ARTICLE 45 EU WORKSHARING PROCEDURE CONDUCTED ACCORDING TO PAEDIATRIC REGULATION *(EC) NO. 1901/2006*: WHAT HAS BEEN ACCOMPLISHED FOR PAEDIATRIC USE ? - A RETROSPECTIVE ANALYSIS

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Summary

The lack of information and availability of appropriate pharmaceutical formulations exposed children to an increased risk to experience adverse drug reactions due to inappropriate dosing information including a risk for insufficient or even missing efficacy. Consequently, a variety of measures have been implemented by Regulation *(EC) No.1901/2006 as amended* in order to ameliorate medicinal care of paediatric populations. With introduction of *Article 45 (1)* of the Paediatric Regulation, paediatric use information in the SmPC was supposed to be improved by assessing study data from paediatric clinical trials, which have been completed before 26 January 2007. Considering the line-listings submitted by MAHs in January 2008, 167 studies have been provided for centrally authorized medicines; 18,000 studies for nationally authorized small molecules; 609 studies for nationally authorized vaccines and 625 studies for herbal and homoeopathic medicines.

Since the majority of paediatric studies falling under the scope of an *Article 45(1)* of Regulation *(EC) No.1901/2006* have been submitted for nationally licensed medicinal products, the retrospective analysis focussed exclusively on active substances subject to an *Article 45 EU Worksharing Procedure*. Assessment reports of 162 active substances encompassing small molecules; vaccines and biologics have been reviewed and summarized in Annex A. Information collated in Annex A has been utilized to evaluate what has been accomplished for paediatric use by investigating the following subjects:

1. Time from enrolment to completion of an *Article 45 EU Worksharing Procedure*
2. Number of *Article 45 EU Worksharing Procedures* completed by Rapporteur Member State versus enrolment by 31 December 2014
3. Recommendations proposed with completion of *Article 45 EU Worksharing Procedures* including an in-depth analysis of (a) the recommendations to different SmPC categories; (b) reasons for deletion of a paediatric indication and (c) proposals of new paediatric indications
4. Review of active substances, which have been selected to additional clinical investigations as indicated by the priority list *EMA/PDCO/98717/2012* (latest revision: 05 August 2013) and Paediatric Investigations Plans published on the EMA homepage.

The duration of *Article 45 EU Worksharing Procedures* took by average 474 days until completion. For 10 medicinal products, the assessment procedure last for more than 1000 days. The UK, DE, the NL; SE and DK/MT took the Rapporteur's role for more than 50% of the active substances, which had been enrolled to an *Article 45 EU Worksharing Procedure* over the past six years. Proportionally, these NCAs finished most of the assessment procedures. Two out of three active substances (106 active substances in total) received a SmPC recommendation based on submitted paediatric study data; literature and/or public guidelines. Of those, 26 active substances were not recommended for paediatric use. New indications got recommended for about 7% of the active substances including six active substances, which never had been licensed for a paediatric condition before. A deletion of paediatric indications was recommended for five active

substances and fifty-six active substances passed the Article 45 EU Worksharing Procedure without a recommendation for SmPC update.

Although paediatric use information has been further clarified for the majority of active substances, it should be noted nevertheless that, 26% of the 162 active substances did not receive a recommendation for a SmPC update, because robust evidence was missing. Of those, 15 active substances have been included in the priority list for studies on off-patent paediatric medicinal products EMA/PDCO/98717/2012 (latest revision: 05 August 2013), which was established to enable research on medicines with the highest need in the paediatric population. It is without doubt that medicinal products with a long regulatory history represent a valuable source for paediatric healthcare. This has been further substantiated by the number of Paediatric Investigations Plans, which have been agreed for 22 active substances which got assessed in an *Article 45 EU Worksharing Procedure*. However, missing high quality investigations in a randomized and controlled setting may be considered as one of the major constraints of this regulatory procedure and questions the aim of Article 45 (1) of Regulation (EC) No 1901/2006 as amended. Another major limitation identified for this regulatory procedure was related to the different license status of paediatric indications and approved posology, which prevented that valuable paediatric information could be implemented in the SmPC across all EU MSs either for the reasons that some CMS did not agree with the conclusions of the Rapporteur MS or, if the proposal got endorsed, that the recommended wording could not be brought into the appropriate context, because the paediatric indication or even the active substance never got licensed in a CMS. This issue contradicts the purpose of the Paediatric Regulation, which was aiming to grant children the same access to authorized medicinal products suitable for their use across EU.

Therefore, in the long run, the assessments conducted under the scope of an *Article 45(1)* of the Paediatric Regulation may need to be re-evaluated and replaced by dedicated research and development activities involving a PIP.

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute lymphoblastic leukaemia
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures - Human
CMS	Concerned Member States
CNS	Central Nervous System
CSR	Clinical Study Report
DCP	Decentralized Procedure
EMA	European Medicines Agency
EU	European Union
GORD	Gastric Oesophageal Reflux Disease
HCP	Health Care Providers
Lit	Literature
LoQ	List of Questions
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
MSs	Member States
NAP	National Authorization Procedure
NC	Non Clinical Studies
NCA	National Competent Authority
PRAC	Pharmacovigilance Risk Assessment Committee
PD	Pharmacodynamics
PEG	Paediatric Expert Group
PDCO	Paediatric Committee
PI	Product Information
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PUMA	Paediatric Use Marketing Authorization
PSUR	Periodic Safety Update Report
SAG	Scientific Advisory Group
SmPC	Summary of Product Characteristic
SPC	Supplementary Patent Certificate
TA	Therapeutic Area
TBC	Tuberculosis
W/O	Without
WS	Worksharing Procedure

Introduction

Based on reviews conducted prior to year 2004 on the availability of medicinal products licensed for use in paediatric populations, it was noted with concern that, the use of unlicensed and off-label medicines in children was widespread and had been increasing over the past years (Ref 1,2). In the EU, at least 50% of products used in children, as defined by *ICH Guideline E11* (preterm born to end of 17th year of age), had never been studied in this population, but only in adults, and not necessarily in the same indication (Ref 1-3).

The lack of information and availability of appropriate pharmaceutical formulations exposed children to an increased risk to experience adverse drug reactions due to inappropriate dosing information including a risk for insufficient or even missing efficacy (Ref 1, 3-5). Further to this concern, the European Medicines Agency (EMA) reviewed publications and databases, such as the Eudravigilance database, by investigating the evidence of harm from off-label or unlicensed medicines in children (Ref 5). This review represented a snap-shot of the current situation in the EU and collected data might not be representative, because underreporting of Adverse Drug Reactions (ADRs) in paediatric patient is known to occur even more frequently than in adults. However, the review provided valuable evidence that a greater incidence of ADRs occurred through off-label use or administration of medicines not authorized for paediatric use, which might be a result of no proper labelling information and dosing recommendation, and, hence, led to medication errors.

Market forces alone did not stimulate adequate research, development and authorization of medicinal product for paediatric use. Therefore, the introduction of a legal obligation forcing pharmaceutical companies to conduct paediatric studies as part of their drug development program was unavoidable in order to change the situation for paediatric patients in the EU.

Consequently, a variety of measures had been undertaken by the EU governmental institutions (EU Parliament, European Commission and EMA) to ameliorate the medicinal treatment options for paediatric patients. As a result, Directive *2001/20/EC* on good clinical practice for clinical trials was adopted in April 2001 specifying criteria for protection of children participating in clinical trials. In addition, the Paediatric Regulation (*EC) No.1901/2006* had been adopted in December 2006 with the aim to (a) facilitate the development and accessibility of medicinal products; (b) ensure that medicinal products are subject to ethical research of high quality; (c) medicinal products are appropriately authorized for paediatric use and (d) make information about paediatric use widely available (Ref 2). Whilst the Paediatric Regulation *(EC) No.1901/2006* was under development, the Committee for Human Medicinal Products (CHMP) took the initiative of creating PEG, an ad-hoc Expert Group on Paediatrics, which was transformed into a temporary working party by implementation of Title IV of Regulation (*EC) No.726/2004* (Ref 1). The PEG coordinated necessary actions and advised the EMA and the scientific committees on all questions relating to the development and use of medicinal products in children. The PEG ceased its activities and was replaced by the Paediatric Committee (PDCO) in July 2007 as in accordance with the Paediatric Regulation.

One important step initiated by PEG had been a survey conducted in the EU on therapeutic areas (TA) where there should be research and development of medicinal products, either old (i.e. off patent) or new ones (including those under development) (Ref 6). For this purpose, PEG consulted (a) experts in relevant areas; (b) contact points at NCA and (c) European Learned Societies relevant to the TA. Fifteen TA had been identified essential for appropriate medicinal care: anaesthesiology, cardiovascular, diabetes, endocrinology, gastroenterology, immunology, infectious diseases, nephro-urology, neurology, obstructive lung disease, oncology, ophthalmology, pain, psychiatry and rheumatology. With implementation of the Paediatric Regulation, the inventory of therapeutic needs had become a legal requirement as laid down in *Art 42* and *Art 43* of Regulation *(EC) No.1901/2006 as amended*. The PDCO is in charge of providing guidance on the content and format of data to be collected by the EU MSs and to establish the inventory of therapeutic needs, by taking into account the discussions held by PEG (Ref 7). The report of the survey about paediatric use of medicinal products in the EU was published 10 December 2010 (Ref 8). This survey was subject to a number of limitations such as: (a) data heterogeneity, (b) MSs representing approximately 50% of the EEA population did not submit any data or (c) some dataset did not distinguish between authorized, unauthorized or off-label use of medicines. However, it still confirmed findings from previous reviews that prescription of off-label and unauthorized medicines for children remained widespread throughout the EU (45-60%). The most frequent medicines used off-label and unauthorized belong to the following therapeutic classes: antiarrhythmics; antihypertensives; proton pump inhibitors and H2-receptor antagonists; antiasthmatics and antidepressants. Extensive off-label use of antimicrobials or corticosteroids was reported for very young children. The analysis concerning the use of pharmaceutical forms indicated that, both, oral and parenteral formulations, were being used unauthorized and off-label due to the lack of age appropriate formulations and strengths. Apart from missing paediatric study data, additional regulatory constraints could be determined for medicines falling under the scope of paediatric needs, e.g. (a) medicinal product may not have an EU-wide MA and, hence, they were being used unauthorized in some EU MS, (b) a medicine had not been licensed for all paediatric age groups, and/or (c) there was a general lack of information for paediatric use or the label information was not harmonized.

The lack of information in the Summary of Product Characteristics (SmPC), however, was supposed to be mitigated by measures implemented by the Paediatric Regulation, which states in *Paragraph (34)*:"*For certain authorised products, pharmaceutical companies may already hold data on safety or efficacy in the paediatric population. To improve the information available on the use of medicinal products in the paediatric populations, companies holding such data should be required to submit them to all competent authorities where the product is authorised. In this way the data could be assessed and, if appropriate, information should be included in the authorised product information aimed at healthcare professionals and patients*."

As of 26 January 2008, MAH were obliged to submit any paediatric studies to the National Competent Authority (NCA), which were already completed by 26 January 2007 as in compliance with *Article 45(1)* of Regulation *(EC) No.1901/2006 as amended*. Based on the line listings, Marketing Authorization Holder (MAH) submitted 167 studies for centrally authorized medicines; 18,000 studies for nationally authorized small molecules; 609 studies for nationally authorized vaccines and 625 studies for herbal and homoeopathic medicines, which all of them had been

collated and become available to the public via the European Clinical Trials Register as in compliance with *Art 41(2)* of Regulation *(EC) No.1901/2006 as amended* (Ref 9).

Since the call for paediatric studies submitted under the scope of *Article 45(1)* lead to such a wealth of information, in particular for nationally licensed products, the EMA - in charge of coordinating the assessment of paediatric studies by medicinal product - first had to prepare an overview of active substances, which were supposed to be assessed under the EU work-sharing procedure. Further, medicinal products had to be prioritized for assessment by taking the priority list of off-patent medicines, *EMEA/226983/2008*, in consideration, which was valid at that point of time (Ref 10, 11). In March 2008, the Coordination Group for Mutual Recognition and Decentralized Procedure human (CMDh) adopted a Best Practice Guide for the *Article 45 EU worksharing procedure* in order to define requirements on the contents of the dossier submitted by the MAH and to streamline the procedural steps for the assessment of paediatric studies (Ref 11). As per work plan 2009 *(CMDh/012/2009*), the CMDh decided of having 4 waves of assessment procedures initiated for selected products each year (Ref 13). It was further decided that, the assessment is conducted as EU worksharing procedures in order to make the best use of available resources and to avoid duplication of the efforts. The recommendation to the SmPC would have to be implemented into national MA via a type IB variation classified as C.I.3a) (Ref 10).

The majority of paediatric studies falling under the scope of an *Article 45(1)* of Regulation *(EC) No.1901/2006* had been submitted for medicinal products, which were licensed in a national Marketing Authorization (MA) Procedure (including MRP and DCP). Therefore, the retrospective analysis focussed exclusively on active substances, which were assessed in an *Article 45 EU Worksharing Procedure,* in order to evaluate what has been accomplished for paediatric use.

Objective and Methods of Analysis

Subject of the present retrospective analysis was an investigation on what has been accomplished for paediatric patients six years after introduction of the Paediatric Regulation and related measures enabling reviews of paediatric studies falling under the scope of an *Article 45 EU worksharing procedure*. For this purpose, the analysis followed a step-wise approach by initially reviewing assessment reports, which were published on the Heads of Medicines Agency (HMA) homepage until 31 December 2014 (Ref. 15). A cut-off date "31 December 2014" was determined in order to allow sufficient time for the analysis. Furthermore, it was not expected that few additional assessment reports of more recently completed procedures would significantly change the conclusions of this analysis.

This retrospective analysis focussed on small molecules, vaccines and biologics. Reports of active substances falling into the category of diagnostics, herbal medicines and/or food supplements have not been taken in consideration for this review.

Information of the following parameter were derived from published assessment reports and collated in a tabulated format, which is attached as *Annex A* to this thesis, below:

a) TA
b) Description of the indication approved at initiation of the *Article 45 EU Worksharing Procedure*
c) ATC code and pharmaceutical forms
d) Type and number of studies submitted
e) Initiation of assessment (wave)
f) Date when the procedure got completed
g) Date of publication on HMA homepage
h) Duration of assessment procedure counted in days
i) Outcome of the assessment/recommendations for the SmPC[1]

Annex A served as source document for the following subsequent analyses:

I. Time from enrolment to completion of an *Article 45 EU Worksharing Procedure*

The duration of the assessment period was calculated by counting the days starting with the first day of the first month of the respective wave (e.g. Q4 is equal to October 1st), when the letter was sent to the MAH, until the actual date of completion.

A descriptive statistical analysis was conducted on the duration of the assessment period determining the following parameter:

[1] The information presented in the package leaflet is supposed to be aligned with the SmPC. Therefore, the review focussed on recommendations provided for the SmPC only.

a) Arithmetic mean
b) Median
c) Minimum duration
d) Maximum duration
e) Duration of 1st quartile (25%)
f) Duration of 3rd quartile (75%)

Possible factors driving the assessment timelines have been further evaluated.

II. Number of *Article 45 EU Worksharing Procedures* processed by Rapporteur MS

It has been determined how many *Article 45 EU worksharing procedures* were enrolled to and completed by EU MSs until 31 December 2014. Further, a direct comparison of Rapporteur MSs was conducted within the group of completed assessment procedures.

Since this retrospective analysis focussed exclusively on small molecules, vaccines and biologics, figures had to be corrected (a) by the number of medicinal products falling into the category of diagnostics; herbal medicines and/or food supplements and (b) by the number of medicinal products, which assessment reports have been published after 31 December 2014.

Considering the exclusion criteria, the number of "enrolled medicinal products" was corrected by removing 25 active substances from the analysis, because these products were falling into the category of diagnostics; herbal medicines and/or food supplements.

The number of completed assessment procedures was corrected by removing 28 active substances in total, i.e. 12 products were removed from the analysis, because reports were not published (6 active substances) or assessment procedures were still ongoing (6 active substances) on 31 December 2014. Further, 16 active substances were removed, because they belong to the category of diagnostics; herbal medicines and/or food supplements. According to *CMDh/151/2009 Rev.43* (status April 2015), the number of removed active substances affected the following Rapporteur MSs: FI (1); SE (2); FR (3); AT (1); DK (6); DE (7); UK (8).

It should be noted that discrepancies have been identified for medicinal products enrolled to *Article 45 EU worksharing procedures* by wave between CMDh list *CMDh/151/2009 Rev.43* (status April 2015) and CMDh list *CMDh/014/2008/Rev.30* (status July 2015). Therefore, the analysis was exclusively based on the CMDh excel sheet "*List of the active substances for which data has been submitted in accordance with Article 45 of the Paediatric Regulatio*n" (*CMDh/151/2009 Rev.43* [status April 2015]) as source document, which is added to this master thesis as *Annex B*.

III. Analysis of recommendations proposed with completion of *Article 45 EU Worksharing Procedures*

An overall assessment of the recommendations to the SmPC have been conducted by reviewing 162 assessment reports published after completion of an *Article 45 EU Worksharing Procedure* by 31 December 2014. A stratified analysis was performed by classifying the recommendations into 6 categories and 3 subcategories. Subsequently, an in depth analysis was performed on selected items of the categories as outlined below.

Description of the categories:

a) Procedures completed with no recommendation for a SmPC change
b) Recommendations for an SmPC update with information for paediatric use
    i Recommendations leading to a major SmPC update. Conditions for a major SmPC update were reached, if the Rapporteur recommended amendments to at least three out of four SmPC categories. In this regard, SmPC categories have been defined as follows:
        1) Indication (SmPC section 4.1);
        2) Posology (SmPC section 4.2);
        3) Safety (SmPC section 4.3-4.9)
        4) Clinical (SmPC section 5).

        As per *Annex A*, no recommendation was provided for any of the pharmaceutical sections of the SmPC.

    ii Clarification of paediatric information for products licensed for paediatric use
    iii Clarification of paediatric information for products w/o a licensed paediatric indication

c) Active substances which received a recommendation for a new paediatric indication
d) Active substances which received a recommendation for a deletion of the paediatric indication
e) Active substances which passed a regulatory procedure for label harmonization prior to an *Article 45 EU Worksharing Procedure*
f) Active substances which were recommended for label harmonization

Items subject to an in-depth analysis:

1) Analysis of recommendations provided for each of the SmPC categories (see item (i))
2) Analysis of recommendations suggesting a deletion of a paediatric indication
3) Analysis of recommendations suggesting a new indication

IV. Review of active substances subject to further investigations with the aim to bring medicines to children

The quality of paediatric studies falling under the scope of *Article 45(1)* of Regulation *(EC) No.1901/2006 as amended* did not always allow conclusions about safe and effective use in paediatric populations. Further, some active substances might have the potential of being safe and effective in a broader range of conditions or indications, and/or investigations in some subpopulations would still be necessary before an active substance could widely be recommended for use within a specified condition.

With this regard, the revised priority list for studies on off-patent paediatric medicinal products *EMA/PDCO/98717/2012* (latest revision: 05 August 2013) and the EMA homepage/section opinions and decisions on PIPs have been reviewed in order to identify active substances selected for additional clinical investigations. A high level review of the objective defined for Paediatric Use Marketing Authorization (PUMA) according to *Article 30* of Regulation *(EC) No.1901/2006* and for the approved PIP was performed and compared with the recommendations provided under the scope of the *Article 45 EU Worksharing Procedure*.

Results

The CMDh list of the active substances (*CMDh/151/2009 Rev.43*) for which paediatric study data were submitted in accordance with *Article 45(1)* of the Paediatric Regulation includes 991 products in total (see *Annex B*). Approximately 38 active substances were removed from this list by the CMDh afterwards, either for the reasons that no paediatric data were available or paediatric studies were being assessed under a different regulatory procedure. Hence, approximately 953 active substances were still supposed to be assessed in an *Article 45 EU Worksharing Procedure*.

By 31 December 2014, overall, 322 out of 953 active substances were enrolled for assessment. Of those, 186 *Article 45 EU Worksharing Procedures* had been completed (*Annex B*, Ref 14). Consequently, 136 assessment procedures were still open-ongoing. Reports of 178 assessment procedures were published on the CMDh homepage by the defined cut-off date.

The retrospective analysis has been performed on assessment reports, which fulfilled criteria as outlined in "Objectives and Methods for Analysis". Therefore, 162 assessment reports were finally reviewed in order to collect information about parameter which have been utilized for subsequent analysis (see section "Objectives and Methods for Analysis" and *Annex A*). Where indicated, comments or additional information have been added by active substance clarifying the reasons for the outcome of an assessment procedure.
Although the quality of information presented in assessment reports was heterogeneous, all parameters selected for subsequent analysis could be identified. Hence, the limitations related to the presentation of regulatory contents in these assessment reports have not been further described or discussed, because it had no impact on the scope of the retrospective analysis.

I. Time from enrolment to completion of an *Article 45 EU worksharing procedure*

As summarized in Table 1 below, an *Article 45 EU Worksharing Procedure* took by average 474 days until completion. Considering the median duration, 50% of the products were assessed within 408 days.

The shortest duration was identified for Fluarix (128 days), an influenza vaccine registered for use in adults and paediatrics with an age of more than six month; the single Clinical Study Report (CSR) did not add any new information to what has already been reflected in the SmPC. The longest duration was calculated for lidocaine (1529 days). The duration was likely being triggered by the complexity of the assessment caused by the number of MAH (8), which all of them provided their paediatric data; and the high number of different formulations, which multiplied the efforts since clinical assessments had to be performed for each pharmaceutical form.

The duration (293 days) calculated for the 1st Quartile (25% of active substances) was more or less in compliance with the assessment timeline as set out by the CMDh Best Practice Guide

CMDh/037/2009/Rev4 (Ref 10). For the majority of active substances falling into this category, no label update has been proposed either for the reasons that no new data were provided or submitted paediatric data were insufficient to draw up any definite conclusion, respectively. Six active substances were subject to other regulatory procedures prior to this assessment procedure (e.g. *Article 29, 30 or 31 referral* according to Directive *2001/83/EC*, or *Article 46 EU Worksharing Procedure* according to Regulation *(EC) No.1901/2006*), and, hence, the Product Information (PI) was already in compliance with the current state of knowledge. Another set of six products, however, underwent a full assessment leading to revisions of two or more SmPC sections; for procarbazepine; mirtazapine; simvastatin; flumazenil and metronidazole, the product label update could even considered of being "major[2]". Despite the wealth of paediatric information assessed for some of these products, the duration of the individual assessment procedures were more or less evenly distributed across the 1st Quartile.

The duration of assessment procedures of products falling into the 4th Quartile took more than 587 days. The reasons for this long assessment period seem not to follow any specific pattern: Twelve products out of this group received a recommendation for a major product label change; five of these twelve products got a recommendation for a new paediatric indication. However, the assessment procedure of nine products was completed without any label update; three products [captopril; azthreonam and azithromycin] had been assessed for more than 1000 days.

Table 1: Descriptive analysis of assessment timelines

Statistical parameter	Days	Active Substance	Rapporteur
Arithmetic mean	474	-/-	
Median	408	Meropenem	France
Minimum Duration	128	Fluarix	Germany
Maximum Duration	1529	Lidocain	Sweden
1st Quartile	293	Famciclovir	Germany
3rd Quartile	574	Clarithromycin	Slovakia

II. Number of *Article 45 EU Worksharing Procedures* processed by Rapporteur MS

As per CMDh spreadsheet *CMDh/151/2009 Rev.43* (status April 2015), twenty-six NCAs took the mandate for leading 297 *Article 45 EU Worksharing Procedures* of active substances falling into the scope of this retrospective analysis (*Annex B*). By 31 December 2014, twenty-two NCAs managed the completion of assessment procedures for medicinal products which outcome have been further analysed in the subsequent sections (162 active substances). Six completed assessment procedures have been omitted from this analysis, because assessment reports were not published on the HMA homepage by the defined cut-off date of this thesis. Consequently, 129 assessment procedures (43%) were still open-ongoing on 31 December 2014.

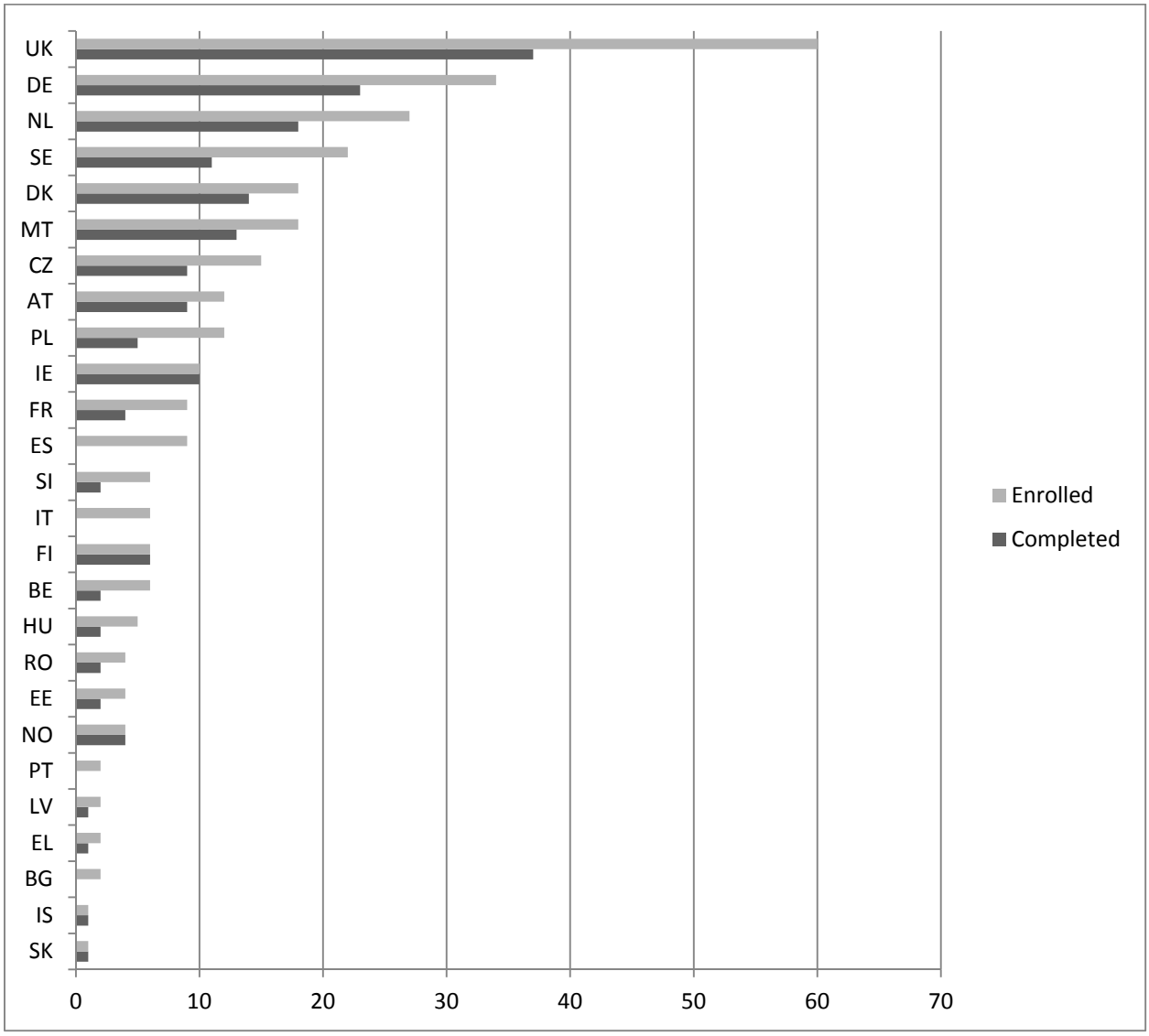
Figure 1 presents a comparative overview of the number of *Article 45 EU Worksharing Procedures* enrolled to and completed by Rapporteur MS until December 31st, 2014.

[2] Definition of major SmPC update is presented in section "Objective and Methods of Analysis"

Based on the evaluation criteria of this thesis, the bar chart illustrates that the UK, DE, the NL; SE and DK/MT took the Rapporteur's role for more than 50% of the active substances enrolled to an *Article 45 EU Worksharing Procedure* over the past six years. Proportionally, these NCAs finished most of the assessment procedures.

Article 45 EU Worksharing Procedures enrolled to the remaining NCA ranged from 1 to 15 by EU MS. When comparing the number of completed procedures against the enrolled ones, then, significant differences were detected for some countries, e.g. IE completed more procedures compared to FR (completed: 10 versus 4) although a similar number of procedures had been enrolled to both countries. Furthermore, enrolment continued for IE as Rapporteur MS after Q1 2011 when FR got assigned to its last *Article 45 EU Worksharing Procedure*. A similar pattern could be determined for NO versus EE and HU (4 versus 2/2). As per CMDh spreadsheet *CMDh/151/2009 Rev.43* (status April 2015), none of the *Article 45 EU Worksharing Procedures* got completed by IT; ES; PT and BG even though they took the first mandate in Q1 2009 or Q2 2009 (IT).

Figure 1: *Article 45 EU Worksharing Procedures* by Rapporteur MS



Limitation: An assessment of the differences between enrolled and completed *Article 45 EU Worksharing Procedures* by EU MS has not been performed, because additional information was missing concerning factors such as internal structure of the NCA and availability of resources, which may have had an impact on the working performance of Rapporteur MS, and hence, a direct comparison would be inappropriate.

III. Analysis of recommendations proposed with completion of *Article 45 EU Worksharing Procedures*

Figure 2 provides an overview of recommendations agreed under the scope of *Article 45 Worksharing Procedures* completed by December 31st, 2014.

Fifty-six active substances received no recommendation for a SmPC update either for the reasons that the PI already complied with the current state of knowledge (61%) or provided paediatric studies were insufficient for drawing up any conclusions about safety and efficacy in the paediatric population (30%). In very rare occasions, no label update was proposed, because of (a) divergent opinions among EU Member States (azithromycin/oral formulations, levofloxacin and trimethoprim); (b) change of product formulation (alginic acid); (c) submission of paediatric literature w/o appropriate analysis (etoposide) and (d) recommendations affecting both, adult and paediatric populations (pentamidine).

Seventeen products passed a regulatory procedure for label harmonization such as referrals (*Article 29, 30* or *31*) according to Directive *2001/83/EC*; *Article 46 EU Worksharing Procedure* according to Regulation *(EC) No.1901/2006*; Type II variations, or the active substance already was included in a previous paediatric worksharing procedure before Regulation *(EC) No.1901/2006* came into force. For those products (except for mirtazapine and topiramate), the Rapporteur did not provide a recommendation, which would further amend the PI, because the SmPCs still complied with the current state of knowledge. Regarding mirtazapine, the Rapporteur felt the wording in the posology section should be further strengthened, but no additional or new information was proposed for inclusion in the SmPC (Ref 16). Regarding topiramate, however, the rapporteur recommended an update to the safety sections of the SmPC based on paediatric studies assessed under the scope of this Article 45 Worksharing Procedure (Ref 17). In addition, the MAH was requested to further investigate the effect on cognitive functions and growth. It has not been specified in the assessment report why these potential safety concerns had not been addressed - or why these additional paediatric studies were not being assessed under the scope of the *Article 30 referral*, which actually was completed shortly before the *Article 45 Worksharing Procedure* got initiated.

