglujan.
[691] Cf. EMA, PIP: questions and answers.

Sitagliptin/ Metformin	Ristfor	Diabetes Type-2, for adults only	-it should not be used in children and adolescents from 10 to 17 years of age due to insufficient efficacy. -it has not been studied in paediatric patients under 10 years of age. -In clinical trials with children suffering of type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that observed in adults. In children that were treated with or without the background insulin, sitagliptin was associated with an increased risk of hypoglycaemia. -There is a waiver for the obligation to submit the results of studies with Ristfor in all subsets of the paediatric population in type 2 diabetes mellitus. The safety and efficacy of the addition of sitagliptin in children aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin was compared to the addition of placebo to metformin or metformin XR. Results: superiority of HbA1c reduction was demonstrated for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, but results from the individual studies were inconsistent. In adddtion, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at Week 54. Therefore, Ristfor is not recommended in children aged 10 to 17 years old because of insufficient efficacy. -Pharmacokinetic studies with sitaglitpin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 and 17 years of age with type 2 diabetes. Results: dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients under 10 years of age.[692]	Date of authorisation: 15/03/2010, but no PIP available[693] → Same company (MSD) as Velmetia, refers to PIP of Velmetia

[692] Cf. EMA, Annex 1 Summary of Product Characteristics Ristfor.
[693] Cf. EMA, EPAR Ristfor.

	Velmetia	Diabetes Mellitus, Type-2, for adults only	-it should not be used in children and adolescents from 10 to 17 years of age due to insufficient efficacy. -it has not been studied in paediatric patients under 10 years of age. -In clinical trials with children suffering of type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions of sitagliptin plus metformin was generally comparable to that observed in adults. In children that were treated with or without the background insulin, sitagliptin was associated with an increased risk of hypoglycaemia. -There is a waiver for the obligation to submit the results of studies with Velmetia in all subsets of the paediatric population in type 2 diabetes mellitus –Safety and efficacy of the addition of sitagliptin in paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin was compared to the addition of placebo to metformin or metformin XR.Results: superiority of HbA1c reduction was shown for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, but results from the individual studies were inconsistent. In addition, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at Week 54. →Therefore, Velmetia is not recommended for children aged 10 to 17 years old because of insufficient efficacy. -Pharmacokinetic studies with sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 and 17 years of age with type 2 diabetes. Results: dose adjusted AUC of sitagliptin in plasma was approximately 18 %	Waiver for whole pediatric population (grounds: no significant therapeutic benefit)[695]

[695] Cf. EMA, European Medicines Agency decision Velmetia.

			lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients under 10 years of age. -it should not be used in children and adolescents 10 to 17 years of age due to insufficient efficacy. -It has not been studied in children under 10 years of age.[694]	
	Janumet	Diabetes Mellitus, Type-2, only for adults	-Janumet is not recommended for the use in children and adolescents 10 to 17 years of age due to insufficient efficacy. -Janumet has not been studied in paediatric patients under 10 years of age. -In clinical trials with Janumet in children with type 2 diabetes mellitus aged 10 to 17 years, the profile of adverse reactions was generally comparable to that observed in adults. In paediatric patients with or without the background insulin, sitagliptin was associated with an increased risk of hypoglycaemia. -There is a waiver for the obligation to submit the results of studies with Janumet in all subsets of the paediatric population in type 2 diabetes mellitus -Safety and efficacy of the addition of sitagliptin in paediatric patients aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. The addition of sitagliptin was compared to the addition of placebo to metformin or metformin XR. Results: There was a superiority of HbA1c reduction for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, but the results from the individual studies were inconsistent.	Waiver for all subsets of the paediatric population and all above-mentioned conditions in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.[697]

[694] Cf. EMA, Annex 1 Summary of Product Characteristics Velmetia.
[697] Cf. EMA, European Medicines Agency decision Janumet.

			In addition, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR compared to metformin was not observed at Week 54. →Therefore, Janumet is not recommended in children aged 10 to 17 years old due to insufficient efficacy. -Pharmacokinetics of sitagliptin (single dose of 50 mg, 100 mg or 200 mg) were investigated in paediatric patients between 10 and 17 years of age with type 2 diabetes. Results: dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. No studies with sitagliptin have been performed in paediatric patients under 10 years of age. -Janumet should not be used in children and adolescents 10 to 17 years of age due to insufficient efficacy. -Janumet has not been studied in children under 10 years of age.[696]	
	Efficib	Diabetes Mellitus, Type-2, only for adults	-Efficib is not recommended for use in children and adolescents 10 to 17 years of age because of insufficient efficacy. No studies have been conducted with children under 10 years of age. In clinical trials with sitagliptin + metformin in children with type 2 diabetes mellitus between 10 and 17 years of age, the profile of adverse reactions was generally comparable to that observed in adults. In paediatric patients with or without the background insulin, sitagliptin was associated with an increased risk of hypoglycaemia. -There is a waiver for the obligation to submit the results of studies with Efficib in all subsets of the paediatric population in type 2 diabetes mellitus	Waiver for all subsets of the paediatric population and all above-mentioned conditions in accordance with Article 11(1)(c) of Regulation (EC) No 1901/2006 as amended, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.[699]

[696] Cf. EMA, Annex 1 Summary of Product Characteristics Janumet.
[699] Cf. EMA, European Medicines Agency decision Efficib.

			-Safety and efficacy of the addition of sitagliptin in children aged 10 to 17 years with type 2 diabetes and inadequate glycaemic control on metformin with or without insulin was assessed in two studies over 54 weeks. There was a comparision between the addition of sitagliptin and the addition of placebo to metformin or metformin XR. Results: -superiority of HbA1c reduction was demonstrated for sitagliptin + metformin / sitagliptin + metformin XR over metformin at Week 20 in the pooled analysis of these two studies, but results from the individual studies were inconsistent. In addition, greater efficacy for sitagliptin + metformin / sitagliptin + metformin XR in comparision to metformin was not observed at Week 54. →Therefore, Efficib is not recommended in patients aged 10 to 17 years, due to insufficient efficacy -Pharmacokinetic studies of sitagliptin were investigated in paediatric patients from 10 to 17 years of age that sufferof type 2 diabetes. In this population, the dose adjusted AUC of sitagliptin in plasma was approximately 18 % lower compared to adult patients with type 2 diabetes for a 100 mg dose. -No studies with sitagliptin have been performed in children younger than 10 years of age.[698]	

[698] Cf. EMA, Annex 1 Summary of Product Characteristics Efficib.

Semaglutide	Ozempic	Diabetes Mellitus, Type-2, only for adults	Safety and efficacy of semaglutide in children and adolescents below 18 years have not yet been established. No data are available. -There is a deferral for the obligation to submit the results of studies with semaglutide in the paediatric population in type 2 diabetes -Semaglutide has not been studied in children.[700]	Waiver for indication treatment of type 2 diabetes mellitus, (grounds: disease does not occur in this population), studies must be done with children from 10 to less than 18 years of age.[701] Waiver for indication treatment of obesity for children from birth to less than 6 years of age (grounds: no significant therapeutic benefit).[702]
	Rybelsus	Diabetes Mellitus, Type-2, only for adults	-Safety and efficacy of Rybelsus in children and adolescents below 18 years have not been established. No data are available. -There is a deferral for the obligation to submit the results of studies with Rybelsus in one or more subsets of the paediatric population in type 2 diabetes. -Semaglutide has not been studied in children[703]	Date of authorisation: 03/04/2020, but no PIP available[704] → Refers to Ozempic, same marketing authorisation holder

[700] Cf. EMA, Annex 1 Summary of Product Characteristics Ozempic.
[701] Cf. EMA, European Medicines Agency decision 2020 Semaglutide.
[702] Cf. EMA, European Medicines Agency decision 2019 Semaglutide.
[703] Cf. EMA, Annex 1 Summary of Product Characteristics Rybelsus.
[704] Cf. EMA, EPAR Rybelsus.