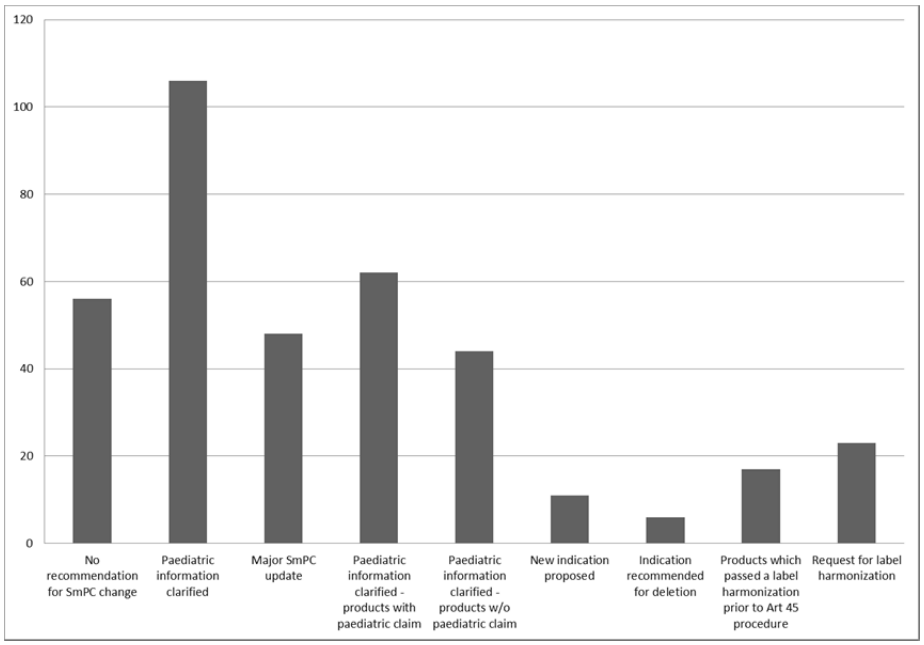
Overall, a recommendation for a SmPC update has been agreed for the majority of the active substances (65%); most of these products were licensed for paediatric use (62 versus 44), already. Forty-eight active substances received a recommendation for a major SmPC update amending at least 3 out of 4 SmPC categories after completion of an *Article 45 EU Worksharing Procedure*. For five products, the Rapporteurs proposed the deletion of a paediatric indication, and 11 active substances received a recommendation for a new paediatric indication.

Twenty-six out of 44 active substances not licensed for paediatric use completed the Article 45 assessment procedure with the conclusion "*this product is not recommended for paediatric use*": acarbose; adenosine (sol.for infusion); alendronate; alprazolam; chondroitin; clonidine; desogestrel; desogestrel+ethinylestradiol; fenofibrate; foscarnet; glucosamine; isradipine; itraconazole; ketoconazole; lovastatin; mirtazapine; nifedipine; nimodipine, paclitaxel; quetiapine; risedronate; salmon calcitonin; testosterone; verapamil; vinorelbine; zolpidem. All medicinal products except for lovastatin received the recommendation, because submitted data did not provide any robust evidence for safe and effective use in the paediatric population either for the reasons that no or very limited paediatric data were submitted, or methodological weakness of the study design did not allow any conclusions in this regard. Four of these medicinal products were later included in the revised priority list for studies on off-patent paediatric medicinal products *EMA/PDCO/98717/2012* (latest revision: 05 August 2013). Lovastatin, however, received this recommendation, because a negative benefit-risk ratio has been concluded.

The remaining 18 active substances not licensed for paediatric use completed the assessment procedure with a recommendation for a SmPC update. Six of these active substances even received a recommendation for a new indication.

As per CMDh guidance *CMDh/141/2009/Rev2* (version March 2013): " *Article 45 is not expected to be a full harmonisation process; where differences are identified in the paediatric aspects of product information, a recommendation can be made in the assessment report that the MAH achieve harmonisation through use of appropriate regulatory procedures. However, it should be possible to recommend consistent wording for existing indications and posology in the SmPC common to MS*". In this context a request for label harmonization was suggested for 23 active substances. For azithromycin/oral formulations, levofloxacin and trimethoprim, a "*consistent wording for existing indications and posology*" was not proposed by the Rapporteur because no consensus could be reached among EU MSs.

Figure 2: Recommendations provided under the scope of the *Article 45 Worksharing Procedure*

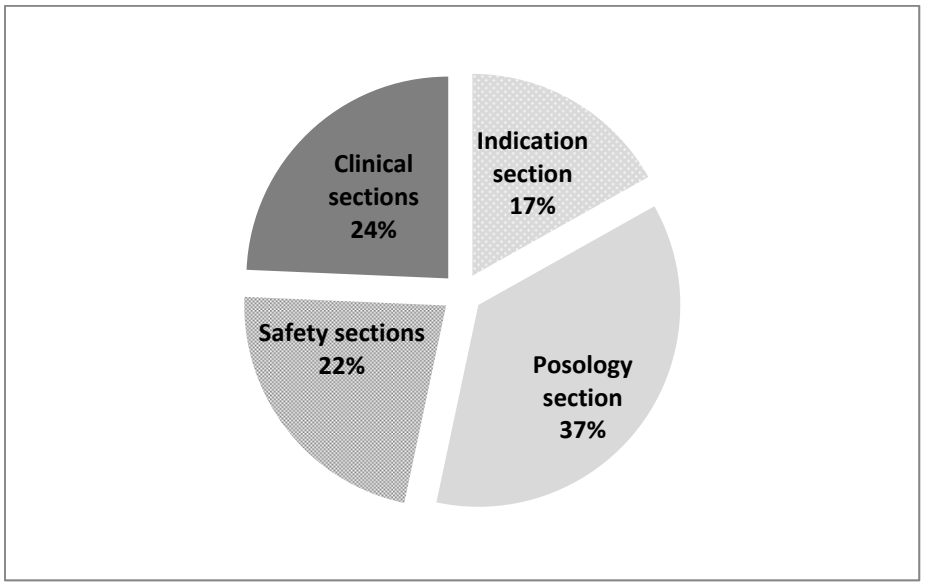


Three types of recommendations provided with completion of the *Article 45 EU Worksharing Procedure* were subject for an in-depth analysis. The results are presented below.

1) Analysis of recommendations provided for each of the SmPC categories

A quantitative analysis has been performed on the recommendations provided per SmPC category (a) indication; (b) posology; (c) safety and (c) clinical. Figure 3 depicts the proportions of changes per category below. The majority of recommendations (93 recommendations) affected the posology section. However, it should be noted that, the conclusion indicating a product is "*not recommended for paediatric use"*, which was supposed to be introduced in SmPC section 4.2 for 26 active substances, has been included in this calculation. Withdrawing these 26 recommendations from the number of posology updates, the proportion of updated dosing recommendations for paediatric use would be less (93-26 = 67) and, hence, comparable with the number of updates recommended for the clinical (62 recommendations) and safety (57 recommendations) sections of the SmPC.

Figure 3: SmPC category subject to clarification for use in paediatric populations



The analysis has been further broken down to assess the nature and type of label recommendation provided for one SmPC category (see Figure 4 below). Subcategories of the safety section and efficacy section were synonym with the respective SmPC section as defined by the SmPC guideline (see section "Objective and Methods of Analyses") (Ref 24).

Regarding SmPC section 4.1 (indication) and section 4.2 (posology), subcategories had to be developed to better characterize the nature of recommendation by grouping recommendations, which were similar regarding one attribute. A grouping of recommendations was necessary, because the actual number of individual recommendations were too small otherwise. Hence, five subcategories had been defined for the indication section and 7 subcategories for the posology section (see Figure 4).

Recommendations to the indication section were mainly driven by updates aiming to further clarify the paediatric indication (24 recommendations), because the wording presented in the indication section was usually kept general and unspecific in the past. The remaining recommendations further clarified the indication section by adding an age limit or age range (16 recommendations), and/or specified the indication by pharmaceutical form (10 recommendations). In few instances, references to official guidelines or SmPC sections had been proposed.

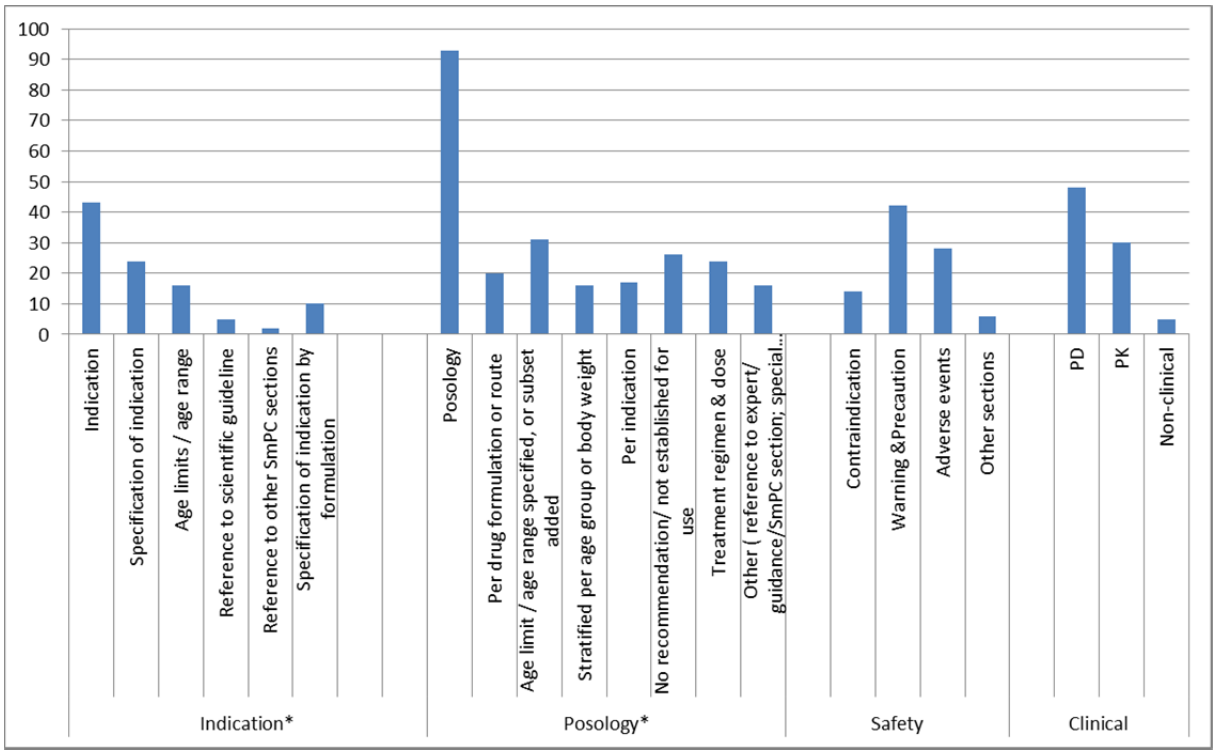
The majority of recommendations to the posology section referred to the subcategories (a) age (age limit/age range/addition of a paediatric subset) and (b) subsets of paediatric populations & related body weight (overall 47 recommendations). The treatment regimen and dose got clarified in 24 instances followed by clarification of the dose per drug formulation & route of administration (20 recommendations) and per indication (17 recommendations).

Safety updates were dominated by revisions to the warning and precautions section (SmPC section 4.4: 42 recommendations) followed by changes to the adverse event section (SmPC section 4.8: 28 recommendations). Revisions to the contraindications section (SmPC section 4.3) were provided occasionally.

As per *Annex A*, non-clinical data had been included in few submissions. Therefore, recommendations for SmPC section 5.3 were provided in rare occasions, only.

Regarding SmPC section 5.1 and 5.2, the number of proposed updates appeared to be surprisingly low with 48 proposed updates to section 5.1 and 30 proposed updates to section 5.2 considering 106 products received a recommendation for a SmPC update based on submitted paediatric study reports and/or literature data. The reasons might be related to the fact that submitted data did not always provide new clinical information. For some medicinal products, an update to the clinical sections was not recommended, deliberately, as this information could mislead and encourage the physician using this product off-label in paediatric populations (see *Annex A*/e.g. isradipine). Indeed, 46 recommendations were provided for SmPC updates pertaining exclusively to the indications-, posology- and/or safety sections.

Figure 4: Nature and type of information specified per SmPC category[3]



*One recommendation could affect several subcategories

2) Analysis of Recommendations suggesting a Deletion of a Paediatric Indication

CMDh guideline *CMDh/141/2009/Rev2* (version March 2013) states the following regarding a recommendation for a deletion of a paediatric indication: "*It is not the aim of Article 45 or 46 procedures to remove existing paediatric indications for products which are already in clinical use in particular member states. Removal of indications, for example if there is new evidence regarding safety, should be considered by individual member states unless there has been prior agreement by CMDh or through another regulatory procedure*".

By December 31st, 2014, a deletion of a paediatric indication was suggested for about five active substances. The reasons are summarized in Table 2 below. For all products - except for Rifamixin - the reasons were comprehensible. Concerning Rifamixin, submitted paediatric data including a meta-analysis demonstrated a positive trend of efficacy for Rifaximin in a special condition [acute diarrhoeas (mainly recurrent or relapsing) caused by non-invasive Rifaximin sensitive bacteria such as Escherichia coli]. Further, safety was confirmed by the low frequency of AEs across all studies (Ref 15). While all paediatric indications were recommended for deletion, the Rapporteur requested the paediatric study results including a dose recommendation for patient of 2-12 years of age are being included in SmPC section 5.1. This measure was recommended in accordance with CMDh guideline *CMDh/141/2009/Rev2 (March 2013)*, which states […]*Inclusion of information in section 5.1 of the SmPC should be considered if the data is not considered sufficient*

[3] One recommendation can affect several SmPC sections. Please refer to analysis of major label updates

for a paediatric indication and/or dose recommendation […]. *This information may be of value for 'off-label' use but such use cannot be directly supported in the SmPC*.

Table 2: Paediatric indications of active substances proposed for deletion

Product	TA/ Indication	Justification
Haloperidol	Psychiatric disorder/ Behaviour disorder associated with hyperactivity and aggression Gilles des la Tourette disorder Psychosis	Limited data did not support a recommendation for use in schizophrenia and Gilles de la Tourette's disorder. Since Art 45 worksharing does not aim to remove approved paediatric indications, the procedure was concluded with a recommendation to include haloperidol on the list of future SmPC harmonisation intending to remove the paediatric claim.
Metoclopramide	Gastrointestinal disease/ Oral and rectal formulation: all indications should be removed Intravenous formulation: - Chemotherapy- and radiotherapy-induced nausea and vomiting - Gastrointestinal motility disorders - Digestive tract explorations	No clear evidence for efficacy in all gastrointestinal motility disorders, and there is no clear evidence for efficacy in chemotherapy- and radiotherapy induced nausea and vomiting. MAH did not intend to harmonize the SmPC sections for indication and posology but sought for harmonization of safety information. Rapporteur recommended continuing the discussion on national level as some of the CMS object the recommendation for deletion.
Permethrin 0.43% solution	Antiparasitic/ prophylactic treatment of *sarcoptes scabei*	License for short lasting prophylactic treatment (1 day) should be removed because treatment regimen might have contributed to emerging head lice resistance
Pentamidine	Infectious disease/ Inhalation route is not recommended for treatment of mild pneumocystis pneumonia (PCP) and should be removed from all PIs. The inhalation route should be used for prophylaxis only.	Efficacy of inhalation route is inferior compared to oral or intravenous treatment in PCP. This recommendation is not restricted to paediatric patients but includes adults as well. Recommendation included a request for label harmonization.
Rifamixin	Infectious disease/ all indications related to paediatric population were recommended for deletion.[4]	Methodological weakness of paediatric studies led to the conclusion that general use of Rifaximin in children in Europe cannot be recommended. The Rapporteur referred to the SmPC guideline (2009). Conclusions were endorsed by other CMS.

[4] Indications proposed for deletion have not been listed due to the lack of space. Please refer to the assessment report (Ref 15)

3) Analysis of recommendations for new indications

Between Q4/2008 until 31 December 2014, a recommendation for a new indication was accomplished for 11 active substances (6%) in return to the efforts done in order to provide paediatric patients with medicine and make information available to Health Care Providers (HCP).

Most of the recommendations had been agreed in year 2011 (5 actives) followed closely by year 2013 (4 actives). The assessment periods last for 50% of the actives substances approximately 620 days or even less (defined by the median). Further to note, five recommendations were provided based on submitted bibliographic data, only. Three of these active substances (adenosine; colchicine; dobutamine) had not been licensed for any paediatric indication before. Table 3 provides a summary of products recommended for a new paediatric indication.

The implementation of proposed paediatric indications had been checked by searching the electronic Medicines Compendium (eMC) providing information about medicines licensed for use in the UK (Ref 18). The product information for the majority of the products got updated with the new paediatric indication except for budenoside, cholchicine, metoprolol and neridronic acid.

Table 3: New indications recommended under the scope of an *Article 45 EU Worksharing Procedure*

Product	Biblio-graphic data	Submitted paediatric studies	Paediatric claim	TA/ Indication	Justification	Completed by Year
Adenosine (solution for injection)	X	---	No	Cardiology/ Rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia	Well established use; paediatric advanced life support guidelines and uncontrolled studies	2013
Budenoside (for Pulmicort Respules only)	X	X	Yes	Respiratory/ laryngitis subglottica with need for hospitalization	The indication pseudocroup (laryngitis subglottica) was approved in Denmark and the NL. Submitted studies confirmed the positive benefit-risk ratio. FR and SE did not endorse the recommendation	2011
Colchicine	X	---	No	Rheumatology/ familial Mediterranean fever for prophylaxis of attacks and prevention of amyloidosis	The rationale and use modalities of colchicine were well documented in patients with Familial Mediterranean Fever. The benefit/risk ratio was clearly favourable especially with regard to the	2011

					prevention of amyloidosis deposition	
Daunorubicin	X	---	Yes	Oncology/ As part of combination therapy indicated for acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) in children.	Well established use. Indication was already approved in the Rapporteur country.	2011
Dobutamine	X	---	No	Cardiology/ inotropic support in low cardiac output hypoperfusion state resulting from decompensated heart failure [..]	Well established use	2013
Idarubicin (intravenous pharmaceutical forms)	X	X	No	Oncology/ acute myeloid leukaemia (AML) in combination with cytarabin	Conclusion was supported by all CMS: paediatric data indicated a positive benefit-risk ratio	2013
Metoprolol succinate	---	X	Yes	Nephrology/ Hypertension	Two CSR sufficiently demonstrated a positive risk-benefit profile. Claim was already approved in the Rapporteur Country. The recommendation extended the indication to the other CMS.	2013
Milrinone	X	X	No	Cardiology/ short term treatment of congestive heart failure unresponsive to conventional maintenance therapy […]	Submitted data confirmed positive benefit-risk ratio for use in paediatric patients. Recommendation was endorsed by all CMS	2011
Neridronic acid	X	Interim analysis of a non-controlled clinical trial	No	Skeletal disorder/ osteogenesis imperfecta	The Rapporteur based the recommendation on available data supporting the use in children. Further, the indication was approved in Italy, already. Since no other biphosphonates got licensed for paediatric use in the EU, the Article 45 WS was not supposed to get	2010

					delayed until the clinical trial gets completed. Conclusion was endorsed by all CMS.	
Ropivacaine	X	X	Yes	Anaesthesiology/ (1) 7.5mg and 10mg/ml (patients >12 years): treatment of epidural blocks; major nerve block and field blocks; (2) 2mg/ml (infants and patients < 12 years): continuous epidural infusion during post-operative or labour pain; field block and continuous peripheral nerve block	Provided data support conclusions about positive benefit-risk ratio	2011
Ursodeoxycholic acid (UDCA)	X	X	yes	Hepatobiliary disorder/ hepatobiliary disorder associated with cystic fibrosis (CFAHD)	Short-term as well as long-term use (up to 12 years) confirmed, UDCA improves/normalise hepatic transaminases, improves hepatic metabolism of essential fatty acids and bile flow in children with cystic fibrosis. There was further some evidence suggesting that treatment with UDCA could decrease bile duct proliferation and halt progression of histological damage and even reverse hepatobiliary changes if administered at early stage.	2012

IV. Review of active substances subject to further investigations with the aim to bring medicines to children

As outlined in section “Objective and Methods of Analysis”, the revised priority list for studies on off-patent paediatric medicinal products EMA/PDCO/98717/2012 (latest revision: 05 August

2013) and the EMA homepage/section O*pinions and Decisions on PIPs* had been reviewed in order to identify which active substances were selected for additional clinical investigations in paediatric patients (Ref 19-20). A high level comparison had been performed on the newly investigated conditions and the recommendation provided under the scope of the *Article 45 EU Worksharing Procedure.* A comparative overview of the new proposed conditions and the recommendation agreed under the *Article 45 EU Worksharing Procedure* is presented by active substance in Table 4 and Table 5 below.

Active substances added to the revised priority list for studies on off-patent paediatric medicinal products with highest paediatric needs according to *EMA/PDCO/98717/2012*

The revised priority list for studies on off-patent paediatric medicinal products *EMA/PDCO/98717/201*2 (latest revision: 05 August 2013) has been established to enable research on medicines with the highest need in the paediatric population (Ref 19). This list is supposed to be used as basis for potential future funding within the *Horizon 2020 Programme* of the European Commission. Products included in this list are recommended for submission of a Paediatric Use Marketing Authorization (PUMA) as in accordance with *Art.30* of Regulation *(EC) No.1901/2006 as amended*.

Twenty five out of 162 active substances assessed in an Article 45 EU worksharing procedure have been included in the list of off-patent medicines. Conditions proposed for PUMA encompass investigations of indications, which failed to obtain approval under the scope of an Article 45 procedure, or which need to be further characterized, because submitted paediatric data were insufficient (13 active substances e.g. amiodarone; cyclophosphamide; topiramate or fluoxetine).

Four products, which were even not recommended for paediatric use as per *Article 45 EU Worksharing Procedure*, have been proposed for use in new paediatric indications (alendronate; clonidine; itraconazole; vinorelbine). One product was supposed to be studied in combination with other medicinal products for use within the same indication (new rifampicin combinations against TBC). Seven active substances, which already had a paediatric claim, were proposed for investigations of new paediatric indications (e.g. clindamycin; colestyramine; cyclosporine); one product (lidocaine) was even suggested for a new indication within a new TA.

Prioritised needs, as listed in the column 'Priority', do not necessarily cover all needs for the treatment of the paediatric population, nor will they automatically cover the regulatory requirements for a Paediatric Investigation Plan (PIP) (Ref 19).

All investigations require a PIP approved by PDCO. So far, PIPs have been submitted for azithromycin, clonidine, cyclophosphamide, ibuprofen and propranolol by April 2015; however, none of the conditions as outlined in the respective PIP had been submitted for the conditions as described in the priority list of off-patent medicines.

Table 4: Active Substances selected for PUMA according to *EMA/PDCO/98717/2012* (Ref 19)

Product	**Conclusions reached under Article 45 WS**	***EMA/PDCO/98717/2012***		
		TA	**Condition**	**Priority**
Alendronate	Not recommended for paediatric use	Metabolism	Osteoporosis induced by immobility (e.g. neuromuscular disorders), corticosteroids, in idiopathic juvenile osteoporosis, in human immunodeficiency virus (HIV) patients	Data on efficacy and short- and long-term safety (oral use)
Amlodipine	Paediatric information clarified for treatment of hypertension. Update of SmPC section 4.2 providing age specific dose recommendations.	Nephrology	Hypertension	Data on PK, efficacy and safety, age group < 6 years; neurodevelopmental adverse reactions; age-appropriate formulation.
Amiodarone	Rapporteur did not recommend use against cardiac arrhythmias in paediatrics, because submitted data were not sufficiently robust justifying a posology.	Cardiology	Supraventricular and ventricular arrhythmia	Data on pharmacokinetics (PK), efficacy and long-term safety.

Azithromycin	No recommendation for a label update. Label information/ indications are inconsistent among different EU countries. Procedure was closed with request for label harmonization.	Pneumology	(1) E.g. cystic fibrosis (CF), severe persistent asthma (2) Prevention of respiratory infection in cystis fibrosis and neuromuscular disorders	(1) Data on PK, anti-inflammatory efficacy, safety; all paediatric age groups. (2) Data on PK, efficacy and safety.
Bisacodyl	Paediatric information clarified for indications currently approved (including constipation). SmPC section 4.2 was updated with age specific dose recommendations. Need for label harmonisation	Gastroenterology	Constipation	Data on long-term efficacy, safety, all age groups; age-appropriate formulation.
Clindamycin	No label update (no new information submitted under Art 45 procedure)	Infections	Osteomyelitis; infections caused by Methicillin resistant *Staphylococcus aureus* and Methicillin resistant *Staphylococcus epidermidis*	Data on PK (unless available) in all age groups; relevant tissue and fluid levels; short- and long-term efficacy and safety.
Colestyramine	No label update. One CSR was submitted which did not support the indication <watery diarrhoea>	Endocrinology	Hypercholesterolaemia	Data on efficacy and safety in children from 6 years. Palatable age-appropriate formulation.

Cyclophosphamide	Licensed for malignant and immune diseases in adults. No label update (no relevant information submitted under Art 45 procedure)	Rheumatology	Systemic lupus erythematosus, systemic vasculitides, juvenile dermatomyositis, systemic sclerosis	Data on PK, efficacy and safety.
Clonidine	Not recommended for paediatric use	Pain	Acute, chronic pain	Data on PK, efficacy and safety. Age appropriate formulations.
Cyclosporine	No label update (no new information submitted under Art 45 procedure)	Immunology	(1) Nephrotic syndrome (2) Juvenile idiopathic arthritis (JIA)-related uveitis, macrophage activation syndrome (MAS) / haemophagocytic lymphohistiocytosis (HLH), juvenile dermatomyositis	(1) Data on PK, long-term efficacy and safety. (2) Data on PK, long-term efficacy and safety.
Daunorubicin	New indication: Daunorubicin, as part of a combination regimen, is indicated for the treatment of acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) in children.	Oncoclogy	Lymphoma	Data on PK and efficacy.
Fluoxetin	No change, since submitted studies do not provide new information. Product was licensed in children > 8years for treatment of depression. Procedure was closed with request for more information	Psychiatry	(1) Major depressive disorder (MDD) with psychotic symptoms (2) General anxiety disorder (GAD), obsessive compulsive disorder (OCD)	(1) Data on short and long term-safety. (2)Data on short and long term-safety and efficacy.

Hydroxychloroquine	No recommendation could be provided about a possible treatment of paediatric patients with: juvenile idiopathic arthritis, systemic lupus erythematosus, cutaneous/discoid lupus erythematosus or malaria. Minor amendments to SmPC sections 4.1 and 4.2 were proposed instead	Rheumatology	Systemic lupus erythematosus, juvenile dermatomyositis	Age-appropriate formulation
Ibuprofen	No new information for symptomatic treatment of mild to moderate pain, and/or fever in children. Data were insufficient to support the use against pain and inflammation in rheumatic disease. Paediatric information got clarified (duration, safety information and body weight limit)	Rheumatology	Juvenile idiopathic arthritis, inflammatory conditions	Data on efficacy and long-term safety.
Ifosfamide	SmPC changes were proposed to SmPC sections 4.1 (reference to section 5.1) and 5.1 (study data about treatment in patients with Ewing's sarcoma; general guidance on dosage level and	Oncology	(1) Nephroblastoma, lymphoma (2) germ cell tumours (3) neuroblastoma (4) Solid tumours and ALL	(1, 2, 3) Data on PK in children with a single kidney, long-term follow up of kidney function and evaluation of other long-term sequelae. (4) Data on PK, efficacy and (long-term) safety; need to define lower age group.

	treatment regimen).			
Itraconazole	Not recommended for paediatric use	Infections	Invasive mycotic infections, aspergillosis, chronic granulomatous disease, febrile neutropenia, cystic fibrosis	Data on PK, efficacy and safety.
Lidocaine	Focus on indications as local anaesthetic. Due to the high variability of products and indications, no general product label update could be provided.	Neonatology	Neonatal seizures	Data on PK, efficacy and safety for intravenous formulation.
Melphalan	No change of product Information due to insufficient study data	Oncology	Before allogenic and autologous HSCT for various conditions.	Data on PK, efficacy, short- and long-term safety; in all paediatric age groups.
Mesalazine	Paediatric use information clarified for use against inflammatory bowel disease. Update to SmPC section 4.2 proposed. One CMS did not accept the final recommendation for paediatric posology	Gastroenterology	Inflammatory bowel disease	Data on efficacy and safety compared to sulphasalazin
Metoprolol	New indication: Recommendation for treatment of hypertension	Nephrology	Hypertension	Data on PK, efficacy and safety.
Propofol	Procedure closed with the conclusion: use in neonates is not recommended.	Anaesthesiology	Short-term sedation for procedures	Data on PK, efficacy and safety; age group < 1 month.
Propranolol	Paediatric information clarified: SmPC change 4.2 and 4.8 specifying the use in paediatric	Cardiology	Supraventricular tachycardia	Data on PK, efficacy and safety.

	patients with arrhythmias.			
isoniazid (H) **Rifampicin (R)** ethambutol (E) pyrazinamide (Z)	Recommendations for SmPC section 4.1 and 4.2 of rifampicin: information for use against tuberculosis, N.meningitidis; H.influenzae; Leprosy based on official guidances	Infectious Disease	Tuberculosis	Age-appropriate fixed dose combinations: HRZE, HRZ, HR. PK and dose recommendations.
Topiramate	Safety sections got completed with paediatric data. Section 5.1 got updated with information about absence seizures	Neurology	(1) Epilepsy syndromes (2) neonatal seizures	(1) Data on efficacy (data available only for partial-onset seizures and Lennox-Gastaut syndrome) (2) Data on PK, efficacy and safety for intravenous formulation. Age-appropriate formulation.
Vinorelbine	Not recommended for paediatric use	Oncology	Solid tumours	Data on efficacy in all age groups. Age-appropriate oral formulation.

Active substances which got a PIP approved according to Regulation *(EC) No.1901/2006 as amended*

A PIP has been implemented as legal obligation by *Article 15* of Regulation *(EC) No.1901/2006* to ensure ethical research and development of high quality medicines for use in paediatric patients. MAH are required to submit a PIP either if a new active substance is supposed to be first registered in the EU according to *Article 7*, or, if marketing authorizations of registered medicinal products – still covered by a patent- are supposed to be extended by (a) a new indication, (b) a new pharmaceutical form or (c) new route of administration according to *Article 8* of the Paediatric Regulation. The same obligation applies to off-patent products, if a MAH intends to develop a product for PUMA according to *Article 30* of the Paediatric Regulation.

The PIP defines (a) the type, nature and extent of paediatric studies aiming to demonstrate quality, safety and efficacy of a medicinal product in a specified condition; (b) the timelines and (c) the subsets of the paediatric population (Ref 2). PIPs have to be assessed and approved by PDCO, a scientific committee, which members were nominated based on their expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations (Ref 2). The assessment of a PIP should consider the significant therapeutic benefits for the paediatric patients involved in a study in order to avoid unnecessary exposure to a study environment. In this regard, paediatric studies initiated or completed prior to 26 January 2007 may be included in the PIP, if these studies are fulfilling the criteria of being “significant” according to *Article 45(3)* of the Paediatric Regulation. Criteria specifying the significance of studies pursuant to *Article 45(3)* of the Paediatric Regulation are set out in *Guideline (2014/338/01)* (Ref 21). After completion of the measures as specified in a PIP, MAH are obliged to submit an application for compliance check performed by PDCO prior to the submission of a marketing authorization. If a MAA is supposed to be submitted before all PIP measures are completed, a “partial compliance check” has to be conducted covering all measures, which initiation and completion have not been deferred. The incentives as set out by *Article 38ff* of the Paediatric Regulation, however, would be granted only, if the MAH demonstrated full compliance with all measures as agreed within the latest PIP decision (Ref 26)

A PIP got approved for 22 out of 162 active substances, which were assessed in an *Article 45 EU Worksharing Procedure* between 2008 until 31 December 2014. Most of the PIPs were approved from 2011 onwards; just for atorvastatin and latanoprost the PIP got approved in 2008 and 2009, respectively. Both products were scheduled to an *Article 45 EU Worksharing Procedure* in 2013, when they already passed the PIP compliance check. No recommendation for an additional SmPC update was provided based o paediatric studies assessed in the EU worksharing procedure.

PIP compliance check according to *Article 23* of Regulation (*EC) No.1901/2006 as amended* was successfully completed by five out of 22 products [atorvastatin (2009); human normal globulin (5 out of 10 PIPs were completed by 2014); latanoprost (2010); propranolol (2013) and tobramycin (1 out of 2 PIPs was completed in 2014)]. Three of these products (human normal globulin, propranolol and tobramycin) had been licensed in the EU several decades ago. Hence, the application for the marketing authorization would fall under the scope of *Article 30* of Regulation *(EC) No.1901/2006*

granting marketing exclusivity for 10 years, if the newly generated paediatric study data support the use in the investigated condition. For atorvastatin and latanoprost, no conclusions could be made because the substance patent still may be valid when the PIP compliance check was completed. In this case, an extension or variation to the marketing authorization would fall under the scope of *Article 8* of Regulation *(EC) No.1901/2006 as amended* allowing a 6 month SPC extension according to *Article 38* of the Paediatric Regulation.

The approved PIPs of the active substances covered the following TA: infectious diseases (8); metabolic disease (1); respiratory (1); cardiovascular (1); neonatology (1); gastroenterology (1); CNS (2); oncology (2); dermatology (1); ophthalmology (1); immunology (1) and pain (2).

Most of the eight active substances falling into the TA "infectious disease" were already licensed for paediatric use in the past and the PIP rather aims to add a new bacterial- or vial species, or to specify the use in a new condition. Submitted paediatric studies of these active substances, which were subject to an *Article 45 EU Worksharing Procedure*, did not exert any new information, and hence, the majority medicinal products passed without any recommendation for a SmPC update. Regarding, levofloxacin, however, the proposed indication in the PIP would be the first one, which would be broadly investigated and licensed EU wide in paediatric patients despite the fact this active substance is known to interfere with the cartilage development in children. With conclusion of the *Article 45 EU Worksharing Procedure*, the contraindication for use in children was re-confirmed by the Rapporteur MS and the proposal from Concerned Member State (CMS) France suggesting to keep levofloxacin as back-up antibiotic got rejected (see comment in *Annex A*).

Paediatric studies described in the PIP of the remaining active substances were aiming to (a) clarify the scope of the approved indication which often was kept very general in the past (7 active substances, e.g. atorvastatin; immunoglobulin; fentanyl); (b) investigate new indications (atorvastatin, budenoside, clonidine, dobutamine and propranolol) or (c) expand the adult indication to paediatric populations (captopril; cyclophosphamide; paclitaxel). Regarding atorvastatin and propranolol, the new indication even fell into new TAs compared to indications supported by paediatric studies, which were evaluated in the *Article 45 EU Worksharing Procedures*.

Considering the outcome of the *Article 45 EU Worksharing Procedure* of these medicinal products, submitted paediatric data led to a SmPC update for five active substances; clonidine and paclitaxel were not recommended for paediatric use, and budesonide and dobutamine got recommended for a new paediatric indication. No recommendation for a SmPC update was provided for atorvastatin, latanoprost, human normal immunoglobulin, rabeprazol and cyclophosphamide

A **new pharmaceutical form** is supposed to be developed for 17 active substances. Quality measures, however, had been added as key binding element to the PIP of 13 products, only, (azithromycin, budenoside, captopril, clonidine, cyclophosphamide, dobutamine, fentanyl, ibuprofen, paclitaxel, propranolol, rabeprazole, valciclovir and vigabatrin) (Ref 20).

Table 5: Approved PIPs for active substances which were assessed in an *Article 45 EU Worksharing Procedure* (Ref 20)

Active Substance	Pharmaceutical form assessed in Art 45 Worksharing Procedure	Outcome of Art 45 Worksharing Procedure	PIP	Pharmaceutical form	Condition
Amikacin sulphate	Solution for injection or infusion; powder for suspension for injection or infusion	Paediatric information has been clarified for treatment of serious infections due to susceptible strains of gram-negative bacteria. Update of section 4.1 (reference to guidance for antibacterial use); section 4.2 (dose recommendation for all paediatric age populations); section 4.4 (warning about use in premature and neonatal infants); section 4.5 (interaction with indomethacin); section 4.6 (potential for foetal harm) and section 5.2 (PK in newborns).	EMEA-000525-PIP01-08-M04 (approved 30JAN2015)	Nebuliser suspension	Treatment of Pseudomonas aeruginosa lung infection/ colonisation in cystic fibrosis patients Treatment of nontuberculous mycobacterial lung infection
Atorvastatin calcium	Tablets	Approved indication: hypercholesterolemia. No change was requested. Gaps in the product information for children from 6 to 10 years remained since no new data could be provided.	EMEA-000073-PIP01-07 (approved 20JUL2008)	Film-coated tablet, Age-appropriate oral formulation	Pure hypercholesterolaemia (heterozygous, homozygous, or otherwise primary hypercholesterolaemia), Combined (mixed) hyperlipidaemia; Prevention of cardiovascular events
Azithromycin	Oral formulations such as capsules, powder for oral suspension, and film-coated tablets.	Approved for *M. avium* and *H.influenza* and other susceptible gram negative infections. No recommendation for a label update. Product efficacy and safety had been well characterized in paediatric patients. Label information is inconsistent among different EU	(1)EMEA-001145-PIP01-10 (approved 02JUL 2012) (2)EMEA-001298-PIP01-12 (approved 27FEB2013)	(1)Gel; (2)Age-appropriate dosage form for parenteral use	(1)Prevention of borrelial infections; (2)Prevention of bronchopulmonary dysplasia

		countries and hence the approved indications. Addition of indications following this Article 45 worksharing procedure appeared to be inappropriate.			
Aztreonam	Powder for solution for injection or infusion	Treatment of urinary tract infections; respiratory tract; septicaemia or meningitis cause by gram negative aerobic pathogens. Paediatric data did not lead to an update of the product information. The rapporteur agrees with the MAH that the product is generally safe and efficacious in paediatrics.	EMEA-000827-PIP01-09-M02 (approved 28MAY2013);	Powder and solvent for nebuliser solution	Treatment of Pseudomonas-aeruginosa pulmonary infection / colonisation in patients with cystic fibrosis
Budesonide	Capsules; inhalation powder; inhalation suspension; nebulizer suspension; nasal suspension; nasal powder	Data supported changes to SmPC. For the majority of pharmaceutical forms updates to SmPC section 4.4, 4.8, 5.1, 5.2 were proposed. For Pulmicort respules, SmPC Section 4.1 was updated with an indication for very serious pseudo croup (laryngitis subglottica) in which hospitalisation is indicated. Consequently, recommendations were proposed to Section 4.2; Section 4.4 ; Section 4.8; Section 5.1 and Section 5.2.	(1) EMEA-001120-PIP01-10 (approved 30NOV2011); (2) EMEA-001087-PIP02-12 (approved 06SEP2013)	(1) Pressurised inhalation, solution; (2) Nebuliser suspension	(1) Prevention of bronchopulmonary dysplasia; (2) Treatment of asthma
Captopril	Tablets [6,25mg, 12,5mg, 25mg, 50mg, 70mg and 100 mg]	ACE-inhibitor for treatment of hypertension, congestive heart failure, myocardial infarction and diabetic nephropathy in adults. No SmPC update; no paediatric studies were completed; current SmPC section 4.2 does clarify that efficacy and safety have not been fully established, it provides a	EMEA-001544-PIP01-13 (approved 08AUG2014)	Age-appropriate oral liquid dosage form	Treatment of heart failure

		dose recommendation for initial dose in children. Procedure was closed because the MAH had no license in the EU anymore.			
Clonidine hydrochloride	Tablets; ampules for injection or intravenous infusion; transdermal applications	Paediatric information clarified for treatment of hypertension, Tourette's syndrome or ADHS: update of SmPC sections 4.2 and 5.1. SmPC section 4.2: clonidine is not recommended in children and adolescents below the age of 18 years; SmPC section 5.1: outcome of the main clinical studies	EMEA-001316-PIP01-12 (approved 26MAR2013)	Solution for infusion	Sedation
Cyclophosphamide	Powder for solution for injection; tablets	Licensed for malignant and immune diseases. Submitted data do not suggest a label update.	EMEA-000530-PIP02-11 (approved 27JAN2012)	Soluble tablets	Treatment of malignant diseases
Dobutamine hydrochloride	Solution for infusion (assessment was done for one pharmaceutical form only. Several other strengths exist in the EU)	SmPC change for new indication based on literature: Treatment recommended for all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock. Paediatric information added to SmPC section: 4.2, 4.4, 4.8, 5.1, 5.2.	EMEA-001262-PIP01-12 (approved 25JAN2013	Solution for injection	Treatment of neonatal circulatory failure
Fentanyl	Transdermal patches	Durogesic licensed for long term management of chronic pain: paediatric information clarified - update of SmPC section 4.1, 4.2 (recommendation for posology across different age groups).	EMEA-001509-PIP01-13 (approved 05MAY2014)	Transdermal system	Treatment of acute pain
Human Normal	Intravenous,	Product is used for a variety of	(1) EMEA-001290-PIP01-	(1-3, 5-6, 8,10)	(1) Treatment of primary

Immunoglobulin	subcutaneous, intramuscular	diseases caused by immunodeficiency. No change since studies do not change the benefit –risk profile of the product	12 (approved 20DEC2012); (2) EMEA-000558-PIP01-09-M02 (approved 04APR2014); (3) EMEA-000775-PIP01-09-M01 (approved 02APR2014); (4) EMEA-001637-PIP01-13 (approved 11MAR2014); (5) EMEA-000415-PIP01-08-M01 (27APR2012) (6) EMEA-000830-PIP02-10-M01 (approved 30JUL2013); (7) EMEA-000454-PIP01-08-M05 (approved 19DEC2014); (8) EMEA-000167-PIP01-07-M02 (29JUL2011); (9) EMEA-000454-PIP01-08-M05 (approved 19DEC2014); (10) EMEA-000167-PIP01-07-M02 (approved 29JUL2011)	Solution for infusion; (4,7,9) Solution for injection	immunodeficiency; (2) Treatment of idiopathic thrombocytopenic purpura (ITP) and Treatment of primary immunodeficiency (PID); (3) Treatment of Primary Immunodeficiency (PID) and Treatment of Idiopathic thrombocytopenic purpura (ITP); (4) Treatment of primary immunodeficiency (PID); (5) Treatment of dermatopolymyositis; (6) Treatment of idiopathic thrombocytopenic purpura as a model for immunomodulation and Treatment of primary immunodeficiency as a model for replacement therapy; (7) Treatment of Primary Immunodeficiency (PID); (8) Neonatal haemolytic disease (ABO - Rh-incompatability), Idiopathic thrombocytopenic purpura (ITP) and Primary immunodeficiency (PID); (9) Treatment of Primary Immunodeficiency (PID); (10) Neonatal haemolytic disease (ABO - Rh-incompatability), Idiopathic thrombocytopenic purpura (ITP) and Primary immunodeficiency (PID)
Ibuprofen	Product is available in oral (tablets, capsules, effervescent tablets, granules, powder,	Paediatric information clarified as an anti-inflammatory, analgesic and antipyretic drug (duration, safety information and body weight limit): SmPC section 4.2,	EMEA-001599-PIP01-13 (approved 30SEP2014)	Solution for injection/infusion	Treatment of febrile disorders Treatment of pain

	suspension) rectal, topical and parenteral formulations	4.4 were updated. Instructions in SmPC section 4.2 of oral medication include a reference to the body weight limit.			
Latanoprost	Eye drops solution	No change. Product label reflects the current state of knowledge. Submitted studies had been carried out under the scope of a PIP. After completion of PIP related trials, an Article 29 procedure was carried out which led to the approval of paediatric indications with a recommendation for a posology	EMEA-000011-PIP01-07-M03 (02NOV2009)	Eye drops, solution	Glaucoma
Levofloxacin	Oral suspension, Film-coated tablets, Solution for infusion	Product is contraindicated in paediatric patients due to cartilage toxicity. In adults the product is licensed for treatment of gram positive and gram negative infections. No changes to SMPC recommened	EMEA-001211-PIP01-11-M01 (approved 08AUG2013)	Nebuliser solution	Treatment of cystic fibrosis
Meropenem	Powder for solution for injection or infusion; powder for solution for injection or infusion	Beta-lactam antibiotic for treatment of susceptible bacterial infections. An Article 30 procedure was conducted aiming to harmonize the SmPC. No additional label update was suggested since all paediatric trials were assessed in the Art.30 procedure already. The procedure was closed with the request to generate clinical studies in paediatric patients with less than 3 years of age.	EMEA-000898-PIP01-10 (approved 26JAN2011)	Powder for solution for injection or infusion	Treatment of bacterial sepsis, Treatment of bacterial meningitis
Paclitaxel	Solution for infusion	Product was licensed in adults for a variety of cancer indications. Data were not sufficient to provide advice for paediatric use.	EMEA-001308-PIP01-12 (approved 26APR2013)	Powder for suspension for injection	Treatment of solid malignant tumours

		SmPC section 4.2 got updated (no recommendation).			
Propranolol	Tablets; solution for injection	Paediatric information got clarified for treatment of arrhythmias: SmPC change of section 4.2 and 4.8. Safety and efficacy data do not support a posology in other indications (migraine, thyrotoxicosis, Fallot tetralogy and pheochromocythoma)	EMEA-000511-PIP01-08-M04 (approved 21JAN2013)	Oral solution	Treatment of haemangioma
Rabeprazole	Tablets	Treatment of GORD. Provided data do not support any label change	EMEA-000055-PIP01-07-M05 (approved 26MAR2012)	Gastro-resistant granules; Gastro-resistant tablets	Treatment of Helicobacter pylori in patients with peptic ulcer disease Treatment of gastric ulcer Treatment of duodenal ulcer Treatment of Zollinger-Ellison syndrome Treatment of gastro-oesophageal reflux disease
Tobramycin	Nebulizer solution; solution for inhalation	Approved for long term management of chronic pulmonary infections caused by *P. aeruginosa* in cystic fibrosis. Essential contents had been introduced with type II variation (UK/H/0361/001/II/051); therefore no further changes to the label were recommended	(1) EMEA-000184-PIP02-14 (approved 06AUG2014); (2) EMEA-000184-PIP01-08-M02 (approved 07JUL2014)	(1) Nebuliser solution; (2) Inhalation powder, hard capsules	Treatment of Pseudomonas aeruginosa pulmonary infection/ colonisation in patients with cystic fibrosis;
Valaciclovir	Tablets	Approved for treatment of herpes simplex- and cytomegalic virus infections. Paediatric studies did not change the recommendation provided with completion of an Article 30 referral	EMEA-001548-PIP01-13 (approved 08AUG2014)	Powder for oral suspension	Treatment and prevention of Varicella Zoster virus disease Treatment and prevention of Herpes simplex virus disease
Vigabatrin	Tablets; granules for oral solution	Approved for treatment of partial epilepsy and West's syndrome. Paediatric information clarified: update of SmPC section 4.2; 4.6	EMEA-000717-PIP02-13 (approved 11JUL2014)	Soluble tablet	Treatment of epilepsy

		(general update applicable to all patients); 4.8 (update applicable to all patients; some ADRs were specifically observed in paediatrics) and 5.2 (completion of existing label information and information specific for paediatric information).			
Zanamivir	Powder for inhalation	Approved for treatment and prophylaxis of influenza. Two paediatric studies supported the existing label. No further update was requested. Recommendation for the upcoming PSUR: monitoring of cases with diarrhoea	EMEA-001318-PIP01-12 (approved 29APR2014)	Inhalation powder, pre-dispensed; Solution for infusion	Treatment of influenza Prevention of influenza

Discussion

The Paediatric Regulation *(EC) No.1901/2006 as amended* had been introduced with the aim to bring new and existing medicines to paediatric patients, and to improve the level of information about the use of authorized medicinal products in different subsets of paediatric populations. *Article 45(1)* of Regulation *(EC) No.1901/2006 as amended* specifically addresses the obligation for collecting and assessing paediatric studies, which were completed before 26 January 2007. Most of the paediatric studies had been conducted before ICH Guideline E6 for *Good Clinical Practice* got adopted by the CPMP in July 1996 (Ref 22). However, these data were considered useful for an update of the product information despite the fact that the data quality would hardly meet current standards.

As per *Annex A*, the assessment and outcome of *Article 45 EU Worksharing Procedures* were driven by two important factors, the Rapporteur and the complexity of products.
Apart from few exceptions, MAH usually did not provide proposals for a SmPC update (see *Annex A*). Therefore, the Rapporteur has a crucial role in driving (a) the assessment of paediatric study data; (b) responses from the MAH and comments from the CMS; and, finally, (c) the recommendation for the SmPC update. The difficulty of managing the *Article 45 EU Worksharing Procedure* got further complicated by (1) the complexity of products; (2) the number of MAH submitting paediatric studies and (3) the wealth of information per se.

The complexity of products was caused by the variety of different pharmaceutical forms and the number of indications, which got approved over the past decade(s). Some of these pharmaceutical forms had been licensed for a specific indication and, therefore, separate assessments were conducted under the scope of same *Article 45 EU Worksharing Procedure*. Differences in the license status of indications, again, became frequently a reason for controversial discussions between the Rapporteur and CMS. A recommendation was provided depending on how strong the Rapporteur felt about his position; positive examples have been noted for e.g. alfentanyl, hydroxychloroquine or budesonide. In some instances, however, the update to the SmPC was delegated to the NCA and subsequent variation application procedure (e.g. azithromycin/oral forms; metoclopramide and trimethoprim).

Considering the standards as set out in *Annex I* and *Annex II* of Regulation (*EC) No.1234/2008 as amended*, the assessment of one active substance conducted in an *Article 45 EU Worksharing Procedure* may comprise information appropriate to support several type II variations and/or line extensions grouped in one regulatory procedure (Ref 23). Thus, the complexity of active substances might have contributed to the timelines of assessment procedures, which took in some instances more than 3 years. Shortages in resources and prioritization of *Article 45 EU Worksharing Procedures* could be another explanation for the duration determined in this thesis.

The retrospective analysis performed on 162 assessment reports demonstrated the aim of *Article 45(1)* of Regulation *EC/1901/2006* got accomplished for two out of three active substances, which received a recommendation for a SmPC update based on submitted paediatric study data; literature and/or public guidelines. Major SmPC updates even have been proposed for every third active substance. New indications were recommended for about 7% of the active substances including six active substances, which never had been licensed for a paediatric claim before. Unfortunately, the new indications were not implemented in all EU MS as demonstrated for budenoside, cholchicine, metoprolol and neridronic acid by searching the eMC.

SmPCs of active substances, which passed the *Article 45 EU Worksharing Procedure* without a recommendation, mainly complied with the current state of knowledge (61%); about 16 products completed a regulatory procedure for a label harmonization earlier. While enrolment to *Article 45 EU Worksharing Procedure* is still pending for a high number of active substances, efforts should be made in future to deprioritize products which already passed regulatory procedure aiming to harmonize the PI. The value of an additional assessment under an *Article 45 EU Worksharing Procedure* might be too limited considering the investment of time and resources.

The accomplishments reached under the *Article 45 EU Worksharing Procedure* should not be limited to recommendations for new indications or SmPC updates ameliorating information about the correct dosage, treatment regimen, safety and/or efficacy. The conclusion “not recommended for paediatric use” (26 active substances) or even a recommendation for deletion of a paediatric indication (5 active substances) might be considered as a positive outcome of this procedure. These types of recommendations may protect children against inappropriate therapeutic interventions, which would expose them to unnecessary risks with no or limited efficacy. In case of no alternative therapies, off-label or unauthorized use may be acceptable only if the benefits clearly outweigh the risks.

However, the negative recommendations should be understood as “preliminary outcome”, because robust evidence was missing for almost all products (25 out of 26 active substances). The same reasons prevented 17 active substances from receiving a recommendation for a SmPC update with completion of an *Article 45 EU Worksharing Procedure*. Overall, 26% of the 162 active substances were affected. This issue clearly sheds light on one of the main limitations of this regulatory measure: in general, the quality of paediatric studies falling under the scope of an *Article 45 EU Worksharing Procedure* hardly met the criteria allowing an appropriate assessment of the full range of possible paediatric conditions and related indications including safety. Consequently, new paediatric indications finally were not recommended due to methodological weakness and sparse data as stated in the Rapporteur’s assessment reports for a variety of active substances (e.g. adenosine/solution for infusion; fluoxetine or glucosamine). This issue got further confirmed by rifaximin, which paediatric indications even were all proposed for deletion. Also products, which were proposed for use in a new paediatric indication, received the recommendation rather on the bases of literature or public guidelines than on submitted paediatric studies (e.g. adenosine/solution for injection; neridronic acid). The lack of appropriately designed paediatric trials may not be a surprise for the Regulators at the NCA considering that ICH Guideline E6 for Good Clinical Practice and Directive 2001/20/EC on good clinical practice for clinical trials were adopted in July 1996 and April 2001, respectively. However, the time and efforts necessary to review all these paediatric studies and literature data in order to retrieve the valuable information for a paediatric label update

appeared to be underestimated considering the number of active substances enrolled by year is decreasing (see *Annex B*).

Another limitation identified for this regulatory procedure was related to the different license status of paediatric indications and approved posology, which prevented that valuable paediatric information could be implemented in the SmPC across all EU MSs either for the reasons that some CMS did not agree with the conclusions of the Rapporteur (e.g. new indication proposed for budesonide) or, if the proposal got endorsed, that the recommended wording could not be brought into the appropriate context, because the paediatric indication or even the active substance never got licensed in a CMS (e.g. sufentanil). The lack of label harmonization might be considered as major issue, since the purpose of the Paediatric Regulation was aiming to grant children the same access to authorized medicinal products suitable for their use across EU. CMDh Guideline *CMDh/141/2009/Rev2* addresses this dilemma by asking MAH to evaluate the most appropriate regulatory option in order to implement the recommended wording. However, the request for a label harmonization is not legally binding and follow up on requests as such remain at the discretion of the respective MAH. The retrospective analysis identified 23 products, which received a request for a label harmonization. For some products, the MAH clearly stated that the recommended SmPC wording would be aligned and implemented according to the nationally approved indications of the respective PI only (e.g. alfentanyl).

It is unquestionable, that off-patent products with a long history still represent a valuable source of suitable therapeutic options for paediatric use; in particular by taking into account that registration of new chemical or biological entities were decreasing over the past years (Ref 4). The EMA/PDCO addressed this issue by establishing a priority list for studies on off-patent medicines, which would be eligible to future funding according to the *Horizon 2020 Programme,* because all selected active substances address highest unmet paediatric needs (Ref 19). The present analysis identified 25 active substances, which were included in the priority list. Paediatric studies assessed according to *Article 45* did not provide sufficient evidence justifying a positive benefit-risk profile for paediatric use in the majority of active substances; the remaining active substances were subject to investigations intending to support new paediatric indications. Hence, funding of clinical investigations may be considered as valuable solution to obtain high quality study data, which would support a MA of these products according to *Article 30* of the Paediatric Regulation. However, the European Generic Medicines Association expressed their concerns in a presentation dated from June 2007 about the (high) risk for a negative outcome; the need for multi-therapy research, the small market (no return on investment) and the missing guarantee regarding reimbursement (Ref 25). Maybe these concerns or any other additional reasons could be hold responsible for the fact that just two active substances obtained a license according to *Article 30* of Regulation *(EC) No.1901/2006 as amended* by 31 December 2014. A review of the EMA homepage/opinions and decisions on paediatric investigation plans, however, exerted that PIPs had been agreed for 22 active substances assessed an *Article 45 EU Worksharing Procedure,* which implies the Paediatric Regulation has been at least successful in stimulating activity and interest in development of older medicinal products for paediatric use.

Conclusions and Outlook

The assessment according to *Article 45* of the Paediatric Regulation should be understood as a first aid measure desperately aiming to mobilize valuable information from available paediatric studies, which may or may not lead to further clarification of paediatric information in the PI. Limitations determined for this regulatory procedure, however, suggest that the workload performed under this regulatory procedure need to be balanced. This could be reached if active substances are being selected to an *Article 45 EU Worksharing Procedure* by taking into account the license status and the type of paediatric studies provided by 26 January 2008. The prioritization criteria for enrolment to an *Article 45 EU Worksharing Procedure* may need to be revisited in order to avoid that valuable time and resources are spent on products which SmPCs have been assessed in other regulatory procedures already. Finally, selected active substances should address unmet paediatric needs. For this purpose, the survey published in December 2010 (*EMA/794083/2009*) may need to be repeated in order to obtain an updated and more accurate snap-shot of existing uses of medicinal products whilst all CMS should be encouraged providing their data with appropriate quality. The 5-year report to the European Commission (EMA/428172/2012) pointed out that a number of PI did not get updated after completion of an *Article 45 EU Worksharing Procedure* (Ref 4). Therefore, a general review of all active substances, just for the reasons that paediatric data had been generated at some point time, may not lead to the desired outcome.

Although the *Article 45 EU Worksharing Procedure* is not supposed to be a full harmonization process according to CMDh guideline *CMDh/141/2009/Rev2,* some of MSs, however, repeatedly requested a harmonization of the paediatric label information under the *Article 45 EU Worksharing Procedure*. This indicates some frustration among EU MSs about the limitation of this procedure and may, perhaps, question the purpose of this tremendous effort. Therefore, conditions for this regulatory measure may need to be improved, e.g. by implementing a two tier approach aiming to sort out discussions which were preventing a harmonized recommendation. The first tier step would be an assessment according to the principles as set out in the Best Practice Guideline *CMDh/037/2009/Rev4* involving the MAH. The second tier step, however, may involve PDCO, and perhaps, PRAC and/or SAG, in order to bring discussions to the next level with the aim of reaching consensus for an EU wide harmonized recommendation. The contribution of the MAH to the second tier step, however, should be kept on voluntary basis.

As pointed out in the discussion, paediatric studies assessed in an *Article 45 EU Worksharing Procedure* did not provide all answers about the full range of possible paediatric indications. Therefore, in the long run, the assessments conducted under the scope of an *Article 45(1)* of the Paediatric Regulation has to be re-evaluated and replaced by dedicated research and development activities involving a PIP. The time, however, when this regulatory procedure will be phased-out, should be selected carefully and balanced with treatment options available for paediatric use.

References

Ref 1 EMEA/17967/04/Rev 1. The European Paediatric Initiative: History of the Paediatric Regulation, 11 July 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf. 15 June 2015

Ref 2 Regulation (EC) No.1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation EEC/1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation EC/726/2004. Eudralex Vol.1: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf. 09June2015

Ref 3 COM (2013) 443 final. European Commission. Better Medicines for Children from concept to Reality: Progress Report on the Paediatric Regulation EC/1901/2006 as amended, 24 June 2013. http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf. 15 June 2015

Ref 4 EMA/428172/2012. 5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation. 08 July 2012. http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. 15 June 2015

Ref 5 EMEA/126327/2004. Evidence of harm from off-label or unlicensed medicines in children. October 2004. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004021.pdf. 15 June 2015

Ref 6 EMEA/175192/2004/Rev 2. EMEA/PEG procedure for identifying paediatric needs. 29 June 2005. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004036.pdf. 15 June 2015

Ref 7 EMEA/575696/2007. Guidance on the content and the format of data to be collected by the MS on all existing uses of medicinal products in the paediatric population, October 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/12/WC500026505.pdf. 15 June 2015

Ref 8 EMA/794083/2009. Reports on the survey of all paediatric uses of medicinal products in Europe. 10 December 2010. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101006.pdf. 15 June 2015

Ref 9 EMA/428617/2011 Rev.2. Publication of results-related information on paediatric studies submitted under Article 45 of the Regulation (EC) No 1901/2006 ('Paediatric Regulation'), 19 August 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108222.pdf. 15July 2015

Ref 10 CMDh/037/2009/Rev4. Best practice guide Article 45 – Paediatric Regulation EU Worksharing Procedure, February 2012. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Guidance_Documents/Art_45/CMDh_037_2009_Rev4_clean_2012_02.pdf. 15 July 2015

Ref 11 Report from CMDh Meeting held on 17 and 18 March 2008. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/cmdh_pressreleases/2008_03.pdf. 11June 2015

Ref 12 CMDh/141/2009/Rev2. Recommendations on submission and assessment in paediatric worksharing. March 2013. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Guidance_Documents/Art_45/CMDh_141_2009_Rev2_Clean.pdf. 15 July 2015

Ref 13 CMDh/012/2009: Workplan 2009, January 2009. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/About_CMDh/Workplans/CMDh_Workplan_2009.pdf. 11 June 2015

Ref 14 HMA homepage/paediatric Regulation/Article 45 worksharing: http://www.hma.eu/269.html. 11 June 2015

Ref 15 Public assessment report of Rifamixin (AT/W/0001/pdWS/001), 09 March 2010: http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Rifaximin_2010_04_45PaedPdAR.pdf. 11 June 2015.

Ref 16 Public assessment report of mirtazapine (UK/H/0016/pdWS/001), 18 June 2010. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Mirtazapine_2011_06_45PaedAR_Amended.pdf. 14 June 2015

Ref 17 Public assessment report of topiramate (MT/W/0002/pdWS/001), 13 November 2010. http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Assessment_Reports/Article_45_work-sharing/Topiramate_2011_05_Art.45PaedPdAR_-_Amended.pdf. 14 June 2015.

Ref 18 The electronic Medicines Compendium. http://www.medicines.org.uk/emc/about-the-emc. 10 April 2015

Ref 19 EMA/PDCO/98717/2012: Revised priority list for studies on off-patent paediatric medicinal products, 05 AUG 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf. 10 April 2015

Ref 20 EMA homepage: opinions and decisions on paediatric investigation plans. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129. 14 June 2015

Ref 21 Guideline (2014/C338/01) on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies. http://ec.europa.eu/health/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf . 16 June 2015

Ref 22 CPMP/ICH/135/95/Step5: ICH Guideline E6 - Good Clinical Practice, July 1996. http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html 27 June 2015

Ref 23 Commission Regulation *(EC) No.1234/2008* concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products, 24 November 2008. http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234_cons_2012-11-02/reg_2008_1234_cons_2012-11-02_en.pdf. 27 June 2015

Ref 24 Guideline on Summary of Product Characteristic (SmPC), 2009. http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf . 27 June 2015

Ref 25 Michael Banks/EGA. Development of off-patent medicines for paediatric use: generic industry perspective, 6 June 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500010800.pdf. 28 June 2015.

Ref 26 EMA/PDCO/179892/2011 Rev. 2: Questions and answers on the procedure of PIP compliance verification at EMA and on paediatric rewards, 15 December 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003916.pdf. 18 July 2015.