Vildagliptin	Xiliarx	Diabetes Mellitus, Type-2, only for adults	Xiliarx is not recommended for use in children and adolescents under 18 years -Safety and efficacy of Xiliarx in children and adolescents below 18 years have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus[705]	Date of authorisation: 19/11/2008, but no PIP available[706] → It is a product of Novartis, same as Galvus and Jalra. Novartis refers to the Galvus approval documents with regard to clinical studies (also PIP).
	Galvus	Diabetes Mellitus, Type-2, only for adults	-Galvus is not recommended for use in children and adolescents under 18 years of age. -Safety and efficacy of Galvus in children and adolescents below 18 years have not been established. No data are available. There is a waiver for the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus[707]	Waiver for indication treatment of type 2 diabetes mellitus for children from birth to less than 10 years of age (grounds: disease does not occur this population). And waiver for children and adolescents from 10 to less than 18 years of age (grounds: medicinal product is likely to be unsafe).[708]

[705] Cf. EMA, Annex 1 Summary of Product Characteristics Xiliarx.
[706] Cf. EMA, EPAR Xiliarx.
[707] Cf. EMA, Annex 1 Summary of Product Characteristics Galvus.
[708] Cf. EMA, European Medicines Agency decision Galvus.

	Jalra	Diabetes Mellitus, Type-2, only for adults	Jalra is not recommended for use in children and adolescents under the age of 18 years) -Safety and efficacy of Jalra in children and adolescents below 18 years have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with vildagliptin in all subsets of the paediatric population with type 2 diabetes mellitus.[709]	Date of authorisation: 19/11/2008, but no PIP available[710] → It is a product of Novartis, Novartis refers to the Galvus approval documents with regard to clinical studies (also PIP)
Vildagliptin/ Metformin	Icandra	Diabetes mellitus, Type-2, only for adults	Icandra is not recommended for use in children and adolescents under 18 years -Safety and efficacy of Icandra in children and adolescents below the age of 18 years have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with vildagliptin in combination with metformin in all subsets of the paediatric population with type 2 diabetes mellitus[711]	Date of authorisation: 30/11/2008, but no PIP available[712] → Icandra is a generic product of Eucreas
	Eucreas	Diabetes mellitus, Type-2, only for adults	-Eucreas is not recommended for use in children and adolescents below 18 years. -Safety and efficacy of Eucreas in children and adolescents under the age of 18 years have not been established. No data are available. -There is a waiver for the obligation to submit the results of studies with vildagliptin in combination with metformin in all subsets of the paediatric population with type 2 diabetes mellitus.[713]	Waiver for indication treatment of type 2 diabetes mellitus, for children from birth to less than 18 years of age (grounds: no significant therapeutic benefit).[714]

[709] Cf. EMA, Annex 1 Summary of Product Characteristics Jalra.
[710] Cf. EMA, European Medicines Agency decision Jalra.
[711] Cf. EMA, Annex 1 Summary of Product Characteristics Icandra.
[712] Cf. EMA, European Medicines Agency decision Icandra.
[713] Cf. EMA, Annex 1 Summary of Product Characteristics Eucreas.
[714] Cf. EMA, European Medicines Agency decision Eucreas.

Annex 6: Clinical trials in EudraCT conducted for the European Union

Title	Where conducted	Indication	Main objectives	Outcome	Further information
An open-label, randomised, multicentre, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus[715]	DE, FR, Outside EU/ EEA	Type 2, in children, adolescents and under 18 years	To evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus.	-Limitations of the trial such as mall numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date: 26 Feb 2016
A Randomized, Multi-Center, Parallel Group, Single-Dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus[716] [717]	Outside EU/ EEA (USA, Mexico)	Type 2 diabetes mellitus, children adolescents, under 18	To evaluate the pharmacokinetics of dapagliflozin in pediatric subjects with T2DM.	"The present results showed that administration of a single oral dose of dapagliflozin in paediatric patients with T2DM was generally well tolerated and was not associated with any unexpected or clinically significant safety findings. Additionally, the dapagliflozin tablet formulation was easy to swallow for patients with T2DM in the age group of 10–17 years. On the basis of the present results, and on	Important: -Age range between 10-17 because in younger children, the disease does not occur (Acc. Study report) -enrolment

[715] Cf. EU Clinical Trials Register, Clinical trial results to the study "an open-label, randomised, multicentre, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus".
[716] Cf. EU Clinical Trials Register, Clinical trial results to the study "Randomized, Multi-Center, Parallel Group, Single-Dose, Pharmacokinetics and Pharmacodynamics Study of Dapagliflozin in Children and Adolescents Aged 10 to 17 Years with Type 2 Diabetes Mellitus".
[717] Cf. G S Tirucherai,F LaCreta,F A Ismat,W Tang,D W Boulton, Pharmacokinetics and pharmacodynamics of dapagliflozin in children and adolescents with type 2 diabetes mellitus.

				additional modelling and simulation analyses comparing the exposure–response relationship of dapagliflozin in adult and paediatric patients and the potential impact of covariate effects the same dapagliflozin dosage as that used in adults can also be evaluated in future phase III efficacy and safety studies of paediatric patients with T2DM, for whom treatment options are currently limited."	was difficult
Post-marketing study of Amaryl ® (Glimepiride) in patients with type 2 diabetes to investigate pediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study][718]	Outside EU/ EEA (only Japan)	Type 2 diabetes mellitus, children adolescents, under 18, elderly	To investigate the pharmacokinetics of Amaryl in pediatric subjects (8 to 16 years of age) with type 2 diabetes in comparison with adults subjects (17 years or older of age) with type 2 diabetes under steady state.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 13 May 2008
A trial investigating the pharmacokinetic properties of FIAsp in children,	DE	Diabetes Mellitus, Type 1, Children, adolescents, under 18, adults	To compare the total exposure of faster-acting insulin aspart (also known as FIAsp) between children,	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 24 Jul 2014

[718] Cf. EU Clinical Trials Register, Clinical trial results to the study "post-marketing study of Amaryl ® (Glimepiride) in patients with type 2 diabetes to investigate pediatric and adult population pharmacokinetics [multicenter, non-comparative, 12-28 weeks, non-blind titration (0.5-6 mg/day) study]".

adolescents and adults with type 1 diabetes[719]			adolescents and adult subjects with type 1 diabetes.		
A Study of Effectiveness and Safety of Apidra in Combination With Lantus Therapy in Basal-bolus Insulin Regimen in Inadequately Controlled Children and Adolescents With Type 1 Diabetes in the Russian Federation.[720]	Outside EU/ EEA (only Russia)	Diabetes mellitus type 1, children, adolescents, under 18	To evaluate the percentage of subjects achieving glycosylated hemoglobin (HbA1c) level < 8% (in subjects of 6-12 years old) and HbA1c level < 7.5% (in subjects of 13-17 year old) at 6 and 12 months of treatment.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 18 Oct 2012
A Trial Investigating the Pharmacokinetic Properties of NN1250 (Insulin degludec) in Children, Adolescents and Adults with Type 1 Diabetes[721]	DE	Diabetes mellitus type 1, children, adolescents, under 18, adults	To investigate the pharmacokinetic total exposure of SIBA (NN1250, IDeg) in children, adolescents and adult subjects with type 1 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 03 May 2010
A trial comparing the pharmacokinetic properties of fast-acting insulin aspart between children,	DE	Diabetes mellitus type 1, children, adolescents, under 18, adults	To compare the total exposure of faster aspart between children, adolescents and adult subjects with type 1 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 05 Jul 2018

[719] Cf. EU Clinical Trials Register, Clinical trial results to the study “a trial investigating the pharmacokinetic properties of FIAsp in children, adolescents and adults with type 1 diabetes”.
[720] Cf. EU Clinical Trials Register, Clinical trial results to the study “a Study of Effectiveness and Safety of Apidra in Combination With Lantus Therapy in Basal-bolus Insulin Regimen in Inadequately Controlled Children and Adolescents With Type 1 Diabetes in the Russian Federation.”
[721] Cf. EU Clinical Trials Register, Clinical trial results to the study “a Trial Investigating the Pharmacokinetic Properties of NN1250 (Insulin degludec) in Children, Adolescents and Adults with Type 1 Diabetes”.