Declaration

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Annexes

Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Acarbose/ NO/W/0005/pdWS/001	Endocrinology	Diabetes mellitus (adults)	ATC: A10BF01. Tablets	CSR (8); literature: clinical (7)	Q4/2010	05/08/2011	25/11/2011	309	Paediatric information clarified; update of SmPC section 4.2 (no recommendation for paediatric use because available data from MAH-sponsored clinical trials did not provide robust evidence supporting the use of arcabose in paediatric patients)	Initially, MAH did not claim an indication for paediatric use. This was supported by the Rapporteur. Then, the MAH provided with the response submission a proposal for a label update (4.4; 4.8 and 5.1) based on a recommendation and comments received from a MS, which requested a proposal for SmPC section 4.8 and 5.1. The Rapporteur did not support the proposal due to limitations of the studies/published articles (methodological weakness); updating the proposed sections would mislead the prescriber.
Aciclovir/ DK/W/011/pdWS/001	Infectious disease	Treatment of herpes simplex virus infections in neonates, children and adolescents. Treatment of varicella infections in children and adolescents.	ATC: J05AB01. Tablets; powder for injection; oral suspension; cream; powder for infusion.	CSR (13); literature: clinical including guidelines (10)	Q2/2010	13/04/2011	05/08/2011	378	Information about paediatric use got clarified. Separate updates to SmPC for oral formulations and injectable formulations were proposed. Oral form - section 4.1 (Neonatal herpes simplex virus (HSV) and severe HSV infections in immunocompromised children are excluded); section 5.2 (PK results in neonates receiving a higher dose). Injectable form - section 4.2 (recommendation for treatment duration; dose recommendation for infants and recommendation for dose adjustments in patients with renal impairment); section 5.2 (PK results in neonates receiving a higher dose)	

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Adenosine/ UK/W/040/pdWS/001	Cardiology	Treatment of rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia (PSVT), including those associated with accessory by-pass tracts (Wolff-Parkinson-White syndrome). Licensed as an aid to diagnosis of broad or narrow complex supraventricular tachycardias/ (adults)	ATC: C01EB10. Solution for injection or infusion	Literature (NC (2); clinical including guidelines (42))	Q4/2011	12/06/2013	31/07/2013	620	**New indication recommended for solution of injection:** Clarification for use in other indications, such as Wolff-Parkinson-White syndrome (WPWS). Update of SmPC section 4.1 (rapid conversion to a normal sinus rhythm of paroxysmal supraventricular tachycardia in children aged 0 to 18 years); section 4.2 (Instructions for precautionary measures; dose recommendations and instructions for administration) section 4.4 (Warning for atrial arrhythmias if used in patients with WPWS Section) section 5.1 (Discussion of literature data). Solution for infusion: SmPC section 4.2 (no dose recommendation); section5.1 (Literature data)	MAH did not request a paediatric claim but provided a proposal for a bolus injection. The Rapporteur recommended a new indication based on the reasons that for more than 20 years of clinical experience, several paediatric advanced life support guidelines, formularies and uncontrolled clinical studies provide dosing recommendations despite no controlled or MAH sponsored paediatric studies were available. Posology information in the SmPC was based on the combination of currently approved paediatric life support guidelines, results of uncontrolled clinical studies, well established clinical use and expert views. MAH supported substantial bibliographic review.
Alendronate sodium/ UK/W/022/pdWS/001	Skeletal disorder	Treatment and prevention of postmenopausal osteoporosis and steroid-induced osteoporosis in postmenopausal women and for treatment of osteoporosis in men to prevent fractures/ (adults)	ATC: M05BA04. Tablets	CSR (1); literature (4)	Q2/2010	25/05/2011	06/07/2011	420	Paediatric use information got clarified. Update of SmPC section 4.2 (no recommendation for paediatric use) and section 5.1 (Results generated in small patient numbers are insufficient to support the use of alendronate sodium in paediatric patients with osteogenesis imperfecta).	MAH tried to obtain a claim for osteogenesis imperfecta in a previous paediatric worksharing procedure; proposal was rejected due to insufficient data. For the Article 45 worksharing procedure, the MAH did not propose a label update for the paediatric claim again. PK data submitted under the Article 45 worksharing procedure were not proposed for inclusion in SmPC section 5.2 because data may be misleading

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Alfentanil/ BE/W/0003/pdWS/001	Anaesthesia	Opiate analgesic in general as well as intravenous adjuvant to regional anaesthesia and for both short (bolus injections) and long (bolus, supplemented by increments or by infusion) surgical procedures/ (adult and paediatric)	ATC: N01AH02. Solution for injection	Literature (97)	Q3/2010	28/02/2012	02/04/2013	608	Information about paediatric use got clarified. Update of SmPC section 4.1 (indication specified for use in neonates, infants, and children); section 4.2 (dose recommendation for bolus application and maintenance of analgesia clarified; guidance for dose adjustments in children less than 12 years); section 4.4 (warning about respiratory complications; need for muscle relaxants; guidance for use in neonates due to variable pharmacokinetics) section 4.6 (administration during childbirth); section 4.8 (muscle rigidity in neonates) and section 5.2.	Approved indications and dose recommendation varied between EU Member States; this led to discussions between Rapporteur and CMS. Rapporteur pushed back on comments and proposed a harmonized recommendation for a label update based on scientific and medical grounds. Applicant however pointed out that the recommendation for section 4.1 will be implemented in local labels to the extent as it would fit into the current approved text.
Alginic acid/ AT/W/0015/pdWS/001	Gastrointestinal Disease	Treatment of vomiting, regurgitation and gastro-oesophageal reflux (GORD) in infants	ATC: A02BX13. Tablets; oral suspension	CSR (8)	Q3/2012	17/04/2013	31/07/2013	291	The active substance “alginic acid” is not included in any Gaviscon formulations anymore; new formulations had been developed containing alginate salts. No change to the existing product information.	
Alprazolam/ UK/W/032/pdWS/001	Psychiatric disorder	Hypnotic for treatment of short-term treatment of moderate or severe anxiety states and anxiety associated with depression (adults)	ATC: N05BAI2. Tablet; oral solution	CSR (4); literature (7)	Q1/2011	19/11/2011	07/03/2012	323	Paediatric information got clarified. Update of SmPC section 4.2 (not been established for paediatric use; therefore use of alprazolam is not recommended).	Available data from MAH-sponsored clinical trials and published medical literature remain inconclusive and hence there was no robust evidence supporting the use of alprazolam in paediatric patients

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Amikacin sulphate/ SE/W/003/pdWS/001	Infectious disease	Aminoglycoside indicated for short-term treatment of serious infections caused by susceptible strains of gram-negative bacteria. (adult and paediatrics)	ATC: DB00479. Solution for injection or infusion; powder for suspension for injection or infusion	CSR (2)	Q4/2008	22/12/2009	23/02/2010	448	Paediatric information got clarified. Update of section 4.1 (reference to guidance for antibacterial use); section 4.2 (dose recommendation for all paediatric age populations); section 4.4 (warning about use in premature and neonatal infants); section 4.5 (interaction with indomethacin); section 4.6 (potential for foetal harm) and section 5.2 (PK in newborns).	A harmonized text for paediatric data in SmPC was mutually agreed; implementation via a type II variation
Amiodarone/ NL/W/0015/pdWS/001	Cardiology	Treatment of adults with supraventricular and ventricular tachyarrhythmia. The tablet got an approved paediatric posology (section 4.2) in the UK and in Belgium without any specific paediatric indication. In Germany, there is a mention regarding the adjustment of dose according to body weight and in Finland, there is a mention regarding restricted use of amiodarone in children in section 4.1.	ATC: C01B D01. Tablets; solution for injection	Literature (30)	Q1/2010	08/12/2010	24/03/2011	342	Clarification of information for paediatric use. Update of SmPC section 4.2 (referencing 5.1; 5.2); section 4.3 (contraindication for children with less than 3 years); section 4.4 (warning about benzyl alcohol); section 5.1 (dose description used in paediatric trials) and section 5.2.	Rapporteur did not recommend an indication for paediatric use, because submitted data were not sufficiently robust to support a posology. The SmPC guideline states: in cases there is no specific paediatric indication, no posology would be mentioned under section 4.2. Paediatric information from studies was considered important; a type II variation to include paediatric data in the product information. MAH was requested to consider a harmonization of the label to give children the same access to authorised medicinal products across the EU.
Amisulpride/ IE/W/0009/pdWS/001	Psychiatric disorder	Antipsychotic for treatment of schizophrenia in adults. Treatment of dysthymia (50mg) is registered in few Member States only (adults)	ATC: NO5AL05. tablets	CSR (4); literature (4)	Q3/2012	04/09/2013	08/01/2014	431	Submitted paediatric studies did not lead to an amendment of the SmPC.	

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Amlodipine/ NL/W/0002/pdWS/001	Cardiovascular	Treatment of adults with hypertension and/or for angina pectoris	ATC: C08CA02. Tablets	CSR (2)	Q4/2008	21/10/2009	26/11/2009 *Update: 06/04/2010	386	Clarification of information for paediatric use. Update of SmPC sections 4.2 (age range specified); section 5.1 (description of efficacy in patients with secondary hypertension) and section 5.2	
Amoxicillin/ SE/W/009/pdWS/001	Infectious disease	Beta-lactam antibiotic for treatment against gram-positive bacterial infections. Various indications approved in the EU, non-of the indications are specific for paediatrics	ATC: J01CA04. Oral suspension; tablets; capsules; powder for solution for injection or infusion	Literature (16)	Q2/2009	13/05/2010	05/08/2010	408	Paediatric information got clarified aiming for a harmonized label information. Update of SmPC section 4.2 (dose recommendation for children weighing less than 40kg; dose recommendations specified per indication (tonsillitis, otitis media, early lyme disease, prophylaxis of endocarditis); dosage for patients with renal impairment). Section 4.4 and section 5.2	
Amoxicillin / Clavulanic Acid/ DE/W/002/pdWS/001	Infectious disease	Broad-spectrum antibiotic covering lactamase-producing pathogens. Approved indications depend on amoxilin/ clavulanic acid ratio (adults and paediatrics)	ATC: J01CR02. Oral and intravenous formulations (no further specified)	CSR (5)	Q1/2009	14/06/2010	05/08/2010	530	Product information passed an Article 30 Referral EMEA/H/A-30/979 in 2009. No further update was requested.	
Atorvastatin calcium/ IE/W/0013/pdWS/001	Metabolic disease	Treatment of hypercholesterolemia and hyperlipidaemia (adults and paediatrics)	ATC: C10AA05. Tablets	CSR (4)	Q3/2013	24/02/2014	03/06/2014	239	No change was requested. Gaps in the product information for children from 6 to 10 years remained since no new data could be provided.	A three year efficacy and safety study in children 6-15 years old with heterozygotic familial hypercholesterolemia was still ongoing. This study was conducted under the scope of a PIP. Data of this study had not been assessed during the Article 45 worksharing procedure.

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Atracurium besilate/ IE/W/0008/pdWS/001	Anaesthesiology	An adjunct to general anaesthesia to enable tracheal intubation to be performed, to relax skeletal muscles and to facilitate controlled ventilation during a wide range of surgical procedures (adults and paediatrics)	ATC: M03AC04. Solution for injection or infusion	CSR (7); literature (23)	Q3/2011	04/12/2012	09/05/2013	522	Submitted paediatric studies did not suggest changes to the label information. However SmPC section 4.2 and 5.1 were updated about the lack of information in neonates	Literature review was requested by Rapporteur to verify if data allow an extension of indication to children below 1year.
Azithromycin Part I / HU/W/0002/pdWS/001	Infectious disease	Macrolide antibiotic for treatment of susceptible gram-negative bacterial organisms, particularly Mycobacterium avium complex and Haemophilus influenzae. (adults and paediatrics)	ATC: J01FA10. Oral formulations such as capsules, powder for oral suspension, and film-coated tablets.	CSR (300)	Q3/2009	17/07/2012	28/09/2012	1112	No recommendation for a label update. Product efficacy and safety had been well characterized in paediatric patients. Label information/indications however were inconsistent among different EU countries. Use of azithromycin for treatment of diarrhea caused by Shigella was under discussion since it got a recommendation from national and international expert fora. MAH pointed out that alignment of the wording could only be done for the same approved indications. Procedure closed with request for label harmonization.	
Azithromycin Part II / HU/W/0002/pdWS/001	Infectious disease	Treatment of purulent bacterial conjunctivitis, Trachomatous conjunctivitis caused by Chlamydia trachomatis (adults and paediatrics)	Eye drops	CSR (3)	Q3/2009	17/07/2012	28/09/2012	1112	A type II variation was submitted extending the indication to paediatric patients based on studies which were submitted under the scope of Article 46 of Regulation EC/1901/2006. Therefore no changes were proposed under the scope of this Article 45 worksharing procedure.	

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Aztreonam/ NL/W/0019/pdWS/001	Infectious disease	Beta-lactamase resistant monobactam against gram-negative aerobic pathogens treating infections of the urinary tract, lower respiratory tract, septicaemia, meningitis (H.influenza or N. meningitis), skin & soft tissue infections gynaecological infections, gonorrhoea (adults and paediatrics)	ATC: J01DF01. Powder for solution for injection or infusion	CSR (6)	Q2/2010	25/03/2013	09/05/2013	1089	Paediatric data did not lead to an update of the product information. The Rapporteur agreed with the MAH that the product is generally safe and efficacious in paediatrics.	
Baclofen/ UK/W/005/pdWS/001	Neurological disorder	Treatment of spasticity of the skeletal muscles due to various conditions (adults and paediatrics)	ATC: M03BX01. Solution for injection; solution for infusion; oral solution; tablets	NC (2); CSR (19); literature (8)	Q1/2009	12/05/2010	26/01/2011	497	Paediatric information got clarified; update of SmPC sections for oral formulations: Section 4.1 (different diagnosis causing spasms have been clarified); section 4.2 (dosage and treatment regimen) and section 4.4 (patients with < 1year). Intrathecal formulation: section 4.1 (clarification about indication); section 4.2 (dosage recommendation during screening-, titration and maintenance phase) and section 4.4 (no recommendation in patients with head injury and patients less than 4years)	On D 89, MAH was requested reviewing the national SmPCs as well as other available data in order to propose harmonised SmPC regarding paediatric indications and dosage recommendations. Following additional information provided by the MAH, a recommendation with a finalized wording for inclusion in the SmPC of all products containing baclofen across EU got fully endorsed by CMS.

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Beclometasone dipropionate/ IE/W/001/pdWS/001	Respiratory	Treatment of hay fever; asthma and COPD (several indications presented across different labels depending on licensed pharmaceutical form) (adults and paediatric)	ATC: R03BA01. Nasal spray; inhalation powder; inhalation solution; tablets	CSR (10)	Q1/2009	11/01/2010	24/05/2010	376	Submitted paediatric studies did not provide any new information about paediatric use. Study design of some studies was insufficient.	The NL proposed harmonization of the label information under this procedure. The rapporteur did not support this proposal because the assessment under Art 45 aims to review information related to clinical and safety emerging from clinical trials which had not been seen by, or submitted to, regulatory authorities. Harmonization of the label should be done outside this procedure.
Bisacodyl/ DK/W/002/pdWS/001	Gastrointestinal Disease	Short term relief of constipation; Constipation, either chronic or of recent onset, whenever a stimulant laxative is required; Bowel clearance before surgery or radiological investigation. Replacement of the evacuant enema in all its indications. (adult and paediatric)	ATC: A06AB02. Tablets; suppositories; enema	CSR (6); literature (15)	Q4/2008	20/11/2009	11/01/2010 *update:07/07/2010	416	Paediatric information clarified: update of SmPC section 4.2 (Instructions added for use in children with less than 10 years: treatment given under supervision of a physician; use in patients with less than 2 years is not recommended. Dosage instructions provided for short-term treatment: paediatric population range from 2year to 17year. Dosing instructions prior to diagnostic procedures and surgery: 4 year to 17years.)	Rapporteur provided a recommendation for clarification the posology [product from Guerbert not included due to the specific pharmaceutical form (bottle containing a phosphate laxative and 4 film -coated bisacodyl tablets)]. Further dosage instructions for short term constipation were removed for patients less than 2 years of age. However, harmonisation of posology section cannot be achieved due to different approved posology and different strength. Hence the Rapporteur recommended to initiate a type II variation for the purpose of label harmonization.
Bisoprolol fumarate/ UK/W055/pdWS/001	Cardiovascular	Treatment against: angina pectoris; heart failure; hypertension; hyperkinetic heart syndrome; ventricular extra systole (adults)	ATC: C07AB07. Tablets	CSR (2); Literature (2)	Q4/2012	20/01/2014	06/05/2014	477	No change to SmPC proposed because data were to sparse to support an indication. Update to section 5.1 not recommended because it may mislead the prescriber.	History: MAH tried to obtain an indication for paediatric use; FDA and MHRA rejected because efficacy could not be demonstrated.

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Budesonide/ NL/W/0001/pdWS/001	Respiratory	Corticosteroid for treatment against acute Crohn's disease (adults an paediatric >8 years); allergic rhinitis and nasal polyps (paediatrics >6y); bronchial asthma (paediatrics >2y); COPD (paediatrics >6y)	AYC: A07EA06. Capsules; inhalation powder; inhalation suspension; nebulizer suspension; nasal suspension; nasal powder	CSR (24); Literature (26)	Q4/2008	25/10/2011	04/03/2014	1120	Data supported changes to SmPC. For the majority of pharmaceutical forms updates to SmPC section 4.4, 4.8, 5.1, 5.2 were proposed. Rhinocort Turbohaler:update to SmPC section 4.2 (use in paediatrics not established). Pulmicort respules: SmPC Section 4.1 was updated with an indication for very serious pseudo croup (laryngitis subglottica) in which requires hospitalisation of patients. Consequently, recommendations were proposed to Section 4.2 (dose specified by indication); Section 4.4 and 4.8; Section 5.1 and 5.2.	A new indication was recommended for Pulmicort Respules (nebulizer suspension) only. SE and France did not endorse the recommendation and the indication was not implemented.
Budesonide + Formoterol/ DE/W/046/pdWS/001	Respiratory	Asthma: license (adults and paediatric). COPD (for higher strengths)	ATC: R03AK07. Dry powder for inhalation	CSR (39)	Q4/2011	07/11/2012	30/01/2013	403	New study data lead to update of SmPC section 4.2 (administration under supervision of an adult); 5.1 (paediatric data)	
Bupivacaine hydrochloride/ DE/W/042/pdWS/001	Anaesthesiology	Local anaesthesia (adults and adolescents >15 y)	ATC: N01BB01. Solution for injection	Literature (57)	Q1/2011	31/10/2012	19/12/212	669	Paediatric information clarified. For 7.5mg/ml solution for injection: update SmPC section 4.1 (indication got limited to paediatric patients > 12 years); section 4.2 (age limit; no specific dose instructions) and section 4.8. For remaining products strengths: Section 4.1. (Indications and age limits per indication got specified); SmPC section 4.2 (Dose instruction by route of administration or body weight; age range; dose instruction for specific interventions or patient group) Section 4.4; Section 4.8; Section 5.1 and 5.2. SmPC section 4.3 got updated for the combined use with adrenaline in areas of end arteries.	

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Bupropion hydrochloride/ NL/W/0008/pdWS/001	Psychiatric disorder	Treatment of depression (adults)	ATC: N06AX12. Tablet	CSR (3)	Q3/2009	30/11/2009	23/03/2012	153	No change proposed: data did not provide evidence for efficacy in ADHS and depression. Information about class labeling for antidepressants and suicidal events was already reflected.	
Captopril/ CZ/W/0007/pdWS/001	Cardiovascular	ACE inhibitor for treatment of hypertension; congestive heart-failure; myocardial infarction and diabetic nephropathy (type-I) (adult)	ATC: C09AA01. Tablets [6,25mg, 12,5mg, 25mg, 50mg, 70mg and 100 mg]	Literature (2)	Q1/2010	22/01/2013	02/04/2013	1117	No SmPC update; no paediatric studies were completed; current SmPC section 4.2 did alreade state that efficacy and safety had not been fully established, it provided a dose recommendation for initial dose in children, however. Procedure was closed because the MAH had no license in the EU anymore.	
Carbomer/ AT/W/0011/pdWS/001	Ophthalmology	Dry eyes (adult)	ATC: S01AX20. Eye gel	Literature (5)	Q3/2011	03/07/2012	28/09/2012	368	Paediatric information clarified: Update of SmPC section 4.2 (referring to adult posology which got established by clinical experience; clarification about the fact that no clinical trial data were available)	SmPC change was proposed based on grounds that despite the lack of clinical data, carbomer could not not be restricted to adults because carbomer had no pharmacological properties but physical properties suitable to moisten the eyes.
Chondroitin Sulfate/ UK/W/007/pdWS/001	Skeletal disorder	Treatment of osteoarthritis (adult)	ATC: M01AX25. Capsules	CSR (2)	Q2/2009	02/09/2009	01/10/2010	185	Paediatric information clarified: update SmPC section 4.2 with a statement that chondroitin is not recommended for paediatric use because available data were insufficient to extend the indication to paediatric patients	
Cyclosporine/ CZ/W/04/pdWS/01	Immunology	Immuno-suppression after organ or bone marrow transplantation (adult and paediatric)	ATC: L04A D01. Soft gelatine capsules; oral solution; solution for infusion	CSR (14)	Q4/2009	16/05/2010	01/07/2010	228	No SmPC change: submitted information is in line with the current SmPC	

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Clarithromycin/ SK/W/0001/pdWS/001	Infectious disease	Infections of respiratory tract; skin/tissue infection (adults and paediatrics). helicobacter pylorii (adults).	ATC: J01FA09. Tablets; granules for oral suspension; drinking straw; powder for solution for injection	CSR (55); literature (3)	Q2/2009	26/10/2010	24/11/2010	574	Paediatric information clarified: update of SmPC section 4.1 (reference the official guidance for appropriate use of antibacterial agents); section 4.2 (specifying age limits per oral formulation and duration of treatment).	
Clindamycin/ DK/W/009/pdWS/001	Infectious disease	Treatment of susceptible Gram-positive bacterial infections; acne vulgaris (adults and paediatric)	ATC: D10AF01, J01FF01, G01AA10. Topical lotion; topical solution; vaginal cream; solution for injection; topical gel; granules for oral solution; capsules.	CSR (16); literature (36)	Q1/2010	30/03/2011	06/06/2011	454	Submitted data do not suggest any update to the product label.	
Clobazam/ UK/W/018/pdWS/001	Psychiatric disorder	Treatment of acute and chronic anxiety state; adjunctive therapy in patients with epilepsy (adult and paediatric)	ATC: N05BA09. Tablets, capsules	Literature (40); CSR (1)	Q4/2009	16/12/2010	27/04/2011	442	Paediatric information clarified: update of SmPC section 4.2 (dose recommendation for patient with ≥6 years of age for initiation and maintenance of treatment of epilepsy; no posology for anxiety, i.e. adolescents were removed from posology). Further, amendments to the adult posology has been proposed as well.	
Clonidine hydrochloride/ NL/H/0017/pdWS/001	Pain	Menopausal flushing, hypertension, withdrawal symptoms after stopping treatment with opiates. Therapy and prophylactic treatment of migraine or recurrent vascular headaches (adult)	ATC: M04AC01 . Tablets; ampules for injection or intravenous infusion; transdermal applications	CSR (12)	Q1/2010	12/01/2011	27/04/2011	377	Paediatric information clarified: update of SmPC sections 4.2 and 5.1. SmPC section 4.2: clonidine is not recommended in children and adolescents below the age of 18 years; SmPC section 5.1: outcome of the main clinical studies	

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Colchicine/ UK/W/015/pdWS/001	Rheumatology/ Systemic disease	Rheuma including gout attack and prevention of gout attack; mediterranean fever, behcet's disease (adult)	ATC: M04AC01. Tablets	Literature (39)	Q3/2009	03/10/2011	29/02/2012	825	SmPC changes were proposed for SmPC sections 4.1, 4.2, 4.4, 4.9 and 5.2. New indication proposed for use against Familial Mediterranean Fever (for prophylaxis of attacks and prevention of amyloidosis). Section 4.2 got updated with an age-specific posology.	Product was introduced before 1910; first authorization was granted in France, 1947.
Cholecalciferol/ UK/W/041/pdWS/001	Skeletal disorder	Prophylaxis of rickets (paediatrics); Prophylaxis in recognisable risk of a vitamin D deficiency disease; Supportive treatment of osteoporosis; Prophylaxis in recognizable risk of a vitamin D deficiency in malabsorption; Treatment of rickets and osteomalacia; Treatment of hypoparathyroidism	ATC: A11CC05. Tablet; oral solution	Literature (76)	Q1/2012	24/05/2013	06/05/2014	509	Paediatric information clarified: update of SmPC sections 4.1 (for each indication the paediatric population got specified), 4.3, 4.4. A posology specified for each subset could not be provided.	
Cholecalciferol / sodium fluoride/ UK/W/046/pdWS/001	Skeletal disorder	Prophylaxis of rickets and tooth decay; combined rickets and dental caries prophylaxis (paediatrics)	ATC: A11CC80 and A11JB. Tablets	Literature (20)	Q1/2012	02/07/2013	26/09/2013	548	Paediatric information clarified: cholecalciferol and fluoride combination products -update of SmPC sections 4.2 (age limit of 6 months) and 5.1 (brief summary of clinical information including a dose recommendation). Specific change for combination cholecalciferol + sodium fluoride - SmPC section 4.1: prophylactic use in children 6months to 3years for rickets and caries and recommendation for posology in section 4.2 .	

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Colestyramine/ CZ/W/002/pdWS/001	Hepatobiliary disorder	Adult and paediatric indication: Reduction of serum cholesterol levels and prevention of coronary heart disease; For the relief of pruritus associated with partial biliary obstruction; As an adjunct to rehydration therapy, for relief of diarrhoea due to bile acid malabsorption	ATC: C10AC01. Powder for oral suspension	CSR (1)	Q1/2009	19/08/2009	11/01/2010	231	No SmPC change recommended	Single study did not provide sufficient evidence for indication "watery diarrhoea". Other indications (lipid lowering drug, treatment of pruritus or detoxification) had not been studied.
Cyclophosphamide/ CZ/W/001/pdWS/001	Oncology	Since 1957 available; treatment of malignant as well as autoimmune diseases	ATC: L01AA01. Powder for solution for injection; tablets	Literature (83)	Q1/2009	23/12/2009	30/09/2011	357	Submitted data did not suggest a label update.	
Daunorubicin/ NL/W/0009/pdWS/001	Oncology	Treatment of acute lymphocytic leukaemia (ALL) and acute non-lymphatic leukaemia, children with ALL should only be treated with daunorubicin if they belong to the high-risk group [the NL (1991)]; paediatric indications and posology were licensed also in BELUX,UK, IRE)	ATC: L01DB02. Powder for solution for infusion	Literature (16)	Q3/2009	02/05/2011	02/04/2013	671	SmPC change: new indication and paediatric information clarified (*the Dutch SmPC didn't reflect completely the clinical practice regarding treatment of children with ALL or AML . For ALL patients the SmPC focus only on the high-risk group. Children with AML were not specifically mentioned*); Recommendation to SmPC section 4.1: Daunorubicin, as part of a combination regimen, is indicated for the treatment of acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) in children. Further, update to section 4.2 (dosing instruction per age range; treatment regimen) and 5.1 recommended.	History: Daunorubicin was used for treatment against acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in children. In 1991, the MEB approved the product for ALL and AML; children with ALL should only be treated if they belong to high risk group. For low risk group, no higher remission was observed.

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Desmopressin/ CZ/W/0017/pdWS/001	Endocrinology	Approved in children. Paediatric indication may vary from country to country. Antidiuretic approved for: Central diabetes insipidus, Renal concentrating capacity testing; primary nocturnal enuresis. Haematological including von Willebrandt disease and mid/moderate haemophilia	ATC: H01BA02. **MINIRIN products**: intranasal formulation; Oral formulation ; injection. **OCTOSTIM products:** nasal spray; Injection. (Pituitary and hypothalamic hormones and analogues, Vasopressin and analogues)	CSR (8)	Q2/2014	17/10/2014	01/12/2014	200	No change. Submitted studies did not provide any (new) information.	
Desogestrel/ CZ/W/005/pdWS/001	Endocrinology/ Women health	Oral contraception (adult only)	ATC: G03AC09. Tablet	CSR (1); literature	Q3/2010	29/07/2011	07/03/2012	394	Paediatric information clarified with standard text from SmPC guideline explaining no information about paediatric use is available: sections 4.2 and 5.1	
Desogestrel+Ethinylestradiol/ CZ/W/005/pdWS/001	Endocrinology/ Women health	Oral contraception (adult only)	ATC: G03AA09. Tablet	CSR (1); literature; WHO guideline	Q3/2010	29/07/2011	07/03/2012	394	Paediatric information clarified: sections 4.2 (use in paediatric patients not established) and 5.1	
Dexamethasone/ MT/W/005/pdWS/001	Systemic disorder	Corticosteroid for treatment of various inflammatory and autoimmune diseases (adults; paediatric indications not specified)	ATC: HO2AB02 Tablets; solution for Injection	Literature (233)	Q4/2011	20/07/2012	24/10/2012	293	New safety information: Section 4.4 (concerning use in preterms); 4.6 and 5.3	

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Dexamethasone combinations/ MT/W/0006/pdWS/001	Ophthalmology/ ear disease	Most of the dexamethasone combinations are not indicated for paediatric use: Dexamethasone can be used alone for short term local treatment of inflammation and in combination with a number of topical antibiotics to control Acute Otitis Externa (AOE) and eye diseases for short term application in the treatment of steroid responsive conditions of the eye, when prophylactic antibiotic treatment is also required, after excluding the presence of fungal and viral disease.	ATC: D07CB04 S01AA20 S01BB05 S01CA01 S01CA06 S02CA06 S03CA01. Eye drops; Eye ointment; ear drops	Literature (4) provided for the combination: Dexamethasone + framycetin + gramicidin	Q4/2011	07/08/2012	06/03/2013	311	Various combinations have been assessed during this procedure. For Dexamethasone + framycetin + gramicidin combinations the paediatric information got clarified: section(s) 4.2 (duration of treatment specified) and 4.4. For the other combination no recommendation was provided.	

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Active Substance	Therapeutic Area	Description of Indication/ (licensed population at start of procedure)	ATC/ Pharmaceutical form	Studies submitted NC = non-clinical CSR= clinical study report Literature	Wave*1	End of Procedure	Date of Publication	Duration of Assessment Procedure (calendar days)*1	Outcome of Assessment/ SmPC update	Notes/Comments
Diclofenac/ DE/W/001/pdWS/001	Pain	NSAID used as anti-inflammatory drug and treatment of painful conditions. recommended for use in paediatric patients as a prescription-only medicine (POM) in acute conditions such as post-traumatic, postoperative pain [POP], inflammations and swelling, and severe painful inflammatory infections of the ear, nose or throat [ENT] (as an adjuvant therapy), as well as in a chronic indication such as juvenile rheumatoid arthritis.	ATC: M02AA **systemic formulations**: solution for injection, oral solution, tablets and suppositories; **topical formulations**: flexible dosed formulations and fixed dosed formulations like plasters; **ophthalmological formulations**: eye drops (adult only)	NC; CSR	Q4/2008	27/09/2010	24/11/2010	727	**Paediatric information clarified. Systemic application**: acute indications (full harmonization of SmPC section 4.1 could not be achieved). Section 4.2 (dose recommendation by pharmaceutical form, age range and body weight. few pharmaceutical form/strengths were not recommended in children). For chronic indication juvenile idiopathic arthritis (JIA) , (update of section 5.1). **Topical formulations**: update of SmPC section 4.2 (Age limit by pharmaceutical form). Section 4.3 (contraindication for paediatric patients below age limit). However, differences between licensed indications across CMS and the objections from the MAH prevented a full harmonization of paediatric information in SmPC. **Ophthalmological formulations:** no update	
Dobutamine hydrochloride/ PL/W/0003/pdWS/001	Cardiovascular	Inotropic support for treatment of low output cardiac failure associated with myocardial infarction, open heart surgery, cardiomyopathies, septic shock and cardiogenic shock. Dobutamine stress echocardiography (adult)	ATC: C01CA07 Solution for infusion (assessment was done for one pharmaceutical form only. Several other strengths exist in the EU)	Literature (30)	Q4/2010	02/01/2013	06/03/2013	824	SmPC change for new indication based on literature. SmPC section 4.1 (recommended (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion state resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock. Paediatric information added to SmPC section : 4.2 (by indication, instruction for titration), 4.4, 4.8, 5.1, 5.2.	

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Esmolol hydrochloride/ FI/W/0004/pdWS/001	Cardiovascular	Treatment for supraventricular tachycardia; for tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia; Paediatric dosing instructions, warnings, pharmacodynamics and pharmacokinetics section in the SmPC of esmolol containing medicinal products got established in 2008 based on post-marketing data and bibliographic data	ATC: N07BB04 Solution for injection, Concentrate solution for infusion, Powder for concentrate for solution for infusion	Literature (5)	Q2/2011	12/06/2012	19/12/2012	438	Submitted data do not suggest further changes to the label	
Estradiol/ CZ/W/08/pdWS/001; Estradiol and norethisterone/ CZ/W/09/pdWS/001	Endocrinology/ Women health	A hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women. Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis (adult)	ATC: G03CA03; Gel	Literature (1 paper in patients with turner syndrome; estradiol only), no data for combination	Q1/2013	17/04/2014	04/08/2014	472	No change (information is not sufficient to propose changes to SmPC)	
Ethosuximide/ UK/W/020/pdWS/001	Neurological disorder	Absence epileptic seizures (children and adults)	ATC:N03AD01; Capsule; syrup	Literature (8)	Q1/2010	07/03/2011	24/03/2011	431	Paediatric information clarified: update of SmPC section 5.1 with information from recently published clinical trial data	

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Etoposide/ SI/W/0001/pdWS/001	Oncology	Small cell bronchial carcinoma; Non-small cell bronchial carcinoma; palliative therapy of advanced incurable disease in patients with Karnofsky index >80%; Hodgkin's disease; reinduction therapy after failure of standard therapies for induction of remission; Non-Hodgkin's lymphomas; induction of remission of intermediary or high malignancy; testicular tumours; chorionic carcinoma. **Indication as per pharmaceutical form -** capsule (soft)**:** Acute myeloid leukaemia (AML); Ovarian carcinoma ; Solution for injection: *Childhood acute myeloid leukemia (AML)* ;Adult acute myeloid leukaemia (AML)	ATC code: L01CB01; concentrate for solution for injection; soft capsules;	Literature (247)	Q2/2009	08/01/2011	10/04/2012	648	Dossier did not comply with standards of current guidance. One MAH claimed that no SmPC change is required. The Rapporteur did not agree with the MAH conclusion, since available data would support a SmPC change. Nevertheless, the Rapporteur did not provide a recommendation for SmPC update. The AR was closed with a statement that the SmPC should be revised after relevant data are presented according to regulatory requirements.	
Famciclovir/ DE/W/008/pdWS/001	Infectious disease	Treatment of viral infections (herpes zoster & ophthalmic zoster; herpes simplex (genital and labialis)) (adults)	ATC: J05A B09; Film-coated tablets	NC (3); CSR (2)	Q4/2009	20/07/2010	01/10/2010	293	No change was recommended due to poor quality of data. Reference was made to an Art.30 procedure completed in April 2010	
Felodipine/ UK/W/002/pdWS/001	Cardiovascular	A highly vascular selective calcium antagonist for management of hypertension and prophylaxis of chronic stable angina pectoris (adult)	ATC: C08CA02; Modified-release tablet; Prolonged release tablet	CSR (2)	Q4/2008	15/10/2009	26/11/2009	380	Paediatric information clarified - SmPC sections 5.1 and 5.2 got updated; paediatric information was limited.	

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Fenofibrate/ IE/W/0007/pdWS/001	Metabolic disease	Treatment of hypercholesterolemia and hypertriglyceridemia alone or combined in patients unresponsive to dietary and other non-drug therapeutic measures. The high dosage forms are contraindicated in children below age 18 due to a lack of safety and efficacy data. Only low strengths of fenofibrate (standard nonmicronised 100 mg capsules and the bioequivalent 67 mg micronised capsules) got an indication for paediatric use in some EU countries (F; PL; UK; RO)	ATC: C10A B05 Capsules; tablets.	Literature (4)	Q1/2011	10/10/2011	30/01/2012	283	Paediatric information clarified: Fenofibrate 67 mg and 100 mg capsules, update of sections 4.2 (no recommendation for posology) and 5.1. For high dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) update of sections 4.2 (no recommendation); contraindication removed since missing data do not justify a contraindication .	
Fentanyl/ UK/W/003/pdWS/001	Anaesthesia	Breakthrough Pain; Premedication before anaesthesia (Durogesic: paediatric indication for the long-term management of chronic pain in children receiving opioid therapy from 2 years of age)	Durogesic transdermal patches; Sublimaze - solution for injection; Actiq - solid formulation for oral transmucosal administration	Durogesic: none; Sublimaze: Literature (7); Actiq: CSR (13)	Q4/2008	22/11/2009	23/03/2010 *update 06/06/2011	418	**Durogesic**: paediatric information clarified - update of SmPC section 4.1, 4.2 (recommendation for posology by age group). **Sublimaze**: paediatric information clarified - update of SmPC section 4.2 (posology by age range; previous approved dosing regimen deleted), 4.4. **Actiq**: paediatric information clarified - update of SmPC section 4.2 (not established for use in paediatrics), 5.1, 5.2.	

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Filgrastim/ SE/W/010/pdWS/001	Oncology	Approved indications in paediatric populations: Established Cytotoxic Chemotherapy (neuroblastoma and acute lymphoblastic leukaemia); Severe Congenital, Cyclic or Idiopathic Neutropenia	ATC: L03AA02 Solution for injection	Literature (18)	Q2/2009	26/04/2010	01/07/2010	391	No change proposed	
Flecainide/ IE/W/004/pdWS/001	Cardiology	Variety of indications associated with ventricular tachycardia, atrio-ventricular reciprocating tachycardia, wolff-parkinson-white, paroxysmal atrial fibrillation and atrial flutter (adult).	ATC: C01BC04 Tablets; prolonged release capsules; solution for injection	CSR (5)	Q1/2010	13/03/2012	27/04/2012	802	No change proposed because data were of poor quality and did not support a paediatric indication/posology	
Fluarix/ DE/W/0054/pdWS/007	Infectious disease	Influenza vaccine (adult and children > 6 months).	ATC: J07BB02; Suspension for injection	CSR (1)	Q2/2014	06/08/2014	09/10/2014	128	No change	
Flumazenil/ IE/W/0006/pdWS/001	Anaesthesia	Reversal of conscious sedation (children > 1 year)	ATC: V03AB25 Solution for injection or infusion	CSR (1 relevant) ; Literature	Q3/2010	17/02/2011	06/06/2011	232	Paediatric information clarified; a posology, which was approved by some CMS, had been proposed for implementation in all labels. SmPC changes were proposed for sections 4.1 (indication further clarified), 4.2 (age limit and dosing regimen specified) and 5.2;	
Fluoxetine/ EL/W/001/pdWS/001	Psychiatric disorder	Moderate and severe depression if depression is unresponsive to psychological therapy after 4-6 sessions (children > 8 years)	ATC: N06A B03; Oro-dispersible tablets; capsules; oral solution	NC (10) CSR (14)	Q3/2009	05/01/2011	29/02/2012	554	No Change, since submitted studies did not provide new information that would recommend paediatric use beyond approved indication (low number of paediatric patients enrolled).	Procedure was closed with request for more information

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Foscarnet/ DK/W/016/pdWS/001	Infectious disease	Treatment of Cytomegalovirus (CMV) and Herpes simplex virus (HSV -1 and 2) (adult)	ATC: J05AD01; Solution for infusion	Literature (20)	Q2/2011	23/02/2012	02/07/2012	329	Paediatric information clarified: SmPC changes were proposed for sections 4.2 (no established safety and efficacy), 4.4 (ulceration of genital area due to renal excretion), 4.8 and 5.3 (Foscarnet deposits in bone and cartilage).	
Gentamicin sulphate/ DE/W/003/pdWS/001	Infectious disease	Treatment of serious infections caused by susceptible strains of gram-negative bacteria: indications include sepsis, infective endocarditis, neutropenia and fever, burn wound infections and ulcers, intraabdominal infections, nosocomial pneumonia, pyelonephritis, osteomyelitis, septic arthritis, and meningitis. Most indications were approved for adults, children and neonates.	ATC: J01GB03; eye drops solution, eye ointment, solution for injection, sponge, solution for injection for intrathecal administration, cream and ointment	Literature (21)	Q1/2009	06/01/2010	23/02/2010 *update 18/10/2010	371	Paediatric information clarified: SmPC of formulations for systemic use got updated: section 4.1 (reference to guidance), section 4.2 (posology specified for paediatric subpopulations); sections 4.3, 4.4, 5.2. For otic use: update of SmPC section 4.3 (perforation of ear drum) and section 4.4 (need to check integrety of ear drum).	
Glatiramer acetate/ NL/W/0039/pdWS/001	Systemic disorder	Treatment of relapsing remitting multiple sclerosis (MS) (adult)	ATC: L03AX13, Solution for injection	Literature (11)	Q4/2012	28/08/2013	04/03/2014	332	No change: SmPC reflected the current state of knowledge	
Glucosamine/ UK/W/008/pdWS/001	Skeletal disorder	Treatment for symptomatic relief of mild to moderate osteoarthritis of the knee (adults)	ATC: M01AX05; Hard capsules ; film-coated tablets; powder for oral solution, Solution for injection	CSR (4)	Q2/2009	28/09/2009	26/11/2009	181	No new indication because data were not sufficient to support a new indication in paediatrics. Paediatric information clarified: updates to SmPC sections 4.2 (use not recommended) and 4.4 were recommended for all labels approved across CMS.	

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Gonadorelin/ UK/W/048/pdWS/001	Endocrinology/ Andrology	A nasal spray solution for treatment of unilateral and bilateral cryptorchidism, a solution for intravenous or subcutaneous injection for distinction between central and peripheral gonadal dysfunction (children > 1 year)	Hypothalamic hormones ATC: H01CA01, Fertility testing ATC: V04CM01; Solution for injection, nasal spray	Literature (24)	Q2/2012	04/03/2013	09/05/2013	338	Paediatric information (safety: alopecia) clarified: SmPC section 4.8 updated	
Haloperidol/ FR/W/011/pdWS/001	Psychiatric disorder	Neuroleptic used in children for treatment of: behaviour disorder associated hyperactivity and aggression (autistic syndrome), Gilles de la Tourette's disorder, psychosis (schizophrenia)	ATC: N05AD01, Tablets; oral solution ; injectable solution	Literature (49)	Q2/2010	31/01/2012	02/04/2013	671	Paediatric information clarified by adding safety information in SmPC section 4.4	No recommendation on indications could be made, purpose of Art. 45 is not to remove indications. However, assessor recommended a procedure for harmonisation of SmPCs with the aim to remove approved paediatric indications which could not be supported.
Human Insulin/ DK/W/018/pdWS/001	Endocrinology	Diabetes mellitus (adults and paediatrics)	ATC: A10AB01 ATC: A10AC01 ATC: A10AD01 Solution for injection; Suspension for injection	CSR (3), Literature (2)	Q3/2011	22/02/2012	27/04/2012	237	No change because studies did not add any new information	
Human Normal Immunoglobulin/ DE/W/0014/pdWS/001	Immunology	Past 60 years routinely given to children for a variety of different diseases caused by immunodeficiency (primary and secondary) requiring enhancement of IgG concentrations with good efficacy and safety results	ATC: J06BA01/02. Intravenous, subcutaneous, intramuscular	CSR (41)	Q4/2009	02/05/2010	02/03/2011	214	No change since studies did not change the benefit –risk profile	

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Hydroxychloroquine/ UK/W/029/pdWS/001	Pain/ Systemic disorder	Treatment of juvenile idiopathic arthritis, systemic lupus erythematosus, cutaneous/discoid lupus erythematosus) and malaria in children	ATC:PA1BAO2. Tablet	Literature (10)	Q4/2010	19/04/2012	04/06/2012	566	No new data became available that would change the risk –benefit profile of the product. Minor amendments to SmPC sections 4.1 and 4.2 were requested by the UK.	The NL requested an update of Section 5.1 with clinical data about juvenile idiopathic arthritis. Germany requested removal of indication malaria. On balance this was not followed by the UK rapporteur since the purpose of the Art. 45 procedure is not to harmonise the SmPC. The Rapp. acknowledged the differences concerning clinical usage and existing indications across EU-MS. However, the UK label indicated the treatment of JIA and the treatment and prophylaxis of malaria, the UK position with regard to these indications and the SmPC wording was kept. The Rapp. acknowledged the fact that the NL and DE might not wish to follow the proposed wording. Day 115 comments provided by CMS had not been taken in consideration by the Rapporteur since additional clarification from MAH was considered unreasonable at this stage of procedure.
Ibuprofen/ DE/W/040/pdWS/001	Pain	Non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic actions; the age limit for children varies according to strength, formulation and indication.	ATC: M01AE01. Product is available in oral (tablets, capsules, effervescent tablets, granules, powder, suspension) rectal, topical and parenteral formulations	CSR (60, [22 were not examined as they were conducted in mixed populations and paediatric data cannot be separated out])	Q4/2010	11/11/2013	04/02/2014 *update 06/05/2014	1137	Paediatric information clarified (duration, safety information and body weight limit): SmPC section 4.2, 4.4 got updated.	Harmonization of SmPC section 4.2 was requested by NL. This was not supported by Rapporteur who felt the dose recommendation was rather similar. Changes to the label sections were rather general.

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Idarubicin/ DE/W/024/pdWS/001	Oncology	Product is licensed for treatment of acute myeloid leukaemia (AML) and acute lymphatic leukaemia (ALL) (adult)	ATC: L01DB06. injection solution; powder and solvent for reconstitution of an injection solution; hard capsules	CSR (9), Literature (13)	Q2/2010	22/10/2013	08/01/2014	1300	New indication: Update of SmPC sections 4.1 (indication for AML treated in combination with cytarabin by taking into account current therapeutic guidelines), section 4.2 (specific guidance on posology for combination therapy in AML). It was left to the CMS whether they want to add or leave in the second indication (ALL as second line treatment) in the SmPC. The Rapporteur did not support the paediatric use for ALL.	Two LoQ were circulated because the MAH provided new data and a new proposal for a SmPC and PL update on D90. Controversial discussion about the proposed deletion of ALL. Initial proposal to section 5.2 got removed due to objections from some CMS; at the end, agreement was reached that information presented in other SmPC sections (i.e. from SMPC section 4.3 onwards) was left to the discretion of the individual NCA, no specific recommendation was provided. Recommendation for Art. 30 referral was made.
Ifosfamide/ PL/W/0001/pdWS/001	Oncology	Treatment of adulthood sarcomas and a variety of paediatric tumours. Approved indications for children as follows: testicular tumours, soft tissue sarcomas, Ewing sarcoma, Non-Hodgkin's lymphomas, Hodgkin's Disease	ATC: L01AA06; powder for solution for injection (vials)	Literature (86)	Q3/2009	08/11/2011	22/02/2012	861	Changes were proposed for SmPC sections 4.1 (reference to section 5.1) and 5.1 (inclusion of study data about treatment in patients with Ewing's sarcoma; general guidance about dosage level and regimen).	

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Ipratropium Bromide/ DK/W/014/pdWS/001	Respiratory	Approved for the treatment of acute asthma attack or other causes of respiratory distress in adults as well as children from 0 years of age. Approved for maintenance of asthma treatment when used in combination with inhaled steroids and/or beta-2 agonists in children. Ipratropium nasal spray was not approved in children with less than 12 years of age in most EU countries.	ATC: R03BB01, R01AX03. Nebuliser solution/ unit dose vial; pressurised inhalation solution; Inhalation powder; capsule; nasal spray	CSR (42)	Q4/2010	03/05/2011	06/06/2011	215	No change since provided studies did not provide any new information.	
Ipratropium Bromide + Salbutamol/ DK/W/015/pdWS/001	Respiratory	Treatment of chronic obstructive lung diseases in adults and children of more than 12 years of age, when monotherapy with ipratropium bromide was insufficient	ATC: R03AK04. Nebuliser solution/ unit dose vial; Pressurised inhalation solution	CSR (5)	Q4/2010	03/05/2011	06/06/2011	215	No change since provided studies did not provide any new information.	
Isradipine/ UK/W/027/pdWS/001	Cardiovascular	Treatment of essential hypertension/ (adult)	ATC: C08C A03. Tablets; capsules	Literature (3)	Q3/2010	20/06/2011	30/09/2011	355	Paediatric information clarified: section 4.2 (explaining that no paediatric data are available)	Although some effect was shown by submitted studies, but data from these studies should not be added to section 5.1 of the SmPC. In the absence of paediatric PK information, inclusion of such summaries would create false conclusions and mislead the prescriber.
Itraconazole/ EE/W/0004/pdWS/001	Infectious disease	Antifungal - infections due to *dermatophytes spp* ., and variety of *yeast spp.* (adult)	ATC: J02AC02. Capsules, hard; oral solution; concentrate and solvent for solution for infusion	CSR (5)	Q3/2009	26/11/2010	24/03/2011	514	Paediatric information clarified in SmPC sections 4.2 (use in children not recommended unless benefit outweighs the risk), 4.8 (description of most frequent adverse events based on study data), 5.1 and 5.2	

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Ketoconazole/ DK/W/0012/pdWS/001	Infectious disease	Antifungal - infections due to *dermatophytes spp* ., and variety of *yeast spp.* (oral form); *malassezia furfur* and seborrheic dermatitis and pityriasis (shampoo); Candidiasis, pityriasis and seborrheic dermatitis (cream)/ (adults; recommendation for use in children varies from country to country)	ATC: D 01 AC 08; J 02 AB 02. Shampoo; Cream; Tablets	CSR (13)	Q2/2010	19/12/2012	06/03/2013	993	MAH proposed a label update supporting paediatric use in all formulations. However, lack of data lead to the following label updates - SmPC section 4.2 (use of ketoconazole (for oral formulations only) had not been estblished due to limited data on safety & efficacy). An Article 31 referral was ongoing evaluating the risk for hepatotoxicity. Shampoo: for adolescents only. Cream: for adults only. SmPC section 5.2 for cream got updated with paediatric information only.	
Lamotrigine/ NL/W/003/pdWS/001	Neurological disorder	Antiepileptic/ (adult; approved in children 2-12 years of age for adjunctive treatment in partial seizures and generalized seizures […] and monotherapy of typical absence seizures)	ATC: N03AX09. Tablets, Dispersible/chewable tablets	CSR (6)	Q4/2008	13/03/2009	31/07/2013	164	No change. Quality of studies do not allow further conclusions on efficacy. Information of submitted studies did not change the benefit - risk profile as assessed in an Article 30 procedure used to harmonize the product label which included indications for paediatric use.	
Latanoprost/ IE/W/0010/pdWS/001	Ophthalmology	Treatment for reduction of elevated intraocular pressure in paediatric patients and paediatric glaucoma	ATC: S01EE01. eye drops solution	CSR (2), Literature	Q1/2013	09/09/2013	02/12/2013	252	No change. Product label reflected the current state of knowledge. Submitted studies had been carried out under the scope of a PIP. After completion of PIP related trials, an Article 29 procedure was carried out which led to the approval of paediatric indications with a recommendation for a posology	
Latanoprost/Timolol/ IE/W/0011/pdWS/001	Ophthalmology	Reduction of intraocular pressure which is unresponsive to single agent therapy and the treatment of glaucoma in adults	ATC: S01ED51. Eye drops	No relevant studies were submitted	Q1/2013	09/09/2013	02/12/2013	252	No change. Product got a paediatric waiver due to lack of benefit.	

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Lenograstim/ DE/W/025/pdWS/001	Oncology	Reduction in duration of neutropenia in patients (with non myeloid malignancy) undergoing myeloablative therapy followed by bone marrow transplantation (BMT). Reduction of duration of severe neutropenia and associated complications in patients undergoing cytotoxic chemotherapy associated with a significant incidence of febrile neutropenia. Mobilisation of peripheral blood progenitor cells (PBPCs). Original label did not suggest different dosage levels for children (>2Y) and adults.	ATC: L03AA10. Powder and solvent for solution for injection (lyophilised powder in single-use vials. Water for injection for reconstitution for injection/infusion is provided in ampoules or pre-filled syringes)	NC (2), CSR (7)	Q2/2010	28/11/2011	29/02/2012	332	Paediatric information clarified: current wording in SmPC section(s) 4.1 (further clarified) and 4.2 (age limit, two posologies provided based on body surface area). Additional information had been proposed for inclusion in SmPC section 4.4 (few risks related with ALL have been added) and section 4.8	Original indication was based on guidelines which were state of art in the past. However, guidelines had been revised; therefore information needed to be adapted accordingly.
Levofloxacin/ DE/W/026/pdWS/001	Infectious disease	Fluoroquinolone for treatment of strains applying to gram-positive or gram-negative spectra as well as *legionella spp* , *mycoplasma spp* and *chlamydia spp/ (adults;* product was contraindicated in children and adolescents due to cartilage toxicity observed in juvenile animal studies)	ATC: J01MA12. Oral suspension, Film-coated tablets, Solution for infusion	CSR (3)	Q2/2010	04/10/2010	24/11/2010	187	No changes requested	Product was still not recommended for use in paediatric population due to safety issues (musculo-skeletal disorders) with completion of this worksharing procedure despite the fact that France argued to introduce this product for use in paediatric population due to increasing emergence of bacterial resistance of strains which may remain susceptible to levofloxacin. Request form France was not followed by Rapporteur

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Levothyroxine/ SE/W/004/pdWS/001	Endocrinology	Hypothyroidism as a substitution therapy (adult and children (indication approved in children in DE & ES; other EU countries provide a dose recommendation)).	ATC: H03AA01. Tablets; solution for injection; oral drops	Literature (19)	Q1/2009	10/12/2009	23/03/2010 *update 27/04/2010	344	Submitted data do not suggest any update to the product label. However, since national licenses vary in terms of posology, Rapporteur suggested to harmonise the paediatric posology via a type II variation. A wording was proposed for SmPC section 4.2.	
Lidocaine/ SE/W/008/pdWS/001	Anaesthesia	product licensed since 1940. Focus on indication as local anaesthetic. Other indication were not considered in this assessment report. (adult; paediatric claim not specified)	ATC: N01BB52; C05AA61; J01RA; R02AA; R02AA20; A01AB14; A01AE11. solution for injection, medicated plaster, ointment, suppositories, gingival paste, intraurethral, lozenge, gelsolet, spray, solution	NC (1), Literature (58), CSR (30)	Q2/2009	08/06/2013	31/07/2013	1529	Due to the high variability of products and different type of licenses, no general recommendation to the SmPC was provided by the Rapporteur. MAHs were requested to update SmPC sections 4.1 and 4.2 by specifying the information based on age range and age limit. Few MAHs received specific guidance on the correct use of the respective product type (e.g. Montavit, Novartis, Septodont) for inclusion in SmPC section 4.2 . One product (Novartis) received a recommendation for SmPC section 4.8 clarifying the type and frequency of adverse events were expected to be the same as in adults.	Complexity of this worksharing was caused by the number of MAHs (8) which all provided their paediatric data and by the high number of different formulations which further multiplied the effort because clinical investigations were specific for each pharmaceutical form.
Lisinopril/ SE/W/002/pdWS/001	Cardiology	ACE inhibitor for treatment of hypertension; congestive heart-failure; myocardial infarction and renal and retinal complications of diabetes mellitus (adults)	ATC: C09A A03. Tablets	CSR (3)	Q4/2008	11/09/2009	26/11/2009	346	Paediatric information was clarified: update of SmPC sections 4.2 (paediatric posology added in section dedicated to hypertension specified by body weight; an additional paragraph about limitations for use in section special populations); 4.8 (AE profile is comparable to adults), and further sections 5.1 and 5.2 (paediatric trial data). Type II variation was proposed as adequate measure to implement the label update.	

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Loratadine/ AT/W/0003/pdWS/001	Immunology	Symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria/(adults; children over the age of 2 years with a body weight more than 30 kg)	ATC: R06AX13. Syrup; Tablets	CSR (8), literature (6)	Q3/2009	06/08/2010	27/10/2010	402	No change proposed	
Lovastatin/ UK/W/031/pdWS/001	Metabolic disease	HMG-CoA reductase inhibitor for treatment of hypercholesterolemia (adult)	ATC: C10AA02. Tablets	CSR (3); Literature (21)	Q1/2011	15/08/2012	02/04/2013	592	Paediatric information got clarified; update of SmPC section 4.8 and section 5.1 with paediatric study information which were cross referenced in SmPC section 4.2 (no recommendation for paediatric use) and section 4.4.	
Mefenamic Acid/ UK/W/037/pdWS/001	Pain	NSAID as an anti-inflammatory analgesic for the symptomatic relief of rheumatoid arthritis (including Still's Disease), osteoarthrosis and pain including muscular, traumatic and dental pain, headaches of most aetiology, post-operative and post-partum pain and pyrexia. It is further licensed for primary dysmenorrhoea in adolescents and menorrhagia due to dysfunctional causes and presence of IUD when other pelvic pathology has been ruled out. (adults, some indications licensed in paediatrics)	ATC: M01AG01. Suspension; Capsules; Tablets	Literature (16)	Q3/2011	24/07/2012	24/10/2012	389	No recommendation for a label change: the Rapporteur was of the opinion that data from submitted studies, current literature and national guidelines were inconclusive and did not suggest any changes to the currently licensed antipyretic posology across Europe. The Rapporteur agreed that mefenamic acid is not a first line non steroidal anti-inflammatory drug (NSAID) for juvenile rheumatoid arthritis. The SmPC supports the use of mefenamic acid as an analgesic for symptomatic relief in various conditions. The fact that mefenamic is a NSAID, beneficial analgesic properties for these patients cannot be excluded, even if not widely used or not used as a first line agent. Therefore the removal of this indication was not supported by the Rapporteur.	

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Melphalan/ BE/W/0002/pdWS/001	Oncology	Treatment of multiple myeloma and ovarian cancer at conventional dosage. Treatment of multiple myeloma at high dosage. Treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities when administered by regional arterial perfusion. (adult; in paediatrics licensed for childhood neuroblastoma)	ATC: L01AA03. Powder and solvent for solution for injection/infusion; Tablets	Follow-up survey report (2) for a completed paediatric trial and 3-year survival data	Q1/2010	28/09/2010	27/10/2010	271	No change of product information; The study submitted was a small open study investigating relapse rate, overall survival, progress-free survival, and prognostic factors of paediatric patients with solid tumours and childhood leukaemia. Samples size was insufficient to determine any statistical significance. Hence, the data from this study did not allow re-evaluation of the benefit/risk ratio.	
Mepivacaine/ AT/W/0002/pdWS/001	Anaesthesia	Infiltration anaesthesia and nerve-block in dentistry. Mepivastesin is indicated for simple extractions as well as cavity and stump preparations. Mepivastesin is especially suitable for patients to whom vasoconstricting additives are contraindicated (adults; paediatric claim not specified)	ATC: N01BB03. Solution for injection	Literature (9)	Q1/2009	13/10/2010	05/01/2011	651	Paediatric information clarified; Update of SmPC section 4.2 (age limit; dose recommendation and maximal dosage level) and 4.3 (age limit)	The assessor felt the data are insufficient to recommend any change to the label. However, two MAH defended the SmPC update in their response to LoQ.
Meropenem/ FR/W/0009/pdWS/001	Infectious disease	Beta-lactam antibiotic for treatment of various infections in adults and children over 3 months of age	ATC: J01DH02. Powder for solution for injection or infusion; powder for solution for injection or infusion	Literature (5)	Q3/2009	12/08/2010	31/07/2013	408	SmPC was subject to an Article 30 procedure for label harmonization. Therefore no additional label update was suggested since all paediatric trials were assessed during the Art.30 procedure already. The Article 45 EU worksharing procedure was closed with the request to generate clinical studies in paediatric patients with less than 3 years of age.	

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Mesalazine/ DK/W/001/pdWS/001	Gastrointestinal Disease	Treatment of inflammatory bowel disease (Crohn's disease and ulcerative colitis) in paediatric patients. Several MA with different dosing instructions had been approved.	ATC: A 07 EC 02. Prolonged release formulations ; suppositories; tablets - all at different strengths and foam enema 1g/metered dose	Three MAH submitted studies: CSR (31); Literature (13)	Q4/2008	02/12/2009	23/03/2010	428	Paediatric information clarified. Oral form: Update of SmPC section 4.2 (age limit; body weight limit for dose adjustment). One CMS could not accept the final recommendation for the posology section. Hence implementation of the new dosing information was left to the discretion of CMS; the Rapporteur suggested implementation via type II variation. Rectal form: none	Submitted studies were small. Limitations in methodology were weakening the indication for oral mesalazine. The indication was kept, because the Rapporteur believed that efficacy of mesalazine as well as release of slow release formulations are comparable between adults and children. Further, the safety profile was well established.
Metoclopramide/ DE/W/007/pdWS/001	Gastrointestinal Disease	Antiemetic for treatment of post operative nausea and vomiting or chemotherapy induced nausea and vomiting; Gastrointestinal motility disorders; digestive tract explorations (listed indications are approved in France for adult and children; however wide differences of licensed indications across EU-MS)	ATC: A03FA01. Tablets; oral solution suppositories; injectable solution (not every pharmaceutical form got approved for use in children aross the EU)	NC (2), Literature (78), CSR (1)	Q4/2009	24/11/2010	24/03/2011	420	Paediatric information clarified: Update of SmPC section 4.3; 4.4, 4.8 and 4.9. As per Rapporteur, the injectable solution should be recommended for paediatric use only. Therefore recommendations were also made for SmPC section 4.1 (indication clarified) and 4.2 (per indication; maximum dose, treatment regimen). For rectal and oral forms: no indication nor posology was recommended.	High variety of indications and posology across the EU MS, prevented a harmonized recommendation for SmPC section 4.1 and 4.2 which could have been supported by the scientific information submitted under the scope of this procedure. Further the Art. 45 does not intend to remove existing indications agreed by individual Member States in the past. Deletion of indications was left to the discretion of NCA. Moreover the Rapporteur pointed out the need for active contribution by other CMS on the assessment of scientific data in order to support efforts in getting a consolidated label recommendation. The MAH did not intend to harmonize the approved indications but sought for harmonized safety information in the SmPC.