adolescents and adults with type 1 diabetes[722]					
Tight glycaemic control" and the risk of hypoglycaemia: Is this different between multiple injections versus insulin pump therapy? A UK multi-centre, open randomised control trial.[723]	UK	Diabetes mellitus type 1 in children and adolescents	No information available	No results available	Global completion date 04 Nov 2010
A Trial Investigating the Pharmacokinetic Properties of NN5401 in Children, Adolescents and Adults with Type 1 Diabetes[724]	DE	Diabetes mellitus type 1 in children, adolescents, under 18, adults	To investigate the total exposure of SIAC (insulin degludec/insulin aspart) in children, adolescents and adult subjects with type 1 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 30 Nov 2010
A 52-Week, Multinational, Multi-Centre, Open-Labelled Extension Trial of Insulin Detemir in Children and Adolescents 3-17 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin	UK, FI, DK, HU, CZ, FR, BG	Diabetes mellitus type 1 in children, adolescents, under 18, adults	To study the development of insulin detemir-insulin aspart cross-reacting antibodies following a 104 week-period (52 weeks in NN304-1689 and 52 weeks in NN304-1690) of insulin detemir	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 07 Sep 2009

[722] Cf. EU Clinical Trials Register, Clinical trial results to the study "a trial comparing the pharmacokinetic properties of fast-acting insulin aspart between children, adolescents and adults with type 1 diabetes".
[723] Cf. EU Clinical Trials Register, Clinical trial results to the study "Tight glycaemic control" and the risk of hypoglycaemia: Is this different between multiple injections versus insulin pump therapy? A UK multi-centre, open randomised control trial".
[724] Cf. EU Clinical Trials Register, Clinical trial results to the study "a Trial Investigating the Pharmacokinetic Properties of NN5401 in Children, Adolescents and Adults with Type 1 Diabetes".

Aspart as Bolus Insulin Trial Phase: 3[725]			treatment in children and adolescents.		
Assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes : Phase 3 study[726]	Outside EU/ EEA (only USA)	Type 1 diabetes mellitus in children, adolescents, under 18	The purpose of this study was to assess how glucagon administered nasally, using a nasal dosing delivery device, works in children and adolescents compared with commercially-available glucagon given by injection.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 13 Jan 2015
A trial investigating the efficacy and safety of insulin degludec/insulin aspart (IDegAsp) once daily plus insulin aspart (IAsp) for the remaining meals versus insulin detemir (IDet) once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus[727]	CZ, SI, ES, BE, HR (also in Canada)	Type 1 diabetes mellitus in children, adolescents, under 18	To confirm the efficacy of insulin degludec/insulin aspart administered once daily plus meal-time insulin aspart for the remaining meals in controlling glycaemia with respect to change from baseline in HbA1c after 16 weeks of treatment. This is done by comparing the difference in change from baseline in HbA1c between insulin degludec/insulin aspart + meal-time insulin aspart for	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 07 Nov 2014

[725] Cf. EU Clinical Trials Register, Clinical trial results to the study “a 52-Week, Multinational, Multi-Centre, Open-Labelled Extension Trial of Insulin Detemir in Children and Adolescents 3-17 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin Trial Phase: 3”.
[726] Cf. EU Clinical Trials Register, Clinical trial results to the study “assessment of Intranasal Glucagon in Children and Adolescents with Type 1 Diabetes : Phase 3 study”.
[727] Cf. EU Clinical Trials Register, Clinical trial results to the study “a trial investigating the efficacy and safety of insulin degludec/insulin aspart (IDegAsp) once daily plus insulin aspart (IAsp) for the remaining meals versus insulin detemir (IDet) once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus”.

			the remaining meals and insulin detemir + meal-time insulin aspart to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.		
A Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10 – 17 years old) Subjects with Type 2 Diabetes[728]	UK, SI, BE	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the safety and tolerability of 0.3, 0.6, 0.9, 1.2 and 1.8 mg doses of liraglutide in the paediatric population (10 – 17 years of age).	-Safety, tolerability, and pharmacokinetic profiles was similar to profiles in adults.	Global end of trial date: 30 Sep 2011
A Comparative, Randomized, Open-Label, Multi-Center, Single Dose Pharmacokinetic, Pharmacodynamic and Safety Study of Alogliptin (12.5 mg and 25 mg) Between Children, Adolescents, and Adults with Type 2 (Non-Insulin Dependent) Diabetes Mellitus[729]	Outside EU/ EEA (only USA)	Type 2 diabetes mellitus, children, adolescents, under 18	The purpose of this study is to determine the pharmacokinetic and safety profile of alogliptin in children, adolescents, and adults with type 2 diabetes mellitus.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 22 Nov 2013

[728] Cf. EU Clinical Trials Register, Clinical trial results to the study “a Randomized, Double-blind, Placebo Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics & Pharmacodynamics of Liraglutide in Paediatric (10 – 17 years old) Subjects with Type 2 Diabetes”.
[729] Cf. EU Clinical Trials Register, Clinical trial results to the study “a Comparative, Randomized, Open-Label, Multi-Center, Single Dose Pharmacokinetic, Pharmacodynamic and Safety Study of Alogliptin (12.5 mg and 25 mg) Between Children, Adolescents, and Adults with Type 2 (Non-Insulin Dependent) Diabetes Mellitus”.

Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes[730]	GR (Completed) GB (Completed) HU (Completed) DE (Not Authorised) BE (Completed) ES (Completed) DK (Completed) NO (Completed) SE (Completed) PL (Completed) AT (Completed) FR (Completed) PT (Completed) NL (Prematurely	Type 2 diabetes mellitus, children, adolescents, under 18	To confirm the superiority of liraglutide at the maximum tolerated dose (0.6 mg, 1.2 mg or 1.8 mg) versus placebo when added to metformin with or without basal insulin treatment in controlling glycaemia in children and adolescents (ages 10–17 years) with type 2 diabetes.	Liraglutide was efficacious in improving glycemic control over 52 weeks. Efficacy came at the cost of an increased frequency of gastrointestinal adverse events. [731] "Compared with placebo, liraglutide was associated with statistically significant reductions in BMI/weight parameters at week 52, but not week 26, in children and adolescents with T2D."[732]	Global end of trial date 20 May 2020

[730] Cf. EU Clinical Trials Register, Clinical trial results to the study "Efficacy and safety of liraglutide in combination with metformin versus metformin monotherapy on glycaemic control in children and adolescents with type 2 diabetes".
[731] Cf. Tamborlane et al., Liraglutide in children and adolescents with type 2.
[732] Cf. Bensignor Megan O et al., Effect of liraglutide tretament on body max index and weight parameters in children and adolescents with type 2 diabetes: Post hoc analysis of ellipse trial.

	Ended) also in Canada				
Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥ 10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable Dose of Metformin[733]	Outside EU/ EEA (USA, Brazil)	Patients with type 2 diabetes mellitus (T2DM) on a stable dose of Metformin (receiving standard of care) Children, Adolescents, under 18	To evaluate the pharmacokinetics of canagliflozin after multiple oral doses of canagliflozin in children and adolescent subjects with type 2 diabetes mellitus (T2DM) who were more than or equal to (>=) 10 to less than (<) 18 years of age and on stable dose of metformin.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 01 Apr 2016
A Study to Assess the Pharmacokinetics and Ability for Pediatric Patients with Type 2 Diabetes to Swallow MK-0431A XR Tablets[734]	Outside EU/ EEA (USA)	Type 2 diabetes mellitus, children, adolescents, under 18	The purpose of this study is to assess: (1) The safety and tolerability of two sitagliptin 50 mg/metformin 1000 mg XR tablets in pediatric participants with type 2 diabetes mellitus (T2DM), aged 10 to 17 years (2) The ability of pediatric participants with T2DM, aged 10 to 17 years, to swallow two sitagliptin 50	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 29 Apr 2014

[733] Cf. EU Clinical Trials Register, Clinical trial results to the study “Open-Label, Multicenter, Multiple Oral Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Canagliflozin in Older Children and Adolescents ≥ 10 to <18 years of age with Type 2 Diabetes Mellitus and Currently on a Stable”.
[734] Cf. EU Clinical Trials Register, Clinical trial results to the study “A Study to Assess the Pharmacokinetics and Ability for Pediatric Patients with Type 2 Diabetes to Swallow MK-0431A XR Tablets”.

			mg/metformin 1000 mg XR tablets or two matching placebo tablets (excluding marking) (3) The pharmacokinetics of sitagliptin and metformin following the administration of two sitagliptin 50 mg/metformin 1000 mg XR tablets to pediatric participants with T2DM, aged 10 to 17 years.		
A randomised, double-blind, placebo-controlled, parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus.[735]	FR, PL, IT, Outside EU/ EEA (USA, Canada among others)	Type 2 diabetes mellitus, children, adolescents, under 18	A dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 11 Feb 2016
A 24-Week, Randomized, Open-Label, Parallel Group, Multicenter Comparison of Lantus® (Insulin Glargine) Given Once Daily Versus	Outside EU/ EEA (China)	Type 1 diabetes mellitus in children, adolescents, under 18	To assess the efficacy of insulin glargine given once daily (QD) on glycosylated hemoglobin (HbA1c) levels over a period of 24 weeks in	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 05 Mar 2014

[735] Cf. EU Clinical Trials Register, Clinical trial results to the study "A randomised, double-blind, placebo-controlled, parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus".

Neutral Protamine Hagedorn (NPH) Insulin in Children With Type 1 Diabetes Mellitus Aged At Least 6 Years to Less Than 18 Years[736]			children with type 1 diabetes mellitus (T1DM) aged at least 6 years to less than 18 years.		
A randomised controlled trial of continuous subcutaneous insulin infusion(CSII) compared to multiple daily injection(MDI) regimens on insulin in children and young people at diagnosis of type I diabetes mellitus (TIDM).[737]	GB	Type 1 diabetes mellitus in children, adolescents, under 18	To compare the control of the blood glucose levels, measured by glycosylated haemoglobin (HbA1c), at 12 months after diagnosis of type 1 diabetes mellitus in children and adolescents receiving infusion pumps with those receiving multiple daily injections.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 30 Jan 2017

[736] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 24-Week, Randomized, Open-Label, Parallel Group, Multicenter Comparison of Lantus® (Insulin Glargine) Given Once Daily Versus Neutral Protamine Hagedorn (NPH) Insulin in Children With Type 1 Diabetes Mellitus Aged At Least 6 Years to Less Than 18 Years".
[737] Cf. EU Clinical Trials Register, Clinical trial results to the study "A randomised controlled trial of continuous subcutaneous insulin infusion (CSII) compared to multiple daily injection (MDI) regimens on insulin in children and young people at diagnosis of type I diabetes mellitus (TIDM)."

A Multiple Center, Open Label, Prospective Study to Evaluate the Effectiveness and Ease-Of-Use of AMG504-1 (Glucagon) Administered in the Home or School Environments for Treating Hypoglycemia in Children and Adolescents with T1D[738]	Outside EU/ EEA	Type 1 diabetes mellitus in children, adolescents, under 18	To obtain treatment response and user-experience data following use of AMG504-1 (LY900018) in treating episodes of moderate or severe hypoglycemia.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 21 Aug 2015
A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin Neutral Protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral	HU (Prematurely Ended) IT (Prematurely Ended) DE (Completed) HR (Prematurely Ended) GR (Prematurely Ended) ES (Prematurely Ended) PT	Type 2 diabetes mellitus, children, adolescents, under 18	To compare the efficacy of insulin detemir in combination with metformin and diet/exercise versus insulin neutral protamine hagedorn (NPH) in combination with the maximum tolerated dose (MTD) of metformin and diet/exercise in controlling glycaemia, after 26 weeks of treatment, in children and adolescents (aged 10–17 years) with type 2 diabetes, who are insufficiently treated with the MTD of metformin ± other OAD(s) ± basal insulin.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 14 Jun 2016

[738] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Multiple Center, Open Label, Prospective Study to Evaluate the Effectiveness and Ease-Of-Use of AMG504-1 (Glucagon) Administered in the Home or School Environments for Treating Hypoglycemia in Children and Adolescents with T1D".

antidiabetic drug(s) ± basal insulin[739]	(Prematurely Ended)				
A Double-Blind, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus[740]	DE (Completed) HU (Completed) FR (Completed) SK (Completed)	Type 1 diabetes mellitus in children, adolescents, under 18, elderly	No information available	Information on the righ site --> no further information available	Global completion date 07 Dec 2011

[739] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 26-week open label, randomised, 2-armed, parallel group, multi-centre trial investigating efficacy and safety of insulin detemir versus insulin Neutral Protamine Hagedorn in combination with the maximum tolerated dose of metformin and diet/exercise on glycaemic control in children and adolescents with type 2 diabetes insufficiently controlled on the maximum tolerated dose of metformin ± other oral antidiabetic drug(s) ± basal insulin".
[740] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Double-Blind, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus".

A 26-week, Multinational, Multi-centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Degludec and Insulin Detemir in children and adolescents 1 to less than 18 years with type 1 Diabetes Mellitus on a basal-bolus regimen with insulin aspart as bolus insulin followed by a 26-week extension investigating long term safety.[741]	NL (Completed) FI (Completed) DE (Completed) BG (Completed) GB (Completed) IT (Completed) also in Japan	Type 1 diabetes mellitus in children, adolescents, under 18	To confirm the efficacy of insulin degludec (IDeg) administered once daily plus mealtime insulin aspart in controlling glycaemia with respect to change from baseline in HBA1c after 26 weeks of treatment. This is done by comparing the difference in change in HbA1c between insulin degludec (IDeg) + insulin aspart (IAsp) and insulin detemir (IDet) + insulin aspart(IAsp) to a non-inferiority limit of 0.4%, and if non-inferiority is confirmed, to a superiority limit of 0%.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 30 Jul 2013

[741] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 26-week, Multinational, Multi-centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Degludec and Insulin Detemir in children and adolescents 1 to less than 18 years with type 1 Diabetes Mellitus on a basal-bolus regimen with insulin aspart as bolus insulin followed by a 26-week extension investigating long term safety."

A 24-week, randomized, open-label, parallel group multinational comparison of Lantus® (insulin glargine) given in the morning as once-a-day basal insulin versus Neutral Protamine Hagedorn (NPH) insulin, in children with type 1 diabetes mellitus aged at least 1 year to less than 6 years[742]	HU (Completed) CZ (Completed) ES (Completed) DE (Completed) AT (Completed) Outside EU/EEA	Type 1 diabetes mellitus, aged at least 1 year to less than 6 years	To compare the rate of all hypoglycemia between children treated with Lantus (insulin glargine) and Neutral Protamine Hagedorn (NPH) insulin.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 30 Mar 2011
A 52-Week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus-Regimen with Insulin[743] Aspart as Bolus Insulin[744]	HU (Completed) FI (Completed) CZ (Completed) DK (Completed) BG (Completed) FR (Completed)	Type 1 diabetes mellitus, children, adolescents, under 18	To compare the glycaemic control, measured as HbA1c, of insulin detemir administered once or twice daily plus mealtime insulin aspart with NPH insulin administered once or twice daily plus mealtime insulin aspart in children and adolescents with type 1 diabetes.	No formal statistical analyses have been made between two treatment groups due to the low number of subjects. In conclusion, the present study indicates that Idet is as safe and efficacious as NPH for the treatment of 2–5-yr-old children with T1DM. Children treated with IDet appeared to have less hypoglycaemia, less undesirable weight gain, and fewer AEs than children treated with NPH.[745]	Global end of trial date 03 Sep 2008

[742] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 24-week, randomized, open-label, parallel group multinational comparison of Lantus® (insulin glargine) given in the morning as once-a-day basal insulin versus Neutral Protamine Hagedorn (NPH) insulin, in children with type 1 diabetes mellitus aged at least 1 year to less than 6 years".
[743] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 52-Week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin".
[744] Cf. EU Clinical Trials Register, Clinical trial results to the study "A 52-Week, Multinational, Multi-Centre, Open-Labelled, Randomised, Parallel, Efficacy and Safety Comparison of Insulin Detemir and NPH Insulin in Children and Adolescents 2-16 years with Type 1 Diabetes on a Basal-Bolus Regimen with Insulin Aspart as Bolus Insulin".
[745] Cf. Thalange, Nandu et al, Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus.