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Metoprolol succinate/ NL/W/0037/pdWS/001	Nephrology	Treatment of hypertension (adult; paediatrics)	ATC: C07AB02. Controlled release tablets at various strengths	CSR (2)	Q2/2012	13/07/2013	26/09/2013 *update 04/02/2014	469	New indication recommended. A proposal for an update affected the following SmPC sections: 4.1 (hypertension), 4.2 (age limit, starting dose, titration, maximal dosage level), 5.1, 5.2	MAH proposed a posology for paediatric use with initial submission. However, provided data demonstrated efficacy across the dose range with acceptable safety profile. Hence data were sufficient to recommend a new indication for treatment of hypertension in paediatric population
Metronidazole/ metronidazole + spiramycin/ SE/W/011/pdWS001	Infectious disease	Antibacterial agent for treatment of anaerobic gram negative infections caused by *Bacteriodes fragilis* ; *Fusobacterium spp* ., *Gardnerella vaginalis* , and anaerobic gram positive infections cause by *peptococcus spp* ., *peptostreptococcus spp* ., *clostridium spp* .. Anti-protozoan for treatment of *trichomonas vaginalis* , *Entamoeba histolytica* , *Gardia lamblia* . Product was registered under national procedure leading to different indications across the EU. (adults and paediatrics)	ATC: P01AB, J01XD . Various formulations had been registered (tablets, oral suspensions, suppositories, intravenous solution, vaginal pessaries/tablets); oral and iv. formulations were assessed under the scope of this procedure.	Literature: (140)	Q2/2010	05/10/2010	05/01/2011	188	Paediatric information clarified; recommendation for SmPC update was provided for section 4.1 (reference to guideline); 4.2 (posology per indication; recommendation for patients ≤ 3y) and 4.8 (AE: reference to adults).	Proposed label update was provided as a recommendation to the CMS (optional). A type II variation was sugested for implementation in order to allow discussions on local level. Recommendation for indication section was unspecific since the approved indications may vary across EU MS. Further it was proposed to determine a posology for patients with an age of less than 8 weeks during the subsequent variation procedure.
Mianserin/ UK/H/0019/pdWS/001	Psychiatric disorder	Tetracyclic antidepressant (adult)	ATC: N06AX03. Tablets	Literature (11)	Q1/2010	26/05/2010	01/07/2010	146	No change proposed since no studies were conducted in children. SmPC included the class label information as adopted in Art. 31 referral procedure EMEA/H/A-31/651	

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Miconazole nitrate (+/- Zinc oxide)/ NL/W/0027/pdWS/001 NL/W/0029/pdWS/001	Infectious disease	Treatment of fungal infections caused by *dermatophytes* , *yeasts* , some molds and some gram positive cocci and bacilli (adults and paediatrics)	ATC: G01AF04. Gel; cream; powder; tablets; ointments	Literature (36)	Q3/2011	14/12/2012	06/03/2013	532	Paediatric information got clarifed for each approved pharmaceutical form. Recommendation was provided for SmPC section 4.2 (posology for all pharmaceutical forms). Further new safety information was included in SmPC section 4.3 and 4.4 of the oral gel.	MAH proposed changes to the label, which were further revised as an outcome of this assessment.
Milrinone/ AT/W/0004/pdWS/001	Cardiology	Various indications related to treatment of heart failure (incl.congestive) had been approved in the EU; low cardiac output syndrome. No indication for paediatrics was specified.	ATC: C01CE02. Solution for infusion	Literature (28); CSR (1); NC (1)	Q1/2010	09/04/2011	06/07/2011	464	New indication proposed (short term treatment of congestive heart failure unresponsive to conventional maintenance therapy) ; changes to SmPC section: 4,1; 4,2 (by age group and duration specified); 4,4; 4,8; 5,1; 5,2; 5,3. Conclusions of the assessment were endorsed by all Member States.	MAH already proposed a label update with the initial submission of the Article 45 dossier
Minoxidil/ MT/W/0003/pdWS/001	Cardiovascular	Treatment of severe refractory systemic hypertension (adult and paediatrics)	ATC: CO2DC01. Tablets	CSR (2); Literature (2)	Q3/2010	11/10/2011	30/01/2012	468	New study data lead to SmPC update of sections: 4,2 (age range; titration; maximal dose); 4,4; 4,8; 5,1; 5,2; 5,3.	
Mirtazapine/ UK/H/0016/pdWS/001	Psychiatric disorder	Treatment of depressive disorders (adults)	ATC: N06AX11; Tablets/ orodispersible tablets; oral solution	CSR (3); Literature (13)	Q4/2009	18/06/2010	05/08/2010	261	New data lead to SmPC update of section 4.2; 4.8; 5,1. It was further clarified this product should not be used in paediatric populations. Wording in section 4.2, which was adopted in a Art. 30 referral before, got further strengthened.	
Mivacurium chloride/ PL/W/007/pdWS/01	Anaesthesiology	Adjunct to general anaesthesia to relax skeletal muscles (adults and paediatrics)	ATC: M03AC10. solution for injection	CSR (3);	Q2/2011	30/04/2012	09/10/2012	395	New data lead to clarification of paediatric information; Update of SmPC section: 4.1 (indication specified; age limit); 4,2 (age limit); 4,4; 4,8.	
Mycophenolic acid/ SI/W/0002/pdWS/001	Immunology	Prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants	ATC: L04AA06. Film-coated gastro-resistant tablets	CSR (2)	Q2/2010	10/11/2011	31/07/2012	589	New data did not suggest any changes to the SmPC. Efficacy data were of limited value.	

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Naltrexone/ NO/H/001/pdWS/001	Psychiatric disorder	Treatment of alcohol dependence (adults)	ATC: N07BB04. Tablets	CSR (1); Literature (1)	Q1/2009	28/05/2009	13/07/2009	148	New data did not suggest any changes to the SmPC. Efficacy data were of limited value.	
Neridronic acid/ UK/W/006/pdWS/001	Skeletal disorder	Treatment of ostegenesis imperfecta; Paget's disease (adults; paediatric use was not specified in original label)	ATC: none. Solution for injection	CSR (1 interim analysis of a clinical trial); Literature (4)	Q1/2009	09/01/2010	27/10/2010	374	Paediatric information clarified/ indication as licensed in Italy proposed for implementation across EU. Recommendation for an update of SmPC section 4.1 (osteogenesis imperfecta); SmPC section 4.2 (posology based on body weight).	Product was licensed in Italy only. No other bisphosphonate was currently licensed in the EU. An open label study was still ongoing. Label update was supposed to be implemented by a separate procedure.
Netilmicin sulphate/ FI/W/001/pdWS/001	Infectious disease	Treatment of severe infections in hospital setting (adult; paediatrics)	ATC: J01GB07. Solution for injection	Literature (8)	Q4/2010	11/09/2011	31/01/2013	346	No label change: available safety, pharmacokinetic and efficacy data and the extensive clinical experience of netilmicin confirm positive benefit-risk ratio	Paediatric use of netilmicin, like other aminoglycosides,was governed by paediatric specialists and neonatological units which follow local treatment guidelines
Nifedipine/ NL/W/0023/pdWS/001	Cardiovascular	Calcium antagonist for treatment of hypertension; angina pectoris; Raynaud's syndrome (adult)	ATC: C08CA05. Tablets	CSR (2); Literature (58)	Q1/2011	25/09/2012	27/04/2012	633	Paediatric information clarified. Update of SmPC section 4.2 (not established for paediatric use) and section 5.1. Data were insufficient to confirm efficacy.	
Nimodipine/ FI/W/005/pdWS/001	Vascular disease	Treatment of aneurysmal subarachnoid haemorrhage (adult)	ATC: C08CA06. Tablets; solution for infusion; oral drops	CSR (6); Literature (49)	Q4/2013	14/05/2014	09/10/2014	226	Paediatric information clarified: update of SmPC section 4.2. Published information was too limited in order to reliably assess the benefit/risk ratio. No posology was recommended.	
Nystatin/ DK/W/0019/pdWS/001	Infectious disease	Treatment and prevention of candida infections of mucosa and skin (adult; paediatric)	ATC: A01AB33; A07AA02; D01AA01. Oral suspension; tablets; cutaneous paste	Literature (25)	Q3/2011	17/05/2013	30/10/2013	686	Paediatric information clarified: update of SmPC section 4.2 (posology provided by age group; per indication). Data supported safe and effective use in paediatric populations.	

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Oxazepam/ SE/W/001/pdWS/001	Psychiatric disorder	Treatment of anxiety alone or in association with insomnia or psychosomatic, organic or psychotic illness (adult; paediatric)	ATC: N05BA04. Tablet	CSR (4)	Q4/2008	02/07/2009	29/09/2009	275	No firm scientific conclusions could be drawn up for efficacy or safety. Update of SmPC section 4.4 (need for assessment and advice for limited duration) as per guideline "SmPC for benzodiazepines as anxiolytics or hypnotics"	
Oxybutynin hydrochloride/ UK/W/017/pdWS/001	Neurological disorder/ urology	Neurogenic bladder disorder; Vesical hyperactivity; nocturnal urination; incontinence (adult). Neurogenic bladder disorders; Enuresis (paediatric > 5 years of age)	ATC: G04BD04. Tablet; syrup; oral solution	NC (1); CSR (5); Literature (93)	Q4/2009	06/09/2010	01/10/2010	341	Paediatric information clarified: update of SmPC section 4.1 (clarification about approved indications) and 4.4	
Paclitaxel/ NO/W/0003/pdWS	Oncology	Treatment of breast cancer; non-small lung cancer; ovarian cancer and AIDS related Karposi sarcoma (adult)	ATC: L01CD01. Solution for infusion	Literature (6)	Q2/2009	29/12/2009	27/04/2010	273	Paediatric data were insufficient to provide advice for paediatric use. Update of SmPC section 4.2 (no recommendation for paediatric use).	
Penicillamine/ UK/W/033/pdWS/001	Hepatic disorder/ Pain	Treatment of severe active rheumatoid arthritis; Wilson's disease; cystinuria; lead poisoning; chronic active hepatitis (adult; paediatric (non chronic hepatitis))	ATC:M01CC01. Tablets	Literature (14)	Q1/2011	10/08/2012	24/10/2012	587	Paediatric information clarified: update of SmPC section 4.1 and 4.2 (clarification of posology regarding Wilson’s disease and cystinuria)	

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Pentamidine/ DK/W/020/pdWS/001	Infectious disease	Antiprotozoal for treatment of pneumocystis pneumonia (PCP). Further, African trypanosomiasis and leishmaniasis (adults, paediatric)	ATC: P01CX01. Powder for solution for injection; powder for nebuliser solution	Literature (17)	Q4/2011	22/04/2013	12/06/2013	569	No label change proposed, because recommendations should not be limited for use in children, because these changes apply also to adults. MAH agreed to recommendations and committed to initiate variations in order to achieve harmonized label information across EU: IV treatment is the preferred route of administration for treatment of PCP. Inhalation route is not recommended for treatment of mild PCP and should be removed from all PIs. The inhalation route should be used for prophylaxis only. MAH was further requested to discuss during the next label variation the state of the art treatment for the indications: trypanosomiasis and leishmaniasis.	Deletion of an indication is not scope of the Article 45 worksharing procedure. Therefore, the deletion should be processed in a separate procedure. MAH agreed to update the company core datasheet and implement the changes globally.

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Permethrin/ UK/W/044/pdWS/001	Antiparasitic	Treatment against *Sarcoptes scabei* ; human head lice (adults and paediatric)	ATC: P03AC04. Cream; Cutaneous solution	Literature (5)	Q1/2012	15/07/2013	30/10/2013	561	Paediatric information clarified. 5% permethrin cream: update of SmPC section 4.1 (age range); 4.2 (dose by age group, age limit. instructions for method of administration) and 4.4. 0.43% solution: SmPC section 4.4 got updated with a warning about emerging head lice resistance and further, new AEs were added to SmPC section 4.8. The Rapporteur also recommended to revise SmPC section 4.2 and 4.4 in all EU countries, which approved the use for short lasting prophylaxis (treatment of 1 day instead of 7 days), because this treatment regimen might have contributed to the development of resistance. For both products: a statement added to SmPC section 4.2; 4.4 and 5.1 explaining safety and efficacy had not been established in patients ≤ 2 month of age.	1% permethrin solution was not assessed as no data were provided.

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Phenoxymethylpenicillin/ NO/W/0002/pdWS/001	Infectious disease	Treatment of non beta lactamase producing: aerobic, Gram-positive organisms such as *streptococci* , *enterococci* , and some *staphylococci* (adult and paediatric). In paediatrics, it was primarily used for the treatment of ear, nose and throat infections; lower respiratory tract infections, dental infections, skin and soft tissue infections caused by Group A *ß-haemolytic streptococci* (GABHS), e.g. scarlet fever and erysipelas, and also for prophylaxis against the recurrence of rheumatic fever. In general: various indications & posology got approved across EU MS.	ATC: J01CE02. Tablets (film-coated; soluble); granules or for oral suspension; powder for oral solution; oral suspension	Literature (40)	Q2/2009	06/05/2010	30/01/2012	401	Data did not provide any new information. However, the Rapporteur recommended to address few issues leading to an update of SmPC section 4.1 (reference of official guidance on the appropriate use of an antibiotic) and 4.2 (treatment recommendation for infections with beta-haemolytic streptococci and treatment of acute otitis media). Recommendation for the conduction of additional studies were provided (concomitant administration with food; erythema migrans).	
Phenylephrine/ SE/W/016/pdWS/001	Ophtalmology	Mydriasis. Vasoconstriction to aid superficial bleeding during surgery	ATC: S01GA05. eye drops solution	Literature (11)	Q1/2013	12/10/2014	01/12/2014	615	Paediatric information clarified. Eye drops 25mg/ml: section 4.2 (dosing instructions and method of admininstration clarified. No recommedation for newborns; section 4.3 (contraindication in newborns/infants with cardio-/cerebrovascular disease) 4.4 (warning to not exceed recommended dose and avoid ingestion. Specific warning about AE if admininstered to newborns)	Product was registered before 1960

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Phytomenadione/ LV/W/0002/pdWS/001	Haematology	Prophylaxis and treatment of vitamin K deficiency bleeding (VKDB) in newborns and infants. In some countries: treatment of coumarin anticoagulant overdose bleeding both in children and adults.	ATC: B02BA01. Solution for oral use; solution for injection	CSR (29); Literature	Q3/2011	17/12/2012	02/04/2013	535	Paediatric information clarified: update of SmPC section 4.2 (dosing recommendation for neonates; preterms of less than 36 weeks) and 5.1 (data of a prospective randomised controlled trial).	Indication treatment of coumarin anticoagulant overdose: no studies specifying the optimal dose in paediatrics could be identified. Indication could not be removed, because the indication was of clinical importance. Further studies were requested to establish a dose.
Procarbazine/ PL/W/0009/pdWS/01	Oncology	Treatment of lymphomata and a variety of solid tumours (adult). Treatment of Hodgkin's lymphoma (paediatric)	ATC: L01XB01. Hard capsule	Literature (148)	Q2/2011	05/01/2012	27/04/2012 *update 22/10/2012	280	Paediatric information clarified: update of SmPC section 4.1 (age range); 4.2 (instruction for dose adjustments; reference to expert) and 5.1. **[**MAH proposed amendment of SmPC section 4.1; and 4.2; further 4.4 and 4.8 for the potential of testicular damage. The rapporteur agreed the proposed safety concern should be included in the label. However, the final recommendation did not include the revisions to the two safety sections. No reasons were indicated in the report which would clarify why the proposed revisions to the two safety sections had been omitted from the recommendation**]**	The Rapporteur pointed out: Quality of studies with procarbazine in CNS tumours were not robust and would not be sufficient to approve the indication "treatment of brain tumours", if current standards had been applied for assessment of new medicinal products. However, CNS tumours in children were rare diseases; randomized controlled trials were not conducted. It remained difficult to collect homogenous groups of patients with specific CNS tumours, conduct randomized clinical trials and show statistically significant benefit. Therefore, the recommendation was given to maintain the indication in section 4.1 as in former SmPCs and add a reference to section 5.1.

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Propofol/ DE/W/004/pdWS/001	Anaesthesiology	Short-acting anaesthetic for induction and maintenance of general anaesthesia (paediatric; use in patients of <3 years differes among EU MS). Sedation of ventilated patients or for diagnostic and surgical procedures (adults).	ATC: N01AX10. Emulsion for injection / infusion	CSR (9); Literature (60)	Q1/2009	21/05/2010	06/09/2010	476	Paediatric information clarified: update of SmPC section 4.1 (indication clarified per strength); 4.2 (instructions per strengths and per indication); 4.3 (contraindication removed); 4.4 and 5.2.	Data revealed: use in neonates should not be recommended but data do not justify contraindication (contraindication deleted); contraindication of propofol for PICU sedation remains as long reliable data about incidence of PRIS (propofol infusion syndrome) are available; warning for concomitant use with MP reducing cardiac output; no further dose recommendations should be given for the reasons of safety: the interindividual variability requires titration of the effective dose
Propranolol/ FR/W/013/pdWS/001	Cardiology	Propranolol is authorised in several indications for adults including recommended posologies in children: arrhythmias; migraine; thyrotoxicosis; Fallot tetralogy; pheohromocytoma. In adults, additional indications were approved.	ATC: C07 AA05. Tablets; solution for injection	literature (37)	Q1/2010	09/02/2011	27/04/2011	405	Paediatric information clarified: SmPC change 4.2 (dose instructions per route of administration) and 4.8 pertaining to indication arrhythmias. Safety and efficacy data did not suggest a posology in other indications.	MAH proposed a posology for paediatric use for treatment of arrhythmias, thyrotoxicosis and migraine. However, a posology for arrhythmias could be recommended only. Product was licensed through national procedure; not all indications as per company datasheet had been approved across EU.
Quetiapine/ UK/W/0004/pdWS/001	Psychiatric disorder	Treatment of schizophrenia; bipolar disorder (adults)	ATC: N05AH04. Tablet	CSR (5) literature (2)	Q4/2008	07/12/2009	26/09/2013	433	Paediatric information clarified: SmPC change 4.2; 4.4; 4.8; 5.1. As an outcome of this assessment, quetiapine is not recommended for use in children and adolescents.	Studies were submitted under Article 45 and Article 46 depending when the paediatric trialsgot completed. Conclusions for the label update were drawn based on all submitted studies.
Quinapril/ UK/W/013/pdWS/001	Cardiovascular	ACE-inhibitor for treatment of hypertension and congestive heart failure (adults)	ATC: C09AA06. Tablets	CSR (2)	Q3/2009	24/03/2011	30/09/2011	632	New data lead to an update of SmPC section 5.1 and 5.2. SmPC section 4.2 got a reference to paediatric data presented in SmPC section 5.1 and 5.2	

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Rabeprazole/ UK/W/045/pdWS/001	Gastrointestinal Disease	Various indications approved for adults: duodenal ulcer, gastric ulcer, gatro-oesophgeal - reflux disease (GORD), Zollinger-Ellison-syndrome, combination with antibiotic for treatment of helicobacter pylorii	ATC: A02BC03. Tablets	CSR (2); NC (3)	Q2/2012	21/11/2012	30/01/2013	235	Provided data do not support any SmPC update	Submitted studies investigated treatment of GORD only.
Ramipril/ UK/W/011/pdWS/001	Cardiovascular	ACE-inhibitor for treatment of hypertension, renal disease, heart failure, prevention of cardiovascular morbidity/mortality and secondary prevention after acute myocardial infarction (adult)	ATC: C09AA05. Capsules; tablets	CSR (3)	Q2/2009	16/03/2011	22/02/2012	715	New data lead to an update to SmPC section 5.1 and 5.2. No paediatric posology proposed, but cross reference in section 4.2. Safety information lead to an update of SmPC section 4.8 and 5.3	one CSR was submitted under Article 46.
Ranitidine/ SE/W/007/pdWS/001	Gastrointestinal Disease	Various indications approved in adults. The following indications were approved for adults and paediatric patients (> 3y): Peptic ulcer (short term treatment) and GORD	ATC: A02BA02. Tablet	Literature (14)	Q1/2009	26/11/2009	23/03/2010	330	No change proposed since data did not provide any new information about safety and efficacy	
Remifentanil/ UK/W/0012/pdWS/001	Anaesthesiology	analgesic agent for use during induction and/or maintenance of anaesthesia (adult and paediatric)	ATC: N01AH06. Solution for injection	CSR (4)	Q3/2009	13/09/2010	05/01/2011	440	Paediatric information clarified: SmPC section 5.1 updated with relevant information from clinical studies	

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Rifampicin and combinations/ DE/W/020/pdWS/001; DE/W/021/pdWS/001; DE/W/022/pdWS/001	Infectious disease	Antibacterial agent for treatment of gram-positive and gram negative bacterial strains (various indications were approved). As per medical community guideline, the product is a reserved antibiotic for treatment of *M.tuberculosis* and other mycobacterial infections. Product is used in combination with other antibiotics. Paediatric indications: all forms of tuberculosis; *N.meningitidis* ; *H.influenzae*	Rifampicin + Isoniazid -ATC: J04AM02; Rifampicin -ATC: J04AB02; Rifampicin + Isoniazid + Pyrazyinamide- ATC: J04AM0. Tablet, capsules, powder & solvent for injection	Literature; WHO guidelines	Q4/2009	10/10/2011	22/02/2012	740	Recommendations for SmPC section 4.1 (indication clarified tuberculosis, N.meningitidis; H.influenzae and Leprosy) and 4.2 (dosing instructions were provided for treatment of tuberculosis, N.meningitidis; H.influenzae and Leprosy based on WHO guidance, EMA recommendation or German national public health service). New dosage recommendations for treatment of tuberculosis according to Anti-tuberculosis medicinal products: isoniazide, rifampicine, pyrazinamide, ethambutol, rifabutin (EMEA/H/A-5(3)/1310)	MAH proposed revisions to SmPC section 4.1 and 4.2 for a variety of indications.
Rifaximin/ AT/W/0001/pdWS/001	Infectious disease	Antibacterial treatment of infections of the gastro-intestine. Various indications were approved across different countries (adults and paediatrics)	ATC: A07AA11. tablet; granules for oral suspension	Literature (16)	Q4/2008	08/01/2010	26/04/2010	465	Paediatric information clarified: SmPC section 4.1 and 4.2: deletion of all paediatric indications and posology was recommended. A standard sentence was included in SmPC section 4.2 referring to information presented in SmPC section 5.1. SmPC section 5.1 was updated with paediatric data and dosing instruction	
Risedronate/ UK/W/009/pdWS/001	Skeletal disorder	Prevention and treatment of osteoporosis; Paget's disease; retain bone mass following corticosteroid treatment (adults)	ATC: M05BA07. Tablet; formulations in combination with Ca and Vit D3 are available.	CSR (2); literature (64)	Q2/2009	11/03/2010	01/10/2010	345	Paediatric information clarified: update of SmPC section 4.2 and 5.1. Use of risedronate was not recommended for paediatric use due to increased number of new morphometric vertebral fracture	Submitted studies were related to osteogenesis imperfecta.

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Risperidone/ IS/W/0001/pdWS/001	Psychiatric disorder	Antipsychotic for treatment of schizophrenia; severe manic episodes; aggression associated with Alzheimer dementia (adults). For paediatric older than 5 years: short term treatment of persistent aggression in conduct disorder.	ATC: N05AX08. Tablets; oral solution	Literature (114)	Q4/2009	04/11/2012	30/01/2013	1130	Paediatric information clarified: update of SmPC section 4.4 (weight gain)	
Ropivacaine hydrochloride/ DE/W/027/pdWS/001	Anaesthesiology	Local anaesthetic for epidural administration; local infiltration and peripheral nerve blocks (adult). Paediatric: caudal epidural block	ATC: N01BB09. Solution for infusion; solution for injection	CSR (7); literature (32)	Q3/2010	16.11.2011	29/02/2012	504	New data supported paediatric indications for the strengths 7.5; 10 and 2mg/ml:. Update of SmPC section: 4.1 **[**(1) 7.5mg and 10mg/ml: paediatric patients >12 years for treatment of epidural blocks; major nerve block and field blocks; (2) 2mg/ml: continous epidural infusion during post-operative or labour pain; field block and continous peripheral nerve block in infants and children upt to 12 years**]**; section 4.2 (dosing recommendation by age, route of administration) and section 4.4. 5mg/ml: paediatric information got clarified (no consensus for MAH proposed indication) leading to a statement for SmPC section 4.2 (no information for proposed route of admnistration) and 4.4. All strengths got an update for SmPC section 4.8 and 5.2	

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Salbutamol/ RO/W/0001/pdWS/001	Respiratory	Treatment of conditions with associated reversible airway obstruction, e.g. asthma or chronic obstructive pulmonary disease with a substantial component of reversibility and prevention of asthma attacks induced by exercise or exposure to allergens (adult and paediatrics)	ATC: R03AC02. Inhaler devices, tablets, inhalation powder	Literature (24); CSR (8)	Q2/2009	25/06/2011	27/04/2012	816	Rapporteur recommended that SmPC section 4.1 should state a specific paediatric indication and age range. SmPC section 4.2. should specify the age range per formulation. Further, the Rapporteur requested harmonization of paediatric use information in the SmPC in accordance with Article 30 of Directive 2001/83/EC	
Salmeterol + Fluticasone propionate/ DE/W/047/pdWS/001	Respiratory	Asthma (adults and paediatric), COPD (adult)	ATC: R03AK06. Inhalation powder	CSR (13)	Q4/2010	25/05/2013	31/07/2013	967	Paediatric information clarified: New data supported an update of SmPC section 5.1 and 5.2 specific for the used device	MRP and NAP license. No significant differences among labels
Salmon calcitonin/ UK/W/001/pdWS/001	Skeletal disorder	Treatment of osteoporosis, bone loss; Paget's disease; hypercalcaemia of malignancy (adults)	ATC: H05BA01. Nasal spray; solution for injection	NC (1); literature (12)	Q4/2008	27/03/2009	04/06/2009	178	Update of SmPC section 4.2 (paediatric use cannot be recommended. Studies did not provide sufficient evidence for paediatric osteoporosis)	
Sertraline/ NL/W/0006/pdWS/001	Psychiatric disorder	Treatment of depression (adults); OCD (paediatric; license was obtained after Art. 30 referral procedure)	ATC: N06AB06. Tablets; oral solution	CSR (3)	Q2/2009	10/11/2009	06/03/2013	224	Provided data on obsessive compulsive disorder (OCD) do not support any label change	NAP license
Sevoflurane/ IE/W/002/pdWS/001	Anaesthesiology	Induction and maintenance of general anaesthesia (adult and paediatrics)	ATC: N01AB08. Volatile liquid for inhalation	CSR (2)	Q3/2009	30/11/2009	24/05/2010	153	Submitted data do not support any label change	

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Simvastatin/ DE/H/1347/01-03	Metabolic disease	Statin for treatment of hypercholesterolemia (adult)	ATC: C10A A01. Tablets	CSR (1)	Q4/2008	23/05/2009	28/07/2009	235	Paediatric information clarified: update of SmPC section 4.2 (posology for heterozygous familial hypercholesterolemia in children >10 years); Section 4.4 (unknowns about physical, sexual and intellectual maturation; need for contraceptives); section 4.8; 5.1 and 5.2	At submission, the label contained no indication for paediatrics; however, posology (SmPC section 4.2) and description of studies (SmPC section 5.1) were included
Spironolactone/ RO/W/0003/pdWS/001	Cardiovascular/ Renal disorder/Hepatic disorder	Treatment of hepatic cirrhosis with ascites &oedema; malignant ascites; nephrotic syndrome; primary hyperaldosteroism; congestive heart failure (Listed indications were registered in the UK; indications may vary from country to country) (adults)	ATC: C03DA01. Tablets; capsules	CSR (1); literature (59)	Q4/2009	07/11/2012	17/06/2013	1133	No change	Conclusions of the Rapporteur provided a lot of suggestions for posology and presentation of the paediatric use information. However no concrete recommendation was made and it was somewhat unclear what the purpose of this assessment report was.
Sucralfate/ AT/W/0008/pdWS/001	Gastrointestinal Disease	Treatment of duodenal ulcer; GORD; GI haemorrhage from stress ulceration (reference is made to the Austrian label) (adults and paediatrics)	ATC: A02BX02. Granules; oral suspension; tablet	Literature (12)	Q4/2010	25/01/2012	02/07/2012	482	Paediatric information clarified: Update of SmPC section 4.2; 4.4; 4.8 and 5.1. Paediatric use is not recommended for patients with less than 14 years (reflected in SmPC section 4.2 and 4.4). Posology and method of administration were equal for adults and patients > 14 years. SmPC section 4.4 and 4.8 got updated with the risk for bezoars (not specific to paediatric patients). SmPC section 5.1 proposed a statement explaining that limited data were available and use in paediatric populations was not recommended.	Inadequate study design did not provide a robust basis for assessment of safety and efficacy in patients with less than 14y (endpoints are variable); PSUR did not raise any safety concerns

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Annex A: Completed *Article 45 EU Worksharing Procedures* - Period Q4 2008-31 December 2014

Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Sufentanil/ DE/W/028/pdWS/001	Anaesthesiology	Various label information across EU countries. Analgesic for induction and maintenance of general anaesthesia. Epidural anaesthesia (adults and paediatrics)	ATC: N01AH03. Solution for i.v. or epidural injection	Literature (42)	Q3/2010	26/04/2012	31/07/2012	665	Paediatric information clarified: update of SmPC section 4.1; 4.2 ; 4.3 ; 4.4 ; 4.8; 5.1 and 5.2. As an outcome of the assessment, no reliable dose recommendation could be made for neonates; there is a risk for overdosing or under dosing (SmPC section 4.2 and 4.4). PK parameter for all age groups presented in section 5.2. In section 4.1, the indication got clarified for intravenous and epidural use applying to patients > 1 month; posology was updated by route of administration and age (section 4.2). In section 4.3, any reference to contraindication of use in children should be deleted. Section 5.1 got updated with information related to epidural use only.	Submitted data provided clarification on open questions regarding epidural use, use in neonates, use in intensive care and safety. SE did not have the license for intravenous use in adults or paediatrics and hence could not follow the Rapporteur's recommendation. SE indicated to contact the MAH in order to receive adult data with the aim to update the local label for both, adult and paediatric patients.
Sumatriptan/ NL/W/0012/pdWS/001	Pain	Treatment against acute migraine attacks (adult). (Spray was approved in adolescents)	ATC: N02CC01. Tablet; nasal spray; suppositories; solution for subcutaneous injection	CSR (1)	Q3/2009	07/12/2009	31/07/2013	160	No change. Submitted study failed to meet the endpoint; however conclusions from previous worksharing procedure did not get revised.	One CSR was submitted. The other paediatric studies had been assessed in a paediatric worksharing procedure 2005/2006. Text in SmPC and PIL of different formulations had been determined at that point of time.
Tamsulosin hydrochloride/ UK/W/039/pdWS/001	Urology	Treatment of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (adults)	ATC: G04CA02. Modified release capsules and tablet	CSR (2); literature (6)	Q3/2011	07/03/2012	04/06/2012	250	No change: Article 45 worksharing did not revise the conclusions of the previous Article 46 procedure	Submitted studies investigated dysfunctional voiding in paediatrics under Article 46. None of the studies supported efficacy in neuropathic bladder. As an outcome of this Art.46, the label was updated with clinical information. Further a statement in SmPC section 4.2 was added explaining that safety & efficacy had not been established in patients <18years.