6-Month, Multicenter, Randomized, Open-label, 2-Arm, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected Once Daily in Children and Adolescents age 6 – 17 Years with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period[746]	GB (Completed) HU (Completed) LV (Completed) IT (Completed) DE (Completed) CZ (Completed) FR (Completed) ES (Completed) PL (Completed) SE (Completed) DK (Completed) BG (Completed) Outside EU/EEA (also Canada and Japan)	Type 1 diabetes mellitus, children, adolescents, under 18	To compare the efficacy of a new formulation of insulin glargine (HOE901-U300) to Lantus in terms of change of HbA1c from baseline to endpoint (month 6) in children and adolescents with type 1 diabetes mellitus.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 20 Dec 2018

[746] Cf. EU Clinical Trials Register, Clinical trial results to the study "6-Month, Multicenter, Randomized, Open-label, 2-Arm, Parallel-group Study Comparing the Efficacy and Safety of a New Formulation of Insulin Glargine and Lantus® Injected Once Daily in Children and Adolescents age 6 – 17 Years with Type 1 Diabetes Mellitus with a 6-month Safety Extension Period".

A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR A Pooled Analysis of the Safety and Efficacy of MK-0431A (Sitagliptin/ Metformin) and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin).[747]	CZ (Completed) IT (Completed) HU (Completed) DK (Completed) BG (Prematurely Ended) Outside EU/EEA GR (Completed) (also Canada)	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the effect of the addition of sitagliptin relative to the addition of placebo on glycated hemoglobin (A1C), and the safety and tolerability of the addition of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus with inadequate glycemic control on metformin therapy (alone or in combination with insulin).	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 17 Sep 2019
Randomized, Double-blind, Placebo-controlled, Dose escalation, Study on Safety, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Pediatric Patients with Type 2 Diabetes Mellitus not Adequately Controlled With Metformin and/or Basal Insulin[748]	ES, Outside EU/ EEA	Pediatric Patients with Type 2 Diabetes Mellitus Not Adequately Controlled with Metformin and/or Basal Insulin	To demonstrate safety of 14-day repeated lixisenatide doses of 5 microgram [mcg], 10 mcg and 20 mcg as compared to placebo in paediatric subjects with Type 2 diabetes mellitus (T2DM).	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 27 Jan 2020

[747] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A XR A Pooled Analysis of the Safety and Efficacy of MK-0431A (Sitagliptin/ Metformin) and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin)".

[748] Cf. EU Clinical Trials Register, Clinical trial results to the study "Randomized, Double-blind, Placebo-controlled, Dose escalation, Study on Safety, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Pediatric Patients with Type 2 Diabetes Mellitus not Adequately Controlled With Metformin and/or Basal Insulin".

Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes[749]	BG (Completed) CZ (Completed) EE (Completed) DE (Completed) LV (Completed) LT (Completed) FI (Completed) PL (Completed) Also Canada and Japan	Type 1 diabetes mellitus, infants and toddlers, children, adolescents, under 18	To confirm the effect of treatment with meal-time faster-acting insulin aspart in terms of glycaemic control by comparing it to meal-time NovoRapid® both in combination with insulin degludec using a non-inferiority approach in children and adolescents with type 1 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 03 Mar 2018
Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes[750]	Outside EU/ EEA	Type 2 diabetes mellitus, children, adolescents, under 18	To test the hypothesis that glycemic control, as measured by change in glycated hemoglobin A1c (HbA1c) from baseline to endpoint, with exenatide 5 microgram (mcg) twice daily or 10 mcg twice daily is superior to that of placebo, after 28 weeks of treatment in adolescent participants with type 2 diabetes who are naïve to antidiabetes agents, or participants who were	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 01 Apr 2020

[749] Cf. EU Clinical Trials Register, Clinical trial results to the study “Efficacy and Safety of Faster-acting Insulin Aspart compared to NovoRapid® both in Combination with Insulin Degludec in Children and Adolescents with Type 1 Diabetes”.
[750] Cf. EU Clinical Trials Register, Clinical trial results to the study “Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes”.

			treated with metformin, an sulfonylurea (SU), or a combination of metformin and an SU.		
A Randomized, Double-Blind, Placebo Controlled Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Paediatric (10 – 17 Years Old) and Adult Patients With Type 2 Diabetes[751]	DE, UK, Outside EU/ EEA	Type 2 diabetes mellitus, children, adolescents, under 18	To investigate the effects of a single subcutaneous lixisenatide dose of 5 microgram (mcg) and 10 mcg as compared to placebo in reducing postprandial plasma glucose (PPG) assessed as area under the plasma glucose concentration curve after a standardized liquid meal (breakfast) in type 2 diabetic paediatric population (10 to 17 years old) and adults as controls.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 04 Mar 2014

[751] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Randomized, Double-Blind, Placebo Controlled Trial to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Lixisenatide in Paediatric (10 – 17 Years Old) and Adult Patients With Type 2 Diabetes".

A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control[752]	LV (Completed) LT (Completed) DE (Completed) ES (Prematurely Ended) IT (Completed) BG (Completed) AT (Completed) DK (Completed) SE (Completed) HU (Completed) PL (Completed) SK (Completed) Outside EU/EEA GR (Completed) FR (Completed) Also Canada	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the effect of treatment with sitagliptin compared with placebo on glycated hemoglobin (A1C), and the safety and tolerability of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus with inadequate glycemic control. The primary hypothesis for this study was that sitagliptin reduces A1C more than placebo after 20 weeks of treatment. Amendment 5 of the protocol removed 2 arms from the study (Metformin arm and the Placebo followed by Sitagliptin arm). Participants already in these 2 arms continued in the study. EUPASS4468 is a follow-up, observational assessment of safety of participants who participated in the MK-0431-083 study for up to 5 years.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 09 Oct 2019

[752] Cf. EU Clinical Trials, Clinical trial results to the study “A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Sitagliptin in Pediatric Patients with Type 2 Diabetes Mellitus with Inadequate Glycemic Control”.

A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin IR or metformin XR in pediatric patients with type 2 diabetes who have inadequate glycemic control on metformin alone[753]	BE (Completed) Outside EU/EEA GB (Completed) IT (Prematurely Ended)	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the safety and tolerability of saxagliptin as add on to metformin therapy in pediatric subjects aged 10 to < 18 years when administered for up to 16 weeks of short term therapy and 52 weeks of total therapy.	No statistical analysis has been performed for this end point due to a small number of subjects in the study. Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 22 Apr 2016
A 24 Week Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years[754]	GB (Completed) HU (Completed)	Type 2 diabetes mellitus, children, adolescents, under 18, adults	To compare the mean change from baseline in glycated haemoglobin (HbA1c) achieved with dapagliflozin against the mean achieved with placebo after 24 weeks of double-blind add-on treatment in participants aged 10 to less than 25 years with type 2 diabetes mellitus who have inadequate glycaemic control on diet and exercise with metformin or insulin ± metformin.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 06 Apr 2020

[753] Cf. EU Clinical Trials Register, Clinical trial results to the study “A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin IR or metformin XR in pediatric patients with type 2 diabetes who have inadequate glycemic control on metformin alone”.
[754] Cf. EU Clinical Trials Register, Clinical trial results to the study “A 24 Week Multicentre, Randomised, Double-Blind, Parallel Group, Phase 3 Trial with a 28 Week Long Term Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 10 mg in T2DM Patients Aged 10-24 Years”.

MK-0431A (Metformin plus Sitagliptin) Protocol 170-04: "A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy MK-0431A A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin).[755]	LV (Completed) LT (Prematurely Ended) GB (Completed) IT (Completed) DE (Completed) BG (Prematurely Ended) Also Canada and Australia	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to the addition of placebo on glycated hemoglobin (A1C), and the safety and tolerability of the addition of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus with inadequate glycemic control on metformin therapy (alone or in combination with insulin).	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 17 Sep 2019
A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin (BMS-477118) as monotherapy in pediatric	BE, Outside EU/ EEA	Diabetes mellitus type 2, children, adolescents, under 18	To assess the safety and tolerability of saxagliptin monotherapy in pediatric subjects aged 10 to < 18 years when administered for up to 16 weeks of short-term therapy and 52 weeks of total therapy.	No statistical analysis has been performed for this end point due to a small number of subjects in the study. Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data."	Global end of trial date 22 Apr 2016

[755] Cf. EU Clinical Trials Register, Clinical trial results to the study "MK-0431A (Metformin plus Sitagliptin) Protocol 170-04: "A Phase III, Multicenter, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy MK-0431A A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin)."

patients with Type 2 diabetes.[756]					
A Phase III, Multicenter, Double-Blind, Randomized, Placebo -Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin).[757]	DE, UK also Canada and Australia	Type 2 diabetes mellitus	To assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to the addition of placebo on glycated hemoglobin (A1C), and the safety and tolerability of the addition of sitagliptin, in pediatric participants (ages 10-17 years) with type 2 diabetes mellitus with inadequate glycemic control on metformin therapy (alone or in combination with insulin).	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 17 Sep 2019

[756] Cf. EU Clinical Trials Register, Clinical trial results to the study "A multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin (BMS-477118) as monotherapy in pediatric patients with Type 2 diabetes".
[757] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Phase III, Multicenter, Double-Blind, Randomized, Placebo -Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-0431A A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Patients with Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination with Insulin)."

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-PEDS[758]	DK (Completed) CZ (Completed) DE (Completed) FR (Completed) GB (GB – no longer in EU/EEA) AT (Completed) ES (Ongoing) PL (Ongoing) IT (Ongoing)	Diabetes mellitus type 1, infants, toddlers, children, adolescents, under 18	To compare the study drug LY900014 to insulin lispro (Humalog) in children and adolescents with type 1 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 02 Jul 2021
A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 (Insulin lispro) Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus[759]	DE, Also Canada	Diabetes Mellitus, Type 1, Children, adolescents, under 18, adults	To compare LY900014 with insulin lispro (Humalog) in participants with type 1 diabetes mellitus. There are 2 parts to this study. Part A is investigating how the body processes LY900014 and the effect of LY900014 on blood sugar levels compared to insulin lispro (Humalog) when study treatment is given by	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 14 Nov 2019

[758] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-PEDS".
[759] Cf. EU Clinical Trials Register, Clinical trial results to the study "A Study to Evaluate the Pharmacokinetics and Glucodynamics of LY900014 (Insulin lispro) Compared to Humalog in Children, Adolescents, and Adults with Type 1 Diabetes Mellitus".

			subcutaneous injection. Part B of the study is investigating how the body processes LY900014 and the effect of LY900014 on blood sugar levels compared to insulin lispro (Humalog) when study treatment is given by continuous subcutaneous insulin infusion (CSII) pump. Screening is required within 28 days prior to the start of the study. For each participant, the study will last about 40 days in each part.		
An Open-Label, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus[760]	Outside EU/ EEA (Only USA)	Type 1 diabetes mellitus, adolescents, under 18, adults, elderly	To provide information on the use of insulin lispro in insulin pumps compared to insulin aspart over 6 days of pump reservoir in-use. The study will also compare the in-use characteristics of insulin lispro infused at 6 days with insulin lispro infused at 2 days.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 10 Aug 2011

[760] Cf. EU Clinical Trials Register, Clinical trial results to the study “An Open-Label, Randomized, Crossover Trial of CSII Reservoir In-use Comparing Insulin Lispro Formulation to Insulin Aspart in Patients with Type 1 Diabetes Mellitus”.

A Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Sitagliptin in Adolescents[761]	Outside EU/ EEA (only USA)	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the safety, tolerability and pharmacokinetics of sitagliptin in 10 to 17 year old participants with type 2 diabetes.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 14 Feb 2011
A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes[762]	HU, BG	Type 2 diabetes mellitus, children, adolescents, under 18	To assess the effect on glycemic control, as measured by glycosylated hemoglobin (HbA1c), of exenatide once weekly following 24 weeks of treatment compared with placebo in children and adolescents with type 2 diabetes mellitus.	Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Global end of trial date 05 May 2021

[761] Cf. EU Clinical Trials Register, Clinical trial results to the study “A Single-Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of Sitagliptin in Adolescent”.
[762] Cf. EU Clinical Trials Register, Clinical trial results to the study “A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes”.

Annex 7: Clinical trials with Metformin conducted in Canada

Title	Information	Age	Study type	Location	Results	Status
A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination With Metformin IR or Metformin XR in Pediatric Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone[763] [764]	To evaluate the efficacy, safety, tolerability, of Saxagliptin (BMS-477118) in combination with Metformin in pediatric patients with type 2 diabetes Metformin IR, Metformin XR, Saxagliptin	10-17 years	Phase 3, interventional study	USA, Belgium, **Canada**, India, Mexico, Taiwan, UK	EudraCT: Only 6 participants →Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.	Completed
A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Participants With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination With Insulin)	To assess the effect of the addition of sitagliptin (administered as MK-0431A or MK-0431A XR) relative to the addition of placebo on glycated hemoglobin (A1C), and the safety and tolerability of the addition of sitagliptin, in pediatric participants (ages 10-17	10-17 years	Phase 3, interventional study	28 countries, among them **Canada**, EU, USA, Australia	Results: it showed that addition of sitagliptin to metformin is not an improvement in glycemic control in youth with T2D. But the study showed that sitagliptin is well tolerated in children, safety profile is similar to that reported in adults.	Completed

[763] Cf. EU Clinical Trials Register, A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination With Metformin IR or Metformin XR in Pediatric Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.
[764] Cf. U.S. National Library of Medicine, A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination With Metformin IR or Metformin XR in Pediatric Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone.

(MK-0431A-170/MK-0431A-289)[765]	years) with type 2 diabetes mellitus with inadequate glycemic control on metformin therapy (alone or in combination with insulin).					
Activity and Metformin Intervention in Obese Adolescents (REACH)[766] [767]	To assess the sustainability of a two-year intervention aimed at improving body mass index (BMI) and metabolic and vascular health in obese youth. The study will compare lifestyle changes with diet and exercise alone with changes in lifestyle in combination with metformin medication. An initial intensive exercise program will also be compared with a standard exercise program. Metformin, Placebo, Intensive exercises	10-16 years	Phase 4, interventional study	**Canada**	Results: success in arresting the rise in BMI *z*-score and percent body fat in obese adolescents, independent of initial exercise intensity.	Completed

[765] Cf. U.S. National Library of Medicine, A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Participants With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination With Insulin) (MK-0431A-170/MK-0431A-289).
[766] Cf. U.S. National Library of Medicine, Activity and Metformin Intervention in Obese Adolescents (REACH).
[767] Cf. Van Rongen, Anne et al., Increased Metformin Clearance in Overweight and Obese Adolescents: A Pharmacokinetic Substudy of a Randomized Controlled Trial.

Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™)[768] [769] [770]	The aim of this trial is to assess the efficacy and safety of liraglutide in the paediatric population in order to potentially address the unmet need for treatment of children and adolescents with type 2 diabetes.	10-17 years	Phase 3, interventional study	185 locations, among them USA, **Canada**, EU	Results: inprovement in glycemic control. But increasing in frequency of gastrointestinal adverse events.	Completed

[768] Cf. U.S. National Library of Medicine, Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™).
[769] Cf. EU Clinical Trials Register, Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™).
[770] Cf. Tamborlane, Wilhelm V et al., Liraglutide in Children and Adolescents with Type 2 Diabetes.

Annex 8: overview of numbers of studies which are conducted in Canada

Canada	
Keywords	**Results (Status 2021-12-31)**
Condition or disease: diabetes mellitus Country: Canada	1217 studies, 814 of them are completed. (Since 01/01/2008: 960, 614 of them are completed)
Condition or disease: diabetes mellitus Country: Canada Age: Child	171 studies, 101 of them are completed. (Since 01/01/2008: 139, 73 of them are completed)
Condition or disease: diabetes mellitus Country: Canada Age: >18 years of age	1189 studies, 789 of them are completed. (Since 01/01/2008: 937, 592 of them are completed)
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study	1061 studies, 739 of them are completed. (Since 01/01/2008: 819, 545 of them are completed)
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study Age: Child	111 studies, 77 of them are completed, six are terminated, 11 are in recruiting status, two of them are withdrawn. (since 01/01/2008: 81, 50 of them are completed)
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study Age: >18 years of age	1038 studies, 721 of them are completed. (Since 01/01/2008: 801, 526 are completed)

Table No. 17: overview of numbers of studies conducted in Canada, status 31.12.2021 (own representation based on data from clinicaltrials.gov).