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Terbutaline sulphate/ DK/W/0017/pdWS/001	Respiratory	Relief and prevention of bronchospasm in bronchial asthma and other bronchpulmonary disorder (adult and paediatric)	ATC: R 03 CC 03 (systemic use); ATC: R 03 AC 03 (inhalation). Tablet; oral solution; solution for injection; turbuhaler; nebuliser solution	CSR (2)	Q2/2011	05/09/2013	02/12/2013	888	Limited studies do not provide any information which would change the risk benefit balance: No SmPC change	Approval of age limits and pharmaceutical forms vary across countries. NAP
Testosterone/ NL/W/0026/pdWS/001	Endocrinology	For conditions associated with primary and secondary hypogonadism, either congenital or acquired. May be used for as supportive therapy for female-to-male transsexuals (adult)	ATC: G03BA03. Solution for injection; capsule; implant	Literature (8)	Q2/2011	23/01/2012	02/04/2013	298	Paediatric information clarified. Oral form: SmPC section 4.2 was updated in order to add "adolescents". Product is not recommended for use in paediatric population due to the lack of long-term efficacy and safety data on testosterone in children and adolescents up to 18 years of age.	
Theophylline/ DK/W/0021/pdWS/001	Respiratory	Treatment of bronchial asthma and chronic obstructive pulmonary disease and prevention of asthma attacks (adults and children)	ATC: R03DA04. Capsules; tablets; oral drops; solution for infusion; solution for injection	Different MAH submitted studies including pharmacokinetic studies, efficacy and safety studies, reviews, metaanalyses and Cochrane reviews. CSR (12); Literature (55)	Q4/2011	09/08/2013	04/03/2014	678	Paediatric information clarified: SmPC sections 4.1, 4.2, 4.3, 4.4 and 5.2 are updated. In section 4.1: theophylline should not be used as first choice drug for treatment of asthma in children. Age limit: 6 months (Section 4.2 and 4.3). Addition of risk for acute febrile illness (section 4.4). Effective plasma concentration included in section 5.2.	Limited use of theophylline in children as in line with international and national clinical guidelines for asthma prevention and management (GINA 2010). The pharmacokinetics, efficacy and safety of theophylline, also in children, were well-studied. No new efficacy or safety information emerged from the submitted studies, but it was clear that paediatric doses, recommended therapeutic interval and the paediatric indications vary considerably between SmPCs

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Thiamazole/ DK/W/010/pdWS/001	Endocrinology	Hyperthyroidism (adults and paediatrics)	ATC: H03BB02. Tablet; solution for injection	Literature (21)	Q1/2010	25/08/2011	25/11/2011	602	Paediatric information clarified: update to SmPC section 4.2; 4.5; 4.8. Age limit of 3 years has been specified in section 4.2. No interaction studies in paediatrics were performed (section 4.5) and addition of a safety concern applicable to both adults and paediatrics.	Two MAH submitted studies; one MAH proposed the SmPC change for sections 4.2, 4.5, 4.8 and 5.2. Sweden did not have a paediatric posology in the SmPC; more information was requested to support a paediatric posology in SE (posology would be included if required information would be provided).
Timolol/ AT/W/0005/pdWS/001	Ophthalmology	Reduction of intra-ocular pressure in various conditions including the following: patients with ocular hypertension; patients with chronic open-angle glaucoma including aphakic patients; some patients with secondary glaucoma. (adults)	ATC: S01ED01. Eye drops; solution	Literature (12)	Q4/2009	05/06/2011	30/09/2011	613	Evaluation of data suggest a recommendation for a transitional period for use in primary congenital and primary juvenile glaucoma. Paediatric information clarified: update of SmPC section 4.2 (titration, dosing regimen, duration), 4.4, 5.1 and 5.2.	Recommendations from Rapporteur: Further research and studies would be needed to support an indication for long term use of Timolol in the paediatric population in section 4.1 of the SmPC. Due to the superior risk profile, the development of a 0,1% ophthalmic eye drops solution, preferably preservative – free, should be encouraged.
Tobramycin Part I/ FI/W/002/pdWS/001	Infectious disease	Treatment of infections caused by gram negative bacteria. Long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients ≥6 years.	ATC: J01GB01. Nebulizer solution; solution for inhalation	CSR (6)	Q1/2011	02/06/2012	24/10/2012	518	Essential contents had been introduced with type II variation (UK/H/0361/001/II/051); therefore no further changes to the label have been recommended in conclusion of this procedure.	MAH proposed changes to SmPC section 4.2 and 5.1.

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Active Substance	**Therapeutic Area**	**Description of Indication/ (licensed population at start of procedure)**	**ATC/ Pharmaceutical form**	**Studies submitted** NC = non-clinical CSR= clinical study report Literature	**Wave*1**	**End of Procedure**	**Date of Publication**	**Duration of Assessment Procedure (calendar days)*1**	**Outcome of Assessment/ SmPC update**	**Notes/Comments**
Tobramycin Part II/ FI/W/002/pdWS/001	Infectious disease	Treatment of external infections of the eye and adnexa, caused by bacteria susceptible to tobramycin. In combination with dexamethasone: inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial infection exists or a risk of bacterial ocular infection exists. In combination with diclofenac: treatment of inflammation of the anterior segment of the eye in cataract surgery (adults and paediatrics)	ATC: S01AA12, S01CC. Eye ointment; eye drops suspension, eye drops solution	CSR (2); literature (7)	Q1/2011	02/06/2012	24/10/2012	518	Paediatric information clarified: update of SmPC sections 4.1 (age limit), 4.2 (dosing regimen; age limit), 4.4 (Tobradex only) and 5.1. Tobrex and tobradex retained a paediatric claim in section 4.1. For ocubrax (containing diclofenac), no paediatric recommendation has been given since none of the provided studies tested this combination in paediatric patients.	Request for SmPC harmonization (recommended by Rapporteur)
Topiramate/ MT/W/0002/pdWS/001	Neurological disorder	Monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures. Adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome. Prophylaxis of migraine.	ATC: N03AX. Tablets; capsules; sprinkle capsules	CSR (21);	Q4/2009	13/11/2010	02/03/2011 *update 07/06/2011	409	Additional safety information should be included in the SmPC to make the prescriber more aware of the potential problems which may occur in children. SmPC changes were proposed for sections 4.4; 4.8 and 5.1. Section 5.1: information about absence seizures was added as no reduction in frequency was observed. A type II variation was proposed for incorporation of these label changes	Label was subject to an Article 30 harmonization procedure; a summary of the harmonised indication information comprising instructions for paediatric use was submitted together with additional paediatric studies meeting the Article 45 criteria. As an outcome of this procedure, a recommendation for additional studies was given by the rapporteur in order to investigate the impact on cognitive function and growth.

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Tranexamic Acid/ FR/W/002/pdWS/001	Haematology	Treatment of haemorrhagic events due to generalized primitive fibrinolytic state, or occurred during treatment with a fibrinolytic agent, or sustained by local fibrinolysis. A posology in children of 20mg/kg/day was recommended in France	ATC: B02AA02. Tablet; oral solution; solution for injection	Literature (13)	Q4/2008	07/10/2009	29/01/2010	372	Paediatric information clarified: Update of SmPC section 4.2 (clarifying that data on efficacy, posology and safety are limited); section 4.3; 4.4; 5.1 (summary of study results for injectable solution in cardiac surgery) and section 5.2.	No studies in children conducted. Published studies utilized different treatment regimen. All regimens showed a positive effect. In cardiac surgery, another antifibrinolytic drug was suspended in the EU 2008. For reasons to find a replacement therapy, TXA had been assessed by an ad-hoc expert group involving French cardio-vascular surgeons and anaesthetists in paediatric area (constituted in the early of the year 2008) to further codify the use on the basis of the available efficacy and safety data. Rapporteur did his own literature search on PK/PD, safety and efficacy more specific foruse in cardiac surgery setting. High need for appropriate paediatric treatment options.
Trazodone/ UK/W/060/pdWS/001	Psychiatric disorder	SSRI for treatment of depressive disorders with or without anxiety in adults	ATC: N06A X05. Tablets; oral drops; solution for injection	Literature (25)	Q4/2012	13/03/2013	02/04/2013	164	No change. Published data did not require any additional safety update nor did these data support "Treatment of Resistant Depression in Adolescents".	Product was not licensed in paediatric (SmPC section 4.2 state that use in paediatric patients is not recommended). Standard warning regarding suicidality in SmPC section 4.4 was already included in label.

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Trimethoprim/ PL/W/014/pdWS/001	Infectious disease	Treatment of susceptible infections caused by trimethoprim-sensitive organisms including urinary and respiratory tract infections and for prophylaxis of recurrent urinary tract infections. (adults and paediatrics)	ATC: J01EA01. Tablets, suspension	Literature (50)	Q3/2011	13/03/2012	04/06/2012	256	Product was a well known to paediatricians; it has been on the market for a long time. Safety profile was considered acceptable. Submitted data did not support efficacy of trimethoprim as monotherapy for treatment of infections caused by trimethoprim-sensitive organisms including urinary and respiratory tract infections and for prophylaxis of recurrent urinary tract infections in paediatric patients. Based comments from CMS, which did not share the Rapporteurs opinion, and partly in line with the "recommendations on submission and assessment in paediatric worksharing" the Rapporteurs proposed no changes to the SmPC	
Triptorelin/ MT/W/0001/pdWS/001	Endocrinology	Gonadotropin releasing hormone agonist (GnRHa) for the treatment of central precocious puberty (CPP) in children. Additional indications licensed in adults.	ATC: LO2AE04. Suspension for injection	CSR (6)	Q2/2009	17/02/2010	01/10/2010 *update 02/03/2011	323	Paediatric information clarified: update of SmPC section 4.2 (involvement of paediatric endocrinologist for treatment of central precocious puberty); 4.4 (decrease in bone mineral density; slipped capital femoral epiphysis) and 4.8 (ADR frequency for paediatric).	Following discussions among CMS: dose recommendation of the triptorelin 3.75mg remained as agreed following MRP procedure (NL/H/0263). CMS had divergent opinions concerning the dosage level of 11.25mg; the NL did not accept this dosage for use in paediatrics. Outcome was supposed to be implemented by a type II variation procedure

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Ursodeoxycholic acid/ UK/W/036/pdWS/001	Hepatobiliary disorder	Treatment of cholesterol gallstones, primary biliary cirrhosis (PBC) and in some EU countries bile reflux gastritis (adults). Further, in some EU countries (France, Greece, Hungary, and Netherlands) UDCA preparations were also licensed for the treatment of primary sclerosing cholangitis and cystic fibrosis associated liver disease which were more frequently observed in children and adolescents.	ATC: A05AA02. Tablets; capsules; oral suspension	CSR (2); literature (154)	Q3/2011	29/10/2012	02/04/2013 *update 31/07/2013	486	As an outcome of this procedure, available evidence only supports UDCA's use in hepatobiliary disorder associated with cystic fibrosis (CFAHD) in children aged 1 month to less than 18 years. Treatment with UDCA in this paediatric condition is considered to be safe and effective at a dose of 20 mg/kg/day in 2-3 divided doses with an increase up to 30 mg/kg/day if necessary based on clinical response. A new indication was recommended with a proposal for an update of SmPC section 4.1; 4.2; 4.3 and 5.1. The MAH was requested to provide a RMP	One MAH proposed a SmPC update for section 4.2 regarding cholesterol gallstone and primary biliary cirrhosis, because limited evidence for safe and effective use was available. Second MAH proposed a recommendation for warning and contraindication based on a literature review, but did not provide a wording for a lable update.
Valaciclovir/ AT/W/0006/pdWS/001	Infectious disease	Article 30 referral recommended indications comprising treatment of HSV infections; genital herpes; recurrent ocular HSV; prophylaxis of CMV infections (adults and adolescents). Efficacy had not been evaluated in children less than 12 years.	ATC: J05AB11. Tablets	CSR (9); literature (3)	Q2/2010	09/11/2011	10/04/2012	588	Paediatric studies did not change the recommendation agreed under the scope of the Article 30 referral	
Vecuronium bromide/ DE/W/0043/pdWS/001	Anaesthesiology	Adjunct to general anaesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surge (adults and paediatrics)	ATC: M03AC03. Solution for injection	Literature (2)	Q1/2011	15/05/2012	02/07/2012	500	Paediatric information clarified in terms of age limit (specifying all paediatric populations for indicated use) and duration of drug administration: update of SmPC section 4.1; 4.2 and 5.2 (summary of PK data in different paediatric age groups.	

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Verapamil/ EE/W/0005/pdWS/001	Cardiovascular	Treatment of mild to moderate hypertension and angina pectoris (adult).	ATC: C08DA01. Prolonged release capsules	Literature (32)	Q4/2010	01/04/2011	02/04/2013	183	Paediatric information clarified: update SmPC section 4.2 (paediatric use is not recommended because provided information was inconclusive)	MAH did not perform any studies in paediatric populations
Vigabatrin/ FI/W/003/pdWS/001	Neurological disorder	Treatment in combination with other anti-epileptic drugs for patients with resistant partial epilepsy with or without secondary generalisation, in case if all other appropriate drug combinations had proven to be inadequate or had not been tolerated (adult and paediatrics). Monotherapy in the treatment of infantile spasms (West's syndrome) (paediatrics).	ATC: N03AG04. Tablets; granules for oral solution	NC (19); clinical documentation including CSR and literature (86)	Q3/2011	19/12/2013	07/04/2014	902	Paediatric information clarified: update of SmPC section 4.2 (indication added to posology section; range of paediatric subsets clarified); 4.6 (general update applicable to all patients); 4.8 (update applicable to all patients and further ADRs observed in paediatrics) and 5.2 (completion of existing label information and information specific for paediatric information).	History: safety concern related to severe visual field defects (VFDs) triggered a referral in 1999. Labelling changes were introduced, indications were maintained in 15 EU countries via MRP. CHMP mandated conduction of non-clinical and clinical studies in order estimate the risk of VFDs. Commitments got completed when the Art. 45 worksharing procedure was initiated.
Vinorelbine/ NL/W/0018/pdWS/001	Oncology	Treatment of Non Small Cell Lung Cancer, and Breast Cancer (adults)	ATC: L01CA04. Solution for injection; capsules	Literature (32)	Q2/2010	21/03/2011	12/06/2013	355	Paediatric information clarified: update of SmPC section 4.2 and 5.1. There was no sufficient evidence for save and effective use in paediatric patients. Section 5.1 includes a brief summary of limited study data generated in a range of different sarcoma types. Paediatric use is not recommended, therefore.	
Zanamivir/ NL/W/0021/pdWS/001	Infectious disease	Treatment of influenza A and B in adults and children (greater or equal to 5 years); Prophylaxis of influenza A and B in adults and children (greater of equal to 5 years)	ATC: J05AH01. powder for inhalation	CSR (2)	Q4/2010	19/08/2011	06/03/2013	323	Two paediatric studies supported the existing label. No further update was requested.	

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Zolpidem/ UK/W/067/pdWS/001	Psychiatric disorder	Treatment of insomnia where insomnia is debilitating or is causing severe distress for the patient (adults)	ATC: N05CF02. Tablets	CSR (6); NC (2); Literature (27)	Q2/2013	25/03/2014	04/08/2014	359	Paediatric information clarified: update of SmPC section 4.1; 4.2 and 5.1. Evidence for save and effective use is missing (ADHS - associated insomnia), therefore paediatric use is not recommended. Data of a placebo controlled trial were proposed for inclusion in section 5.1.	

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List of the active substances for which data has been submitted in accordance with Art. 45 of the Paediatric Regulation

****** For the detailed outcome of the worksharing, please refer to the Public AR (http://www.hma.eu/269.html)

INN	WAVE	RAPPORTEUR	CHANGES TO PRODUCT INFORMATION**	OUTCOME OF ASSESSMENT	ATC CODE
Acarbose	9th wave	NO	Section 4.2	Paediatric information clarified	A10BF01
Acebutolol	22nd wave	UK			
Acetic acid + Copper nitrate + Lactic acid + Nitric acid + Oxalic acid					
Acetylcarnitine					
Acetylcysteine					
Acetylsalicylic acid					
Acetylsalicylic acid + Ascorbic acid + Paracetamol					
Acetylsalicylic acid + Caffeine + Paracetamol					
Acetylsalicylic acid + Dipyridamole					
Aciclovir	7th wave	DK	Oral aciclovir Section 4.1 and 5.2 IV aciclovir Section 4.2 and 5.2	Paediatric information clarified	J05AB01
Acidifiers					
Acitretin					
Acrivastine					
Acrivastine + Pseudoephedrine					
Adapalene					
Adenosine	13th wave	UK	Intravenous injection formulation Sections 4.1, 4.2, 4.4 and 5.1 Intravenous infusion formulation Sections 4.2 and 5.1	New indication	C01EB10
Adrafinil					
Adrenaline + Articaine	22nd wave	MT			
Adrenaline + Lidocaine	2nd wave	SE			
Adrenaline + Mepivacaine					
Alanyl glutamine					
Albendazole					
Albumin					
Alcuronium					
Alendronic acid	7th wave	UK	Sections 4.2 & 5.1	Paediatric information clarified	M05BA04
Alizapride					

Alfacalcidol					
Alfentanil	8th wave	BE	Sections 4.1, 4.2, 4.6 & 5.2	Paediatric information clarified	N01AH02
~~Alfuzosin~~				Studies assessed via other regulatory procedures	
Algeldrate + Magnesium hydroxide					
Algeldrate + Magnesium hydroxide + Simeticone					
Alginic acid (combinations)	16th wave	AT	None	No change	A02BX13
Alimemazine					
Almitrine					
Almotriptan	14th wave	ES			
Alpha-estradiol					
Alprazolam	10th wave	UK	Section 4.2	Paediatric information clarified	N05BAI2
Alprostadil	21st wave	HU			
Aluminium Chloride					
Aluminium hydroxide + Magnesium hydroxide					
Aluminium Oxide					
Amantadine					
Ambenonium					
Ambroxol	17th wave	DE			
Ambroxol + Clenbuterol					
Amikacin	1st wave	SE	Sections 4.1, 4.2, 4.4, 4.5, 4.6 & 5.2	Paediatric information clarified	J01GB06
Amino acids					
Amino acids (combinations)					
Aminophylline + Theophylline					
Amiodarone	6th wave	NL	Sections 4.2, 4.3, 4.4, 5.1 & 5.2	Paediatric information clarified	C01B D01
Amisulpride	16th wave	IE		No change	NO5AL05
Amitriptyline	17th wave	UK			
Amlexanox					
Amlodipine	1st wave	NL	Sections 4.2, 5.1 & 5.2	New indication	C08CA02
Ammonium Bituminous Coal tar					
Amorolfine					
Amoxicillin	3rd wave	SE	Sections 4.2, 4.4 and 5.2	Paediatric information clarified	
Amoxicillin + Clavulanic Acid	2nd wave	DE	None	No change	J01CR02
Amphotericin B	5th wave	DE			
Ampicillin					
Ampicillin + Cloxacillin					
Ampicillin + Sulbactam					
Amylmetacresol + Dichlorobenzyl alcohol					
Amylmetacresol + Dichlorobenzyl alcohol + L-Menthol					
Amylmetacresol + Dichlorobenzyl alcohol + Vitamin C					
Anagrelide	15th wave	SI			
Anastrozole	4th wave	ES			

Antazoline + Naphazoline					
Antazoline + Tetryzoline					
Antazoline + Naphazoline + Zinc					
Antidiarrheal microorganisms					
Antithrombin III					
Antithymocyte immunoglobulin (rabbit)	2nd wave	DE-PEI	Section 4.2, 4.8 and 5.1	Paediatric information clarified	L04AA04
Antraquinone + Rhubarb + Salicylic acid					
Apis mellifera - Lyophilised bee venom	2nd wave	DE-PEI	Sections 4.1, 4.2, 4.3 & 4.4	Paediatric information clarified	V01AA07
Apraclonidine					
Aprotinin + Factor XIII + Fibrinogen + Plasmafibronectin + Thrombin + Calcium Chloride					
Arginine glutamate	16th wave	UK		No change	B05XB01
Arnica + Salicilic acid					
Artemether + Lumefantrine					
Articaine					
Articaine + Epinephrine					
Artificial tears and other indifferent preparations					
Ascorbic acid (vit C)	25th wave	DE			
Ascorbic acid + Cafeine + Chlorphenamine + Dextromethorphan + Paracetamol	25th wave	DE			
Ascorbic acid + Chlorphenamine + Paracetamol	25th wave	DE			
Ascorbic acid + Paracetamol	25th wave	DE			
Asparaginase	4th wave	BG			
~~Atomoxetine*~~				Studies assessed via other regulatory procedures	
Atorvastatin	20th wave	IE		No change	C10AA05
Atovaquone + Proguanil					
Atracurium	12th wave	IE	Sections 4.2 & 5.1	Paediatric information clarified	M03AC04
Atropine					
Azelastine					
~~Azidocillin~~				Data submitted for product no longer marketed	
Azithromycin	4th wave	HU		No change	J01FA10
Aztreonam	7th wave	NL	None	No change	J01DF01
Bacampicillin					
Baclofen	2nd wave	UK	Sections 4.1, 4.2 & 4.4	New indication	M03BX01
Bacterial Lysate					
Balsam Peru + Bismuth oxide + Subgallate + Zinc oxide					
Balsam Peru + Bismuth oxide + Zinc oxide					
Bambuterol					
Barium Sulfate					
Beclometasone	2nd wave	IE	None	No change	R03BA01
Befunolol					
Benazepril					

Benazepril + Hydrochlorothiazide					
Bendazac					
Benzalconium + Liquid Paraffin + Triclosan					
Benzalkonium + Dequalinium					
Benzalkonium + Soft paraffin + Triclosan					
Benzathine Benzylpenicillin					
Benzathine Phenoxymethylpenicillin					
Benzatropine					
Benzethonium + Lidocaine					
Benzilic Alcohol + Dextromethorphan					
Benzocaine + Tyrothricin					
Benzocaine + Cetylpyridinium					
Benzocaine + Cetylpyridinium + Dichlorobenzyl + Gramicidin					
Benzocaine + Chlorhexidine					
Benzocaine + Gramicidin					
Benzoxonium					
Benzoxonium + Lidocaine	2nd wave	SE			
Benzoyl peroxide					
Benzoyl peroxide + Clindamycin					
Benzydamine					
Bergapten					
Betahistine					
Betamethasone					
Betamethasone + Clotrimazole					
Betamethasone + Fusidic acid					
Betaxolol					
Betula verrucosa (pendula), allergen extracts from birch/alder/hazel (betula), allergen extract from birch (betula)	2nd wave	DK	Section 4.2	Paediatric information clarified	V01AA05
Bibrocathol					
Bicalutamide					
Bifonazole					
Bifonazole + Urea					
Biotin	15th wave	AT	None	No change	A11JB
Bisacodyl	1st wave	DK	Section 4.2	New indication	A06AB02
Bisoprolol	17th wave	UK		No change	C07AB07
Bisoprolol + Hydrochlorothiazide	17th wave	UK	None	No change	C07AB07
Bleomycin	3rd wave	BE			
Botulinum Antitoxin					
Botulinum toxin					
Bromehexine					
Bromelains					
Bromhexine					
Bromhexine + Ephedrine					
Brotizolam	3rd wave	EE			
Buclizine					

Buclizine + Codeine + Paracetamol					
Budesonide	1st wave	NL	Sections 4.2, 4.4, 4.8, 5.1 and 5.2	New indication	R01AD05, R03BA02, A07EA06
Budesonide + Formoterol	13th wave	DE	Section 4.2 and 5.1	New study data	R03AK07
Bufexamac					
Buflomedil					
Bumetanide	16th wave	DK			
~~**Bumetanide + Potassium Chloride**~~	~~16th wave~~	~~DK~~		No paediatric data identified	
Bupivacaine	10th wave	DE	Sections 4.1, 4.2, 4.3, 4.4, 4.8	Paediatric information clarified	N01BB01
Bupropion	4th wave	NL			
Buserelin					
Buspirone					
Butamirate					
Butylscopolamine					
Butylscopolamine + Paracetamol					
Cabergoline					
Caffeine + Codeine + Paracetamol					
Caffeine + Dimenhydrinate					
Caffeine + Drotaverine + Metamizole + Sodium					
Caffeine + Paracetamol					
Calcipotriol	13th wave	NL			
Calcipotriol	13th wave	NL			
Calcitonin (salmon synthetic)	1st wave	UK	Section 4.2	No change	H05BA01
Calcitriol					
Calcium (combinations)	17th wave	UK		No change	A12AX
Calcium Carbonate	16th wave	UK		No change	A12A A04
Calcium Fluoride + Sodium fluoride	17th wave	UK			
Calcium levofolinate					
Camphor + Diphenhydramine + Zinc					
~~**Candesartan***~~				Studies assessed via other regulatory procedures	
~~**Candesartan + hydrochlorothiazide**~~				Studies assessed via other regulatory procedures	
Canis familiaris (553)	3rd wave	DK	Section 4.2	Paediatric information clarified	V 01 AA 11
Capsaicin	25th wave	DE			
Captopril	6th wave	CZ	None	No change	C09AA01
Carbamazepine	3rd wave	ES			
Carbamide					
Carbocisteine					
Carbocisteine + Promethazine					
Carbomer	12th wave	AT	Section 4.2	Paediatric information clarified	S01AX20
Carbon + Helium + Oxygen					
Carbon dioxide					
Carboplatin	15th wave	BE			
Caries prophylactic agents					
Cefaclor	3rd wave	ES			
Cefadroxil					
Cefalexin					

Cefazolin					
Cefepime					
Cefixime	2nd wave	ES			
Cefodizime					
Cefonicide					
Cefoperazone					
Cefotaxime					
Cefoxitin					
Cefpirome					
Cefpodoxime					
Cefprozil					
Ceftazidime					
Ceftibuten					
Ceftriaxone	7th wave	IT			
~~**Ceftriaxone + Lidocaine**~~				No paediatric data identified	
Cefuroxime	4th wave	EE			
Celecoxib					
Cephaclor					
Cetalkonium + Choline salicylate					
Cetirizine					
Cetirizine + Pseudoephedrine					
Cetrimide + Lidocaine	2nd wave	SE			
Cetylpyridinium					
Cetylpyridinium + Lidocaine					
~~**Ciclesonide**~~				Studies assessed via other regulatory procedures	
Chloramphenicol	15th wave	DK			
Chloramphenicol + Cortisone + Ethacridine + Zinc Oxide	15th wave	DK			
Chloramphenicol + Medroxyprogesterone + Tetryzoline	15th wave	DK			
Chlordiazepoxide + Clidinium					
Chlorhexidine					
Chlorhexidine + Chlorobutanol					
Chlorhexidine + Diphenhydramine					
Chlorhexidine + Lidocaine	2nd wave	SE			
Chlorhexidine + Neomycin					
Chlorhexidine + Tetracaine					
Chlormadinone + Ethinylestradiol					
Chlorobutanol + Choline salicylate + Hexetidine + Propionic acid					
Chloroquine					
Chlorphenamine + Ferrous + Paracetamol					
Chloroquine + Proguanil					
Chlorphenamine + Dextromethorphan + Paracetamol					
Chlorphenamine + Paracetamol					

Chlorphenamine + Tramazoline					
~~**Chlortalidone**~~	~~23rd wave~~	~~UK~~		Studies assessed via other regulatory procedures	
Chlortetracycline					
Choline Salicylate					
Cetalkonium Chloride + Choline Salicylate					
Chondroitin sulfate	3rd wave	UK	Section 4.2	Paediatric information clarified	M01AX25
Chorionic gonadotrophin					
Chromium (51Cr) EDTA	4th wave	FR	Section 4.2	Paediatric information clarified	V09CX04
Ciclesonide					
Ciclopirox					
Ciclosporin	5th wave	CZ	None	No change	L04A D01
Cilastatin + Imipenem					
Cimetidine					
Cimetropium bromide					
Cinchocaine + Hydrocortisone					
Cinchocaine + Framycetin + Hydrocortisone					
Cinchocaine + Hydrocortisone					
Cinnarizine	11th wave	PL			
Ciprofloxacin	1st wave	FR			
Ciprofloxacin + Hydrocortisone					
Citicoline					
Cladribine	19th wave	SI			
Clarithromycin	3rd wave	SK	Sections 4.1 & 4.2	Paediatric information clarified	J01FA09
Clavulanic acid + Ticarcillin					
Clemastine	11th wave	NL			
Clenbuterol					
Clindamycin	6th wave	DK	None	No change	D10AF01, J01FF01, G01AA10
Clobazam	5th wave	UK	Section 4.2	Paediatric information clarified	N05BA09
Clobetasone					
Clomipramine					
Clonazepam					
Clonidine	6th wave	NL	Sections 4.2 & 5.1	Paediatric information clarified	N02CX02
Cloperastine					
Clorquinadol					
Clotrimazole					
Clotrimazole + Salicylic acid					
Cloxacillin					
Clozapine					
~~**Coagulation factor VII**~~	~~22nd wave~~	~~DE~~		Studies assessed via other regulatory procedures	
Coagulation factor VIII					
Coagulation factor IX	21st wave	CZ			
Coal Tar					
Cod Liver + Zinc					
Cod liver oil					
Codeine + Diphenhydramine + L-Menthol					

Codeine + Drotaverine + Paracetamol					
Codeine + Ibuprofen					
Codeine + Paracetamol					
Colchicine	4th wave	UK	Sections 4.1, 4.2, 4.4, 4.9 and 5.2.	New indication	M04AC01
Colecalciferol	14th wave	UK	Sections 4.1, 4.3, 4.4	Paediatric information clarified	A11CC05
Colecalciferol + Sodium fluoride	14th wave	UK	Sections 4.1, 4.2, 5.1	Paediatric information clarified	A11CC80, A11JB
Colestyramine	2nd wave	CZ	None	No change	C10AC01
Colistin					
Corticorelin					
Cromoglicic acid	2nd wave	BG			
Cromoglicic acid + Reproterol					
Cupric + Ferrus					
Cyclizine					
Cyclopentolate					
Cyclophosphamide	2nd wave	CZ	None	No change	L01AA01
Cyclophosphamide + Etoposide + Ifosfamide					
Cyclophosphamide + Ifosfamide					
Cyproheptadine					
Cyproterone + Ethinylestradiol					
Cytarabine	9th wave	SI			
Dacarbazine	17th wave	UK			
Dactinomycin					
Dalteparin	8th wave	IT			
Danazol					
Dantrolene					
Dapiprazole					
Daunorubicin	4th wave	NL	Section 4.1	New indication	L01DB02
Deflazacort					
Dequalinium + Lactose + Prednisolone + Tetracycline					
Dequalinium + Xylometazoline					
Dermatophagoides pteronyssinus	2nd wave	DK	Section 4.2	Paediatric information clarified	V01AA03
Dermatophagoides farinae + Dermatophagoides pteronyssinus	2nd wave	DK	Section 4.2	Paediatric information clarified	V01AA03
~~Desflurane~~	~~24th wave~~	~~IE~~		No paediatric data identified	
Desmopressin	23rd wave	CZ		No change	H01BA02)
Desogestrel	8th wave	CZ	Sections 4.2 and 5.1	Paediatric information clarified	G03AC09
Desogestrel + Ethinylestradiol	8th wave	CZ	Sections 4.2 and 5.1	Paediatric information clarified	G03AA09
Desonide					
Desoximetasone					
Dexamethason + Neomycin + Polymyxin B	13th wave	MT			
Dexamethason + Tobramycin	13th wave	MT			
Dexamethasone	13th wave	MT	Section 4.4, 4.6 and 5.3	New safety information	HO2AB02
Chloramphenicol + Dexamethasone	13th wave	MT			
Dexamethasone + Diphenhydramine	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	D07CB04
Dexamethasone + Framycetin + Gramicidin	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S01AA20