Annex 9: overview of numbers of studies which are conducted in Japan

Japan	
Keywords	**Results (2021-12-31)**
Condition or disease: diabetes mellitus Country: Japan	465 studies, 259 of them are completed. (Since 01/01/2008: 359, 168 of them are completed)
Condition or disease: diabetes mellitus Country: Japan Age: Child (<18 years of age)	50 studies, 20 of them are completed.

Japan	
Keywords	**Results (2021-12-31)**
	(Since 01/01/2008: 38, 13 of them are completed)
Condition or disease: diabetes mellitus Country: Japan Age: >18 years of age	460 studies, 254 of them are completed. (Since 01/01/2008: 355, 164 of them are completed)
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study	402 studies, 247 of them are completed. (Since 01/01/2008: 309, 157 of them are completed)
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study Age: Child	13 studies, 11 of them are completed, one is terminated, and one has an unknown status. (Since 01/01/2008: 7, 6 completed)
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study Age: >18 years of age	399 studies, 334 of them are completed. (Since 01/01/2008: 305, 256 completed)

Table No. 18: overview of numbers of studies conducted in Japan, status 31.12.2021 (own representation based on data from clinicaltrials.gov).

Annex: 10: overview of numbers of studies conducted in Australia

Australia	
Keywords	**Studies (2021-12-31)**
Conditions or diseases: diabetes mellitus Country: Australia	351 studies, 259 of them are completed. (Since 01/01/2008: 242 studies, 168 of them are completed)
Conditions or diseases: diabetes mellitus Country: Australia Age: Child	32 studies, 20 of them are completed. (Since 01/01/2008: 23 studies, 13 of them are completed)
Conditions or diseases: diabetes mellitus Country: Australia Age: >18 years of age	347 studies, 254 of them are completed. (Since 01/01/2008: 239 studies, 164 of them are completed)
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study	330 studies, 247 of them are completed. (Since 01/01/2008: 225 studies, 157 of them are completed)

Australia	
Keywords	**Studies (2021-12-31)**
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study Age: Child	22 studies, 16 of them are completed, 5 have a recruiting status. (Since 01/01/2008: 15 studies, 9 are completed)
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study Age: >18 years of age	327 studies, 243 of them are completed. (Since 01/01/2008: 223 studies, 154 are completed)

Table No. 19: overview of number of studies conducted in Australia, status 31.12.2021 (own representation based on data from clinicaltrials.gov).

Annex 11: overview of number of studies conducted in the EU

EU	
Keywords	**Studies (Status 2021-12-31)**
Conditions or diseases: diabetes mellitus Country: Europe*	5098 studies, 3435 of them are completed. (Since 01/01/2008: 4217 studies, 2704 of them are completed)
Conditions or diseases: diabetes mellitus Country: Europe* Age: Child	586 studies, 375 of them are completed. (Since 01/01/2008: 490 studies, 295 of them are completed)
Conditions or diseases: diabetes mellitus Country: Europe* Age: >18 years of age	4970 studies, 3364 of them are completed. (Since 01/01/2008: 4108 studies, 2646 of them are completed)
Conditions or diseases: diabetes mellitus Country: Europe* Study type: interventional study	4034 studies, 2825 of them are completed. (Since 01/01/2008: 3283 studies, 2193 of them are completed)
Conditions or diseases: diabetes mellitus Country: Europe* Study type: interventional study Age: Child	359 studies, 228 of them are completed. (Since 01/01/2008: 302 studies, 180 are completed)
Conditions or diseases: diabetes mellitus Country: Europe* Study type: interventional study Age: >18 years of age	3931 studies, 2765 of them are completed. (Since 01/01/2008: 3198 studies, 2146 are completed)

Table No. 20: overview of number of studies conducted in the EU, status 31.12.2021 (own representation based on data from clinical trials.gov).

*****Albania, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, United Kingdom.

Annex 12: EU and EudraCT results

Keywords	**Europe Results (Status 2021-12-31)**
Condition: diabetes mellitus (since 2008-01-01)	1682 Outside EU/EEA: 34
Condition: diabetes mellitus (since 2008-01-01) **Status: completed**	1092 Outside EU/EEA: 12
Condition: diabetes mellitus (since 2008-01-01) **Age Range: > 18 years (adults)**	1580 Outside EU/EEA: 10
Condition: diabetes mellitus (since 2008-01-01) Status: completed **Age Range: > 18 years**	1032 Outside EU/EEA: 2
Condition: diabetes mellitus (since 2008-01-01) **Age Range: under 18 years**	140 Outside EU/EEA: 33
Condition: diabetes mellitus (since 2008-01-01) **Age Range: under 18 years** **Status: completed**	74 Outside EU/EEA: 12

Table No. 21: overview of numbers of studies conducted in the EU, status 31.12.2021 (own representation based on data from EudraCT).

Annex 13: overview of numbers of studies for antidiabetics conducted in Australia

Clinicaltrials.gov		**ANZCTR**	
Keywords	**Studies (12/2021)**	**Keywords**	**Studies (12/2021)**
Conditions or diseases: diabetes mellitus Country: Australia	351 studies (Since 01/01/2008: **242 studies**)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine Condition code: diabetes	192 studies since 01/01/2008, 73 of them are completed.

Clinicaltrials.gov		ANZCTR	
Keywords	**Studies (12/2021)**	**Keywords**	**Studies (12/2021)**
		Countries of recruitment: Australia	
Conditions or diseases: diabetes mellitus Country: Australia Age: child	32 studies (Since 01/01/2008: **23 studies**)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine, Condition code: diabetes Countries of recruitment: Australia **Age group: child (>18 years)**	7 studies since 01/01/2008, 7 of them are completed.
Conditions or diseases: diabetes mellitus Country: Australia Age: >18 years of age	347 studies (Since 01/01/2008: **239 studies**)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine, Condition code: diabetes Countries of recruitment: Australia **Age group: >18 years**	175 studies since 01/01/2008, 63 of them are completed.
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study	330 studies (Since 01/01/2008: **225 studies**)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine, Condition code: diabetes Countries of recruitment: Australia Study type: **interventional study**	192 studies since 01/01/2008, 73 of them are completed.
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study Age: child	22 studies, 16 of them are completed, 5 have a recruiting status. (Since 01/01/2008: **15 studies**, 9 are completed)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine, Condition code: diabetes Countries of recruitment: Australia	7 studies since 01/01/2008, 7 of them are completed.

Clinicaltrials.gov		ANZCTR	
Keywords	**Studies (12/2021)**	**Keywords**	**Studies (12/2021)**
		Study type: **interventional study** **Age: child**	
Conditions or diseases: diabetes mellitus Country: Australia Study type: interventional study Age: >18 years of age	327 studies, 243 of them are completed. (Since 01/01/2008: **223 studies**, 154 are completed)	Registry: ANZCTR Intervention code: Treatment: drugs Condition category: Metabolic and Endocrine, Condition code: diabetes Countries of recruitment: Australia Study type: **interventional study** **Age: >18 years**	175 studies since 01/01/2008, 63 of them are completed.

Table No. 22: clinical trials conducted in Australia, status 31.12.2021 (own representation based on data from clinicaltrials.gov and ANZCTR).[771] [772]

Annex 14: overview of numbers of studies for antidiabetics conducted in Canada

Clinicaltrials.gov		Health Canada clinical trial database	
Keywords	**Studies (12/2021)**	**Keywords**	**Studies (12/2021)**
Condition or disease: diabetes mellitus Country: Canada	1217 studies (Since 01/01/2008: 960)	Only contains CTs for phase I-III	-
Condition or disease: diabetes mellitus Country: Canada Age: child	171 studies (Since 01/01/2008: 139)	"-"	-
Condition or disease: diabetes mellitus Country: Canada Age: >18 years of age	1189 studies (Since 01/01/2008: 937)	"-"	-
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study	1061 studies (Since 01/01/2008: 819 studies)	Medical condition: diabetes	191 studies since 01/01/2008, Closed: 71

[771] Cf. U.S. National Library of Medicine, ClinicalTrials.gov.
[772] Cf. ANZCTR- Australian New Zealand Clinical Trials Registry.

Clinicaltrials.gov		Health Canada clinical trial database	
Keywords	**Studies (12/2021)**	**Keywords**	**Studies (12/2021)**
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study Age: child	111 studies, 77 of them are completed, six are terminated, 11 are in recruiting status, two are withdrawn **(Since 01/01/2008: 81, 50 of them are completed)**	Medical condition: diabetes Study population: paediatric	**21 studies since 01/01/2018,** **Closed: 6**
Condition or disease: diabetes mellitus Country: Canada Study type: interventional study Age: >18 years of age	1038 studies, 721 of them are completed (Since 01/01/2008: 801, 526 are completed)	Medical condition: diabetes Study population: Female/male adults	156/ 155 studies since 01/01/2008, Closed: 68/ 67

Table No. 23: clinical trials conducted in Canada, 31.12.2021 (own representation based on data from clinicaltrials.gov and database of Health Canada).[773] [774]

Annex 15: overview of numbers of studies for antidiabetics conducted in Japan

Clinicaltrials.gov	
Keywords	**Results (12/2021)**
Condition or disease: diabetes mellitus Country: Japan	465 studies (Since 01/01/2008: 359)
Condition or disease: diabetes mellitus Country: Japan Age: child	50 studies (Since 01/01/2008: 38)
Condition or disease: diabetes mellitus Country: Japan Age: >18 years of age	460 studies (Since 01/01/2008: 355)
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study	402 studies (Since 01/01/2008: 309, completed: 260)
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study Age: child	13 studies, completed: 11 **(Since 01/01/2008: 7, completed: 6)**

[773] Cf. U.S. National Library of Medicine, ClinicalTrials.gov.
[774] Cf. Health Canada, Health Canada's Clinical Trials Database - Canada.ca.

Clinicaltrials.gov	
Keywords	**Results (12/2021)**
Condition or disease: diabetes mellitus Country: Japan Study type: interventional study Age: >18 years of age	399 studies, completed: 334 (Since 01/01/2008: 305, completed: 256)

Table No. 24: clinical trials conducted in Japan, status 31.12.2021 (own representation based on data from clinicaltrials.gov).[775]

Annex 16: comparison of type 1 and type 2 in the different countries acc. clinicaltrials.gov

	Number of studies				
Keywords	**EU**	**USA**	**Canada**	**Australia**	**Japan**
Condition: **DM type 1** Study type: interventional studies Study start: 01/01/2008	877	963	204	41	58
Condition: **DM type 1** Study type: interventional studies Study start: 01/01/2008 **Status: completed**	621	646	132	30	55
Condition: **DM type 1** Study type:interventional studies Study start: 01/01/2008 **Age: adults (>18 years)**	817	853	188	39	54
Condition: **DM type 1** Study type: interventional studies Study start: 01/01/2008 **Age: adults (>18 years)**	588	567	121	28	51

[775] Cf. U.S. National Library of Medicine, ClinicalTrials.gov.

	Number of studies				
Keywords	**EU**	**USA**	**Canada**	**Australia**	**Japan**
Status: completed					
Condition: **DM type 1** Study type: interventional studies Study start: 01/01/2008 **Age: child (0-17 years)**	201	332	56	10	4
Condition: **DM type 1** Study type: interventional studies Study start: 01/01/2008 **Age: child (0-17 years)** **Status: completed**	120	218	37	6	4
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008	1737	2038	464	166	247
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008 **Status: completed**	1224	1395	341	121	207
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008	1714	1991	456	164	246

	Number of studies				
Keywords	**EU**	**USA**	**Canada**	**Australia**	**Japan**
Age: adults (>18 years)					
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008 **Age: adults (>18 years)** **Status: completed**	1210	1363	335	120	206
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008 **Age: child (0-17 years)**	162	160	39	9	2
Condition: **DM type 2** Study type: interventional studies Study start: 01/01/2008 **Age: child (0-17 years)** **Status: completed**	46	72	12	5	0

Table No. 25: overview of numbers of clinical studies in the different countries, status 31.12.2021 (own representation based on data from clinicaltrials.gov).

Annex 17: Comparison type 1 and type 2 in EU acc. EudraCT

Keywords	**Study results of the EU (Status 2021-12-31)**
Condition: diabetes mellitus Since 2008-01-01	1682 Outside EU/EEA: 34

Keywords	**Study results of the EU (Status 2021-12-31)**
Condition: diabetes mellitus Since 2008-01-01 **Status: completed**	1092 Outside EU/EEA: 12
Condition: diabetes mellitus Since 2008-01-01 **Age Range: > 18 years (adults)**	1580 Outside EU/EEA: 10
Condition: diabetes mellitus Since 2008-01-01 Status: completed **Age Range: > 18 years**	1032 Outside EU/EEA: 2
Condition: diabetes mellitus Since 2008-01-01 **Age Range: under 18 years**	140 Outside EU/EEA: 33
Condition: diabetes mellitus Since 2008-01-01 **Age Range: under 18 years** **Status: completed**	74 Outside EU/EEA: 12
Condition: diabetes mellitus type 1 Since 2008-01-01	1354 Outside EU/EEA: 29
Condition: diabetes mellitus type 1 Since 2008-01-01 **Status: completed**	1090 Outside EU/EEA: 10
Condition: diabetes mellitus type 1 Since 2008-01-01 **Age Range: under 18 years**	118 Outside EU/EEA: 28
Condition: diabetes mellitus type 1 Since 2008-01-01 **Age Range: under 18 years** **Status: completed**	64 Outside EU/EEA: 10

Keywords	Study results of the EU (Status 2021-12-31)
Condition: diabetes mellitus type 2 Since 2008-01-01	1390 Outside EU/EEA: 28
Condition: diabetes mellitus type 2 Since 2008-01-01 **Status: completed**	919 Outside EU/EEA: 10
Condition: diabetes mellitus type 2 Since 2008-01-01 **Age Range: under 18 years**	111 Outside EU/EEA: 27
Condition: diabetes mellitus type 2 Since 2008-01-01 **Age Range: under 18 years** **Status: completed**	60 Outside EU/EEA: 10

Table No. 26: overview of numbers of clinical trials for type 1 and type 2 in the EU since 2008, status 31.12.2021 (own representation based on data from EudraCT).

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- A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Saxagliptin (BMS-477118) in Combination With Metformin IR or Metformin XR in Pediatric Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control on Metformin Alone, U.S. National Library of Medicine, <https://clinicaltrials.gov/ct2/show/NCT01434186?term=Metformin&recrs=e&age=0&strd_s=01%2F01%2F2008&draw=2&rank=7> (06.04.2022)
- A Pooled Analysis of the Safety and Efficacy of MK-0431A and MK-0431A XR in Pediatric Participants With Type 2 Diabetes Mellitus With Inadequate Glycemic Control on Metformin Therapy (Alone or in Combination With Insulin) (MK-0431A-170/MK-0431A-289), U.S. National Library of Medicine, <https://clinicaltrials.gov/ct2/show/NCT01760447?term=Metformin&recrs=e&age=0&strd_s=01%2F01%2F2008&draw=2&rank=10> (06.04.2022)
- Activity and Metformin Intervention in Obese Adolescents (REACH), U.S. National Library of Medicine, <https://clinicaltrials.gov/ct2/show/NCT00934570?term=Metformin&recrs=e&age=0&strd_s=01%2F01%2F2008&draw=2&rank=11> (06.04.2022)
- Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes (Ellipse™), EU Clinical Trials Register, <https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-002605-29/results> (06.04.2022)
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- Increased Metformin Clearance in Overweight and Obese Adolescents: A Pharmacokinetic Substudy of a Randomized Controlled Trial, Van Rongen, Anne et al., <https://pubmed.ncbi.nlm.nih.gov/29748932/> (04.06.2022)
- Liraglutide in Children and Adolescents with Type 2 Diabetes, Tamborlane, Wilhelm V et al, <https://pubmed.ncbi.nlm.nih.gov/31034184/> (04.06.2022)

Declaration of Originality

I confirm that the submitted thesis is original work and was written by me without further assistance. Appropriate credit has been given where reference has been made to the work of others.

The thesis was not examined before, nor has it been published. The submitted electronic version of the thesis matches the printed version.

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