Dexamethasone + Gentamicin	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S01BB05
Dexamethasone + Gentamicin + Tetryzoline	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S01CA01
Dexamethasone + Neomycin	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S01CA06
Dexamethasone + Neomycin + Polymyxin B	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S02CA06
Dexamethasone + Polymyxin B + Trimethoprim	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S02CA06
Dexamethasone + Tobramycin	13th wave	MT	Section 4.2 & 4.4	Paediatric information clarified	S03CA01
Dexibuprofen					
Dexpanthenol					
Dexpanthenol + Polyvinyl alcohol					
~~**Dexrazoxane**~~	~~24th wave~~	~~UK~~		Studies assessed via other regulatory procedures	
Dextromethorphan					
Dextromethorphan + Diphenhydramine + L-Menthol					
Dextromethorphan + Diphenhydramine + L-Menthol + Pseudoephedrine					
Dextromethorphan + Pseudoephedrine					
Dextromethorphan + Pseudoephedrine + Triprolidine					
Dextromethorphan + Triprolidine					
Dextrometorphan + Guaifenesina					
Diastase					
Diazepam					
Dichlorobenzyl alcohol + Lidocaine					
Diclofenac	1st wave	DE	Sections 4.2, 4.3 & 4.8	Paediatric information clarified	M01AB05, M02AA15
Diclofenac + Tobramycin					
Dicloxacillin					
Didanosine					
Dienogest + Ethinylestradiol	24th wave	UK			
Dihydroergotamine					
Diltiazem	21st wave	NL			
Dimetindene					
Dimetindene + Phenylephrine					
Diosmectite					
Diphenhydramine					
Camphor + Diphenhydramine + Zinc					
Codeine + L-Menthol Diphenhydramine +					
Diphenhydramine + Guaifenesin + L-Menthol					
Diphenhydramine + L-Menthol					
Diphenhydramine + Paracetamol					
Diphenhydramine + Paracetamol + Pseudoephedrine					
Diphenhydramine + Paracetamol + Pseudoephedrine					
Dipyridamole	23rd wave	DE			
Dirithromycin					
Disopyramide					

Dithranol					
Dixyrazine					
Dobutamine	9th wave	PL	Sections 4.1, 4.2, 4.4, 4.8, 5.1 & 5.2	New indication	C01CA07
Docusate sodium + Sorbitol					
Dolasetron					
Domperidone	14th wave	BE			
Donepezil					
Dopamine	9th wave	PL			
Dopexamine					
Dorzolamide					
Dorzolamide + Timolol					
Doxazosin	23rd wave	UK	Section 4.2	Paediatric information clarified	C02CA04
Doxycycline					
Droperidol					
Dropropizine					
Drotaverine					
Econazole + Triamcinolone	20th wave	CZ			
Efalizumab					
Electrolytes (combinations)					
Eletriptan					
Enoxaparin	22nd wave	DE			
Epinephrine	22nd wave	MT			
Epinephrine + Lidocaine	2nd wave	SE			
Eplerenone	5th wave	NL			
Erdosteine					
Ergocalciferol					
Erythromycin					
Erythromycin + Ethanol					
Erythromycin + Isotretinoin					
Erythropoietin	8th wave	UK			
Escherichia coli strain Nissle 1917					
Esmolol	11th wave	FI		No change	N07BB04
Esomeprazole					
Estradiol	18th wave	CZ		No change	G03CA03
Estradiol + Norethisterone	18th wave	CZ		No change	G03CA03
Ethambutol	12th wave	ES			
Ethanol + Povidone-iodine + 2-Propanolol					
Ethinylestradiol + Etonogestrel					
Ethinylestradiol + Gestodene					
Ethinylestradiol + Levonorgestrel					
Ethinylestradiol + Norethisterone					
Ethinylestradiol + Norgestimate					
Ethosuximide	6th wave	UK	Syrup formulation Sections 4.2 & 5.1 Capsule formulation Sections 4.2 & 5.1	Paediatric information clarified	N03AD01
Ethyl esters of iodised fatty acids					

Etidronic acid					
Etilefrine					
Etomidate					
Etonogestrel					
Etoposide	3rd wave	SI		No change	L01CB01
Etoposide + Ifosfamide					
Eucalypti aetheroleum	13th wave	DE			
Exemestane					
~~Ezetimibe~~				Studies assessed via other regulatory procedures	
Factor VIII inhibitor bypassing act	22nd wave	SE			
Famciclovir	5th wave	DE	See outcome of Art.30 Procedure in April 2010	Paediatric information clarified	J05A B09
Famotidine	17th wave	UK		No change	A02BA03
Famotidine (combinations)	17th wave	UK		No change	A02BA53
Fat emulsions					
Felbinac					
Felis domesticus	3rd wave	DK	Section 4.2	Paediatric information clarified	V 01 AA 11
Felodipine	1st wave	UK	Sections 5.1 & 5.2	New study data	C08CA02
Fenofibrate	10th wave	IE	Fenofibrate 67 mg and 100 mg capsules Section 4.2 & 5.1 High dosage forms of fenofibrate (300/200/267 mg capsules, 160/145/215 mg tablets) Section 4.2	Paediatric information clarified	C10 AB 05
Fenoterol					
Fentanyl	1st wave	UK	Fentanyl patches Sections 4.1 & 4.2 Fentanyl Injection Sections 4.2, 4.3 & 4.4 Fentanyl Lozenge Sections 4.1, 4.2, 5.1, 5.2 & 5.3	Paediatric information clarified	N01AH01, N02AB03
Fenticonazole					
Ferric oxide dextran complex					
Ferric proteinsuccinylate					
Ferric sodium gluconate complex					
Ferrous					
Fexofenadine	7th wave	EL			
Filgrastim	3rd wave	SE	None	No change	L03AA02
Flecainide	6th wave	IE		No change	C01BC04
Fluarix	23rd wave	DE-PEI	None	No change	C08CA06
Flucloxacillin					
Fluconazole					
Flucytosine					
Fludeoxyglucose	6th wave	FR			

Fludrocortisone					
Flumazenil	8th wave	IE	Sections 4.1, 4.2 & 5.2	New indication	V03AB25
Flunisolide					
Flunitrazepam					
Fluocinonide					
Fluocinonide + Lidocaine	2nd wave	SE			
Fluorescein					
Fluorescein + Oxybuprocaine					
Fluorocinonide					
Fluorometholone	21st wave	CZ			
~~**Fluorometholone + Gentamicin**~~	~~21st wave~~	~~CZ~~		Data submitted for product no longer marketed	
Fluorouracil	7th wave	DE			
Fluoxetine	4th wave	EL		No change	N06A B03
Flurazepam					
Flurbiprofen					
Fluticasone	3rd wave	IT			
Fluticasone + Salmeterol	13th wave	DE	Sections 5.1, 5.2 (SmPC) and 3 (PL).	Paediatric information clarified	R03AK06
~~**Fluvastatin**~~	~~11th wave~~	~~UK~~		Assessed in previous worksharing before Paed. Regulation	
Fluvoxamine					
Folic acid	11th wave	MT			
Fomepizole					
Formoterol					
Foscarnet	11th wave	DK	Sections 4.4, 4.8 & 5.3	New safety information	J05AD01
Fosfocreatine					
Fosfomycin					
Fosinopril	6th wave	HU			
Fosphenytoin					
Fotemustine					
Framycetin					
Framycetin + Polymyxin B					
Framycetin + Oxedrine + Polymyxin B					
~~**Fulvestrant**~~				No paediatric data identified	
Furosemide	4th wave	FR			
Fusafungine					
Fusidic acid					
Fusidic acid + Hydrocortisone					
Gabapentin	4th wave	PT			
~~**Gadobenic acid**~~	~~15th wave~~	~~UK~~		Studies assessed via other regulatory procedures	
Gadodiamide	15th wave	UK		No change	V08CA02
Gadopentetic acid	15th wave	UK	Sections 5.2	New study data	V08CA01
Gadoteric acid	15th wave	UK	Sections 4.1 and 4.2	Paediatric information clarified	V04CA02
~~**Ganciclovir**~~				Studies assessed via other regulatory procedures	

~~**Gelatin agents**~~				Studies assessed via other regulatory procedures	
Gemcitabine	4th wave	ES			
Gentamicin	2nd wave	DE	Intravenous and intramuscular use Sections 4.1, 4.2, 4.4, 5.2 Topical otic Section 4.4 Topical use other than otic None Intrathecal use None	New safety information	J01GB03
Ginkgo folium	13th wave	DE			
Glatiramer	17th wave	NL		No change	L03AX13
~~**Glimepiride**~~				Studies assessed via other regulatory procedures	
Gliquidone					
Glucosamine	3rd wave	UK	Sections 4.2 and 4.4	Paediatric information clarified	M01AX05
Glucose + Glutathione + Sodium Bicarbonate					
Glutamic acid					
Glycerol					
Glycerol + Liquid Sugar					
Glycerol and fat products + Soft paraffin					
Glyceryl trinitrate	24th wave	UK			
Gonadorelin	15th wave	UK	Section 4.8	New safety information	H01CA01, V04CM01
Goserelin					
Granisetron					
Guaifenesin					
Guaifenesin + L-Menthol					
Guaifenesin + Pseudoephedrine					
Guaifenesin + Pseudoephedrine + Triprolidine					
Chlorocycline + Guaifenesin					
Haloperidol	7th wave	FR	Section 4.4	New safety information	N05AD01
Hdroxyapatite					
Helium + Oxygen					
Heparin	14th wave	ES			
Heparin + Levomenol	14th wave	ES			
Hexamidine					
Homatropine					
House dust					
Human normal immunoglobulin	5th wave	DE-PEI	None	No change	J06BA01/02
Hydrocortisone	22nd wave	CZ			
Hydrocortisone + Urea	22nd wave	CZ			
Hydrogen peroxide					
Hydromorphone					
Hydroxychloroquine	9th wave	UK	Sections 4.1 and 4.2	Paediatric information clarified	PA1BAO2
Hydroxyethylstarch					

Hydroxypropyl cellulose					
Hydroxyzine					
Hypertonic solutions					
Ibuprofen	9th wave	DE	Sections 4.2 and 4.4	Paediatric information clarified	M01AE01
Ibuprofen + Pseudoephedrine					
Ichtasol					
Idarubicin	7th wave	DE	Sections 4.1 and 4.2	New indication	L01DB06
Ifosfamide	4th wave	PL	Section 5.1	Paediatric information clarified	L01AA06
Ifosfamide + Mesna					
Imipenem					
Immunoglobulins					
Ifosfamide and cyclophosphamide	4th wave	PL			
Ifosfamide and etoposide	4th wave	PL			
Ifosfamide+etoposide+cyclophosphamide	4th wave	PL			
Ifosfamide +mesna	4th wave	PL			
Indium + Pentetreotid	4th wave	FR	Sections 4.2 and 4.4	Paediatric information clarified	V09IB01
Indometacin	22nd wave	FI		No change	M01AB01
Inosine					
Insulin (human)	12th wave	DK		No change	A10AB01, A10AC01, A10AD01
Interferon alfa-2a					
Interferon gamma					
Iobitridol					
Iodine					
Iodixanol					
Iohexol					
Iopromide					
Iotrolan					
Ioversol					
Ioxaglic acid					
Ioxitalamic acid					
Ipratropium	9th wave	DK	None	No change	R03BB01, R01AX03
Ipratropium + Salbutamol	9th wave	DK	None	No change	R03AK04
Fenoterol + Ipratropium					
~~**Irinotecan**~~				Studies assessed via other regulatory procedures	
Isoflurane	22nd wave	UK			
Isoniazid + Pyrazinamide + Rifampicin	5th wave	DE		Paediatric information clarified	J04AM05
Isoniazid + Rifampicin	5th wave	DE		Paediatric information clarified	J04AM02
Isosorbide dinitrate	12th wave	DE			
Isotonic solutions					
Isotretinoin					
Isradipine	8th wave	UK	Section 4.2	Paediatric information clarified	C08C A03
Itraconazole	4th wave	EE	Sections 4.2, 4.8, 5.1 & 5.2	Paediatric information clarified	J02AC02
Ivermectin					
Kanamycin					
Ketamine					

Ketoconazole	7th wave	DK	Section 4.2 & 5.2	Paediatric information clarified	D01AC08, J02AB02
Ketoprofen					
Ketoprofen + Sucralfate					
Ketorolac					
Ketotifen					
Lactic acid + Salicylic acid					
Lactic acid producing organisms					
Lactic acid producing organisms (combinations)					
Lactitol					
Lactulose					
Lamotrigine	1st wave	NL	None	No change	N03AX09
Lanolin + Soft paraffin and fat products					
Lanreotide					
~~**Lansoprazole**~~	~~13th wave~~	~~UK~~		Studies assessed via other regulatory procedures	
Laratadine					
Latanoprost	18th wave	IE	None	No change	S01EE01
Latanoprost +Timolol	18th wave	IE	None	No change	S01ED51
Laurilsulfate + Sorbitol					
Polidocanol + Urea					
Lenograstim	7th wave	DE	Sections 4.1, 4.2, 4.4, 4.8	Paediatric information clarified	L03AA10
Leuprorelin	1st wave	HU			
Levocabastine	15th wave	DE	Sections 4.1, 4.2, 4.8, 5.2	Paediatric information clarified	R01AC02, S01GX02
Levocarnitine					
Levocetirizine					
Levodropropizine					
Levofloxacin	7th wave	DE	None	No change	J01MA12
Levomepromazine					
Levonorgestrel	25th wave	UK			
Levosimendan					
Levothyroxine	2nd wave	SE	Section 4.2	Paediatric information clarified	H03AA01
Levothyroxine + Liothyronine					
Lidocaine	2nd wave	SE	Sections 4.1 and 4.2	Paediatric information clarified	N01BB52, C05AA61, J01RA, R02AA, R02AA20, A01AB14, A01AE11
Lidocaine + Noradrenaline	2nd wave	SE	Sections 4.1 and 4.2	Paediatric information clarified	N01BB52, C05AA61, J01RA, R02AA, R02AA20, A01AB14, A01AE11
Lidocaine + Prilocaine	2nd wave	SE	Sections 4.1 and 4.2	Paediatric information clarified	N01BB52, C05AA61, J01RA, R02AA, R02AA20, A01AB14, A01AE11
Liothyronine					
Liquid paraffin					
Liquid paraffin + Tar					
Lisinopril	1st wave	SE	Sections 4.2, 4.8, 5.1 & 5.2	New indication	C09A A03
Lisuride					
Lithium					
Lodoxamide					

Lomefloxacin					
Loperamide					
Loperamide + Simeticone					
Loracarbef					
Loratadine	4th wave	AT	None	No change	R06AX13
Lormetazepam					
~~Losartan~~				Assessed in previous worksharing before Paed. Regulation	
Lovastatin	10th wave	UK	Sections 4.8, 5.1 & cross referenced 4.2	New study data	C10AA02
Lumiracoxib					
Lymecycline					
Polidocanol (combinations)					
Madipidine					
Magnesium lactate + Magnesium pidolate + Pyridoxine (vit B6)					
Magnesium lactate + Pyridoxine (vit B6)					
Mannitol	12th wave	PL			
Maprotiline					
Mebendazole					
Mebeverine					
Mecillinam					
Meclozine					
Medroxyprogesterone					
Mefenamic acid	12th wave	UK		No change	M01AG01
Mefloquine					
Melatonin					
Meloxicam					
Melperone					
Melphalan	6th wave	BE	None	No change	L01AA03
Mephenytoin					
Mepivacaine	2nd wave	AT	Section 4.2 & 4.3	Paediatric information clarified	N01BB03
Mequitazine					
Meropenem	3rd wave	FR	None	No change	J01DH02
Mesalazine	1st wave	DK	Section 4.2	Paediatric information clarified	A 07 EC 02
Mesna					
Metamizole					
Metamizole + Scopolamine					
Methoxsalen					
Methoxybutropate					
Methylphenidate					
Methylphenobarbital + Phenytoin					
Methylprednisolone					
Methysergide					

Metoclopramide	5th wave	DE	i.v. Form Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9 Oral & Rectal Forms Sections 4.1, 4.2, 4.3, 4.4, 4.8 & 4.9	New safety information	A03FA01
Metopimazine					
Metoprolol	15th wave	NL	Sections 4.1, 4.2, 5.1 and 5.2	New indication	C07AB02
Metronidazole	7th wave	SE	Sections 4.1, 4.2 & 4.8	Paediatric information clarified	J01XD01
Metronidazole + Spiramycin	7th wave	SE	Sections 4.1, 4.2 & 4.8	Paediatric information clarified	P01AB01
Metyrapone					
Mexiletine					
Mianserin	6th wave	UK	None	No change	N06AX03
Miconazole	12th wave	NL	Sections 4.2, 4.3 and 4.4	New safety information	G01AF04
Miconazole + Zinc	12th wave	NL	Sections 4.2, 4.3 and 4.4	New safety information	G01AF04
Microparticles of galactose					
Midazolam	7th wave	FR			
Midecamycin					
Miglitol					
Milrinone	6th wave	AT	Sections 4.1, 4.2 4.4, 4.8, 5.1, 5.2 & 5.3	New indication	C01CE02
Minerals + Vitamins					
Minocycline	16th wave	NL			
Minoxidil	8th wave	MT	Sections 4.2, 4.4, 4.8, 5.1, 5.2 & 5.3	New study data	C02DC01
Mirtazapine	5th wave	UK	Sections 4.2, 4.8 & 5.1	New study data	N06AX11
Mitoxantrone	11th wave	SI			
Mivacurium	11th wave	PL	Sections 4.1, 4.2, 4.4 & 4.8	Paediatric information clarified	M03AC10
Mizolastine					
Moclobemide					
Modafinil					
Mometasone					
Montelukast					
Morniflumate					
Morphine	6th wave	HU			
Mupirocin					
~~Muromonab-CD3~~				Data submitted for product no longer marketed	
Mycophenolic acid	7th wave	SI	None	No change	L04AA06
Nabilone					
Nabumetone					
Nadroparin					
Nalbuphine					
Nalidixic acid					
Naloxone	13th wave	RO			
Naltrexone	2nd wave	NO	None	No change	N07BB04
Nandrolone					

Naphazoline + Pheniramine					
Naphazoline + Tetracaine					
Naproxen	2nd wave	PT			
Nedocromil					
~~**Neostigmine**~~	~~9th wave~~	~~UK~~		Data submitted for product no longer marketed	
Neridronic acid	2nd wave	UK	Sections 4.1 & 4.2	Paediatric information clarified	M05BA07
Netilmicin	9th wave	FI	None	No change	J01GB07
Nicomorphine					
Nicotine					
Nifedipine	10th wave	NL	Sections 4.2 and 5.1	Paediatric information clarified	C08CA05
Niflumic Acid					
Nifuratel					
Nifuroxazide					
Nimesulide	4th wave	UK			
Nimodipine	21st wave	FI	Section 4.2	Paediatric information clarified	C08CA06
Nitrazepam	8th wave	AT			
Nitrous oxide					
Nitrous oxide + Oxygen					
Nonoxinol-9					
Norfloxacin	18th wave	NL			
Noscapine					
Nutrients without phenylalanine					
Nystatin	12th wave	DK	Section 4.2	Paediatric information clarified	A01AB33, A07AA02, D01AA01
Obidoxime					
Octenidine					
Octreotide	12th wave	IT			
Ofloxacin					
~~**Olanzapine**~~				Studies assessed via other regulatory procedures	
~~**Olmesartan**~~				No paediatric data identified	
Olsalazine					
~~**Omeprazole**~~	~~12th wave~~	~~UK~~		Assessed in previous worksharing before Paed. Regulation	
Ondansetron	13th wave	BE			
Oral rehydration salt formulations	11th wave	PL			
Orciprenaline					
Ornidazole					
Orphenadrine					
Other mineral products					
Other nasal preparations					
Oxacillin					
~~**Oxaliplatin**~~				Studies assessed via other regulatory procedures	
Oxatomide	5th wave	IT			
Oxazepam	1st wave	SE	Section 4.4	New safety information	N05BA04
Oxcarbazepine	2nd wave	NL			
Oxitriptan					
Oxolamine					

Oxolamine + Propyphenazone					
Oxomemazine					
Oxybuprocaine					
Oxybuprocaine + Tetracaine					
Oxybutynin	5th wave	UK	Section 4.1 & 4.4	Paediatric information clarified	G04BD04
Oxycodone	10th wave	FR			
Oxygen					
Oxymetazoline					
Oxytetracycline					
Paclitaxel	3rd wave	NO	Section 4.2	Paediatric information clarified	L01CD01
Pancreatin	25th wave	UK			
Pantoprazole	14th wave	UK			
Paracetamol					
Paracetamol + Phenylephrine					
Ascorbic acid + Paracetamol + Phenylephrine					
Paracetamol + Phenylpropanolamine + Phenyltoloxamine					
Paracetamol + Pseudoephedrine					
Paracetamol + Pseudoephedrine + Triprolidine					
Paracetamol + Tramadol					
Paricalcitol					
~~Paroxetine~~				Studies assessed via other regulatory procedures	
Pefloxacin					
Penciclovir					
Penicillamine	10th wave	UK	Sections 4.1 and 4.2	New indication	M01CC01
Pentamidine	13th wave	DK	None	No change	P01CX01
Pentazocine					
Pentosan					
Pentoxifylline					
Pentoxyverine					
Periciazine					
Perindopril	4th wave	FR			
Permethrin	14th wave	UK	Sections 4.1, 4.2, 4.4. and 5.1	Paediatric information clarified	P03AC04
Perphenazine					
Pethidine	22nd wave	IE			
Phenobarbital					
Phenoxymethylpenicillin	3rd wave	NO	Section 4.1 & 4.2	New indication	J01CE02
Phentolamine	22nd wave	UK			
Phenylephrine	18th wave	SE	Section 4.2, 4.3, 4.4, 4.6 & 4.9	Paediatric information clarified	S01GA05
Phenylephrine + Prednisolone	18th wave	SE			
Phenylephrine + Zinc	18th wave	SE			
Phenytoin	19th wave	UK			
Phleum pratense / Modified, adsorbed grass pollen	3rd wave	DK	Section 4.2	Paediatric information clarified	V01AA02
Phloroglucinol					

Pholcodine					
Phospholipids					
Phospholipids + Vitamins					
Phytomenadione	12th wave	LV	Sections 4.2 & 5.1	Paediatric information clarified	B02BA01
Pidotimod					
Pilocarpine	13th wave	NL			
Pimecrolimus					
Pinaverium					
~~Piperacillin~~				No paediatric data identified	
Piperacillin + Tazobactam	4th wave	NL			
Pipotiazine					
Piracetam					
Pirenzepine					
Piretanide					
Piritramide					
Piroxicam					
Pivampicillin					
Pivmecillinam					
Pizotifen					
Podophyllotoxin					
Polidocanol					
Polymyxin B + Trimethoprim					
Polystyrene					
Potassium clorazepate					
Povidone-iodine	14th wave	AT			
Pralidoxime					
Pranoprofen					
Pravastatin	20th wave	UK		No change	C10AA03
Prazepam					
Praziquantel					
Prazosin	23rd wave	DE			
Prednicarbate					
Prednisolone					
Prednisolone + Sulfacetamide					
Prednisone					
Yeast Cell Extract + Shark Liver Oil					
Primidone					
Pristinamycin					
Procarbazine	11th wave	PL	Sections 4.1, 4.2 and 5.1	Paediatric information clarified	L01XB01
Prochlorperazine					
Progabide					
Progesterone					
Proglumetacin					
Promethazine					
Propafenone	22nd wave	RO			
Propofol	2nd wave	DE	Sections 4.4 & 5.2	Paediatric information clarified	N01AX10
Propranolol	6th wave	FR	Sections 4.2 & 4.8	New indication	C07 AA05

Protamine	17th wave	MT				
Protein-free						
Prothrombin						
Protirelin	15th wave	DE	Section 4.2	Paediatric information clarified	V04CJ02	
Proxymetacaine						
Pseudoephedrine						
Pseudoephedrine + Triprolidine						
Pyrantel						
Pyridostigmine						
Pyritinol						
Pyrvinium						
Quetiapine	1st wave	UK	Sections 4.4, 4.8 and 5.1	New safety information	N05AH04	Assessed in combination with Art. 46 studies
Quinapril	4th wave	UK	Sections 5.1 & 5.2	New study data	C09AA06	
Quinine						
Rabeprazole	15th wave	UK	None	No change	A02BC03	
Racecadotril						
Raltitrexed						
Ramipril	3rd wave	UK	Sections 4.2, 4.8, 5.1, 5.2 & 5.3	New study data	C09AA05	
Ranitidine	2nd wave	SE	None	No change	A02BA02	
Remifentanil	4th wave	UK	Sections 4.1, 4.2, 4.4 & 5.1	Paediatric information clarified	N01AH06	
~~**Retinol**~~	~~21st wave~~	~~MT~~		Data submitted for product no longer marketed		
Reviparin						
Rhubarb + Salicylic acid						
Ribavirin	12th wave	DE				
Rifabutin						
Rifampicin	5th wave	DE	None	Paediatric information clarified	J04AB02	
Rifamycin						
Rifaximin	1st wave	AT	Sections 4.1, 4.2 & 5.1	New study data	A07AA11	
Rimexolone						
Risedronic acid	3rd wave	UK	Sections 4.2 & 5.1	New study data	M05BA07	
Risedronic acid, calcium and colecalciferol, sequential	3rd wave	UK	Sections 4.2 & 5.1 (covered by the report for Risedronic acid)	New study data	M05BB02	
Risperidone	5th wave	IS	Section 4.4	Paediatric information clarified	N05AX08	
Ritiometan						
~~**Rizatriptan**~~				Studies assessed via other regulatory procedures		
Ropivacaine (5mg/ml)	8th wave	DE	Sections 4.1, 4.2 & 4.4	New indication	N01BB09	
Ropivacaine (Other presentations)	8th wave	DE	Sections 4.1, 4.2, 4.4, 4.8 & 5.2	Paediatric information clarified	N01BB09	
~~**Rosuvastatine**~~				Studies assessed via other regulatory procedures		
Roxithromycin						
Salbutamol	3rd wave	RO	Sections 4.1 & 4.2	Paediatric information clarified	R03AC02	

Salbutamol (combination)					
Salicylic acid + Urea					
Salicylic acid					
Salmeterol	4th wave	IT			
Scopolamine					
Secnidazole					
Sermorelin					
Serrapeptase					
Sertaconazole					
Sertraline	3rd wave	NL	None	No change	N06AB06
Sevoflurane	4th wave	IE	None	No change	N01AB08
Sibutramine					
Silybi mariani fructus	13th wave	DE	None	No change	A05BA03
Silymarin					
Simeticone	25th wave	UK			
Simvastatin	1st wave	DE	Sections 4.2, 4.4, 4.8, 5.1 & 5.2	New study data	C10A A01
Sobrerol					
Sodium acetate + Sodium Lauryl					
Sodium Aurothiomalate					
Sodium chloride	13th wave	AT		No change	S01XA03
Sodium Chromate (51Cr)	4th wave	FR	Section 4.2	Paediatric information clarified	V09CX04
Sodium fluoride					
Sodium phosphate					
Soft paraffin and fat products					
Solvents and diluting agents, incl. irrigating solutions					
Somatropin					
Spaglumic acid					
Spiramycin					
Spironolactone	5th wave	RO	None	No change	C03DA01
Streptodornase + Streptokinase					
Sucralfate	9th wave	AT	Section 4.4	New safety information	A02BX02
Sufentanil	8th wave	DE	Sections 4.1, 4.2, 4.3, 4.4, 5.1 and 5.2	Paediatric information clarified	N01AH03
Sulbactam					
Sulfacetamide					
Sulfamethoxazole + Trimethoprim					
Sulfasalazine					
Sulpiride					
Sultamicillin					
Sultiame					
Sultopride					
Sumatriptan	4th wave	NL	None	No change	N02CC01
Sylimarin					
Tacalcitol					
Tamoxifen					

Tamsulosin	12th wave	UK	None	No change	G04CA02
Tars					
Tars + Zinc					
~~**Tegafur + Uracil**~~	~~16th wave~~	~~NL~~		Data submitted for product no longer marketed	
Technetium (99mTc) medronic acid	8th wave	FR			
Teicoplanin					
Temocillin					
Teniposide					
Tenoxicam					
Terbinafine					
Terbutaline	11th wave	DK	None	No change	R03CC03 (systemic use), R03AC03 (inhalation)
Terfenadine					
Terlipressin					
Testosterone	11th wave	NL	Section 4.2	New safety information	G03BA03
Tetrabenazine					
Tetracosactide	8th wave	LV			
Tetrazepam					
Tetryzoline					
~~**Thallium**~~				Data submitted for product no longer marketed	
Theophylline	13th wave	DK	Sections 4.1, 4.2, 4.3, 4.4 and 5.2	Paediatric information clarified	R03DA04
Thiamazole	6th wave	DK	Section 4.2	New indication	H03BB02
Thiamphenicol					
Thiethylperazine					
Thiocolchicoside					
Thymosin alpha-1					
Tiagabine					
Tiapride					
Ticlopidine					
Timolol	5th wave	AT	Sections 4.2, 4.4, 5.1 & 5.2	Paediatric information clarified	S01ED01
Tinidazole					
Tinzaparin	21st wave	DE	Section 5.2	New study data	B01AB10
Tioconazole					
Tirofiban					
Tizanidine					
Tobramycin	10th wave	FI	sections 4.1, 4.2, 4.4 (Tobradex only) and 5.1	Paediatric information clarified	J01GB01
Tocopherol (vit E)	18th wave	DE			
Tolnaftate					
Topiramate	5th wave	MT	Sections 4.4, 4.8 & 5.1	New study data	N03AX
Tramadol	26th wave	IE			
Tramazoline					
Tranexamic acid	1st wave	FR	Section 4.2, 4.3, 4.4, 4.8, 5.1 & 5.2	New study data	B02AA02
Trazodone	17th wave	UK	None	No change	N06A X05
Tretinoin	17th wave	AT			

Tretracaine					
Triamcinolone	20th wave	CZ			
Trientine					
Trihexyphenidyl					
Trimebutine					
Trimethoprim	12th wave	PL	None	No change	J01EA01
Trimipramine					
Triprolidine					
Triptorelin	3rd wave	MT	Sections 4.2, 4.4 and 4.8	Paediatric information clarified	LO2AE04
Trobramycin					
Tropicamide					
Tropisetron					
Trospium					
Ubidecarenone					
Urea					
Urinay concrement solvents					
Ursodeoxycholic acid	12th wave	UK	Section 4.1 & 4.2	New indication	A05AA02
Valaciclovir	7th wave	AT		No change	J05AB11
Valproic acid	19th wave	UK			
Valpromide					
Polidocanol + Protein-free					
~~Valsartan~~				Studies assessed via other regulatory procedures	
Vecuronium	10th wave	DE	Sections 4.1, 4.2 & 5.2	Paediatric information clarified	M03AC03
~~Venlafaxine~~				No paediatric data identified	
Verapamil	9th wave	EE	Section 4.2	Paediatric information clarified	C08DA01
Vespula spp. /Lyophilised wasp venom	3rd wave	DE-PEI	Sections 4.1, 4.2, 4,3 & 4.4	Paediatric information clarified	
Vigabatrin	12th wave	FI	Sections sections 4.2, 4.6, 4.8 and 5.2	Paediatric information clarified	N03AG04
~~Viloxazine~~				Data submitted for product no longer marketed	
Vinorelbine	7th wave	NL	Sections 4.2 and 5.1	Paediatric information clarified	L01CA04
Vitamins	12th wave	PL			
Vitamins (combinations)					
Von Willebrand factor and coagulation factor VIII in combination					
Warfarin	24th wave	DE			
Xylometazoline					
Zafirlukast					
Zanamivir	9th wave	NL	None	No change	J05AH01
Zinc oxyde					
Ziprasidone					
Zolmitriptan					
Zolpidem	19th wave	UK	Sections 4.1, 4.2 and 5.1	Paediatric information clarified	N05CF02
Zopiclone	19th wave	UK	Sections 4.1, 4.2 and 4.4	Paediatric information clarified	N05CF01