EXPERIENCES WITH A REFERRAL PROCEDURE ART 31 ON AN OTC-PRODUCT: A COMPANY PERSPECTIVE

DGRA Annual Congress
7 and 8 May, 2015, Bonn
Clinical Trial Regulation, Pharmacovigilance

Disclaimer and Special thanks

- The views expressed in this presentation are purely personal views from individuals and do not represent any official view of a company or any department thereof

- Special thanks for the great support in the preparation of this presentation go to Martina Nittel, global CHC Regulatory Affairs

Dr. Petra Kammann
My goal today

Share my personal experience

Focus on process rather than on contents

Explain the particular challenges

Point out most important lessons learned

Dr. Petra Kammann

Bromhexine and Ambroxol

- Registered in the EU Member States for decades:
  - Bromhexine since 1963
  - Ambroxol since 1978

- The majority of marketing authorizations are purely national

- Bromhexine (Bisolvon®) developed for secretolytic treatment
- Ambroxol (Mucosolvan®) also investigated for effects on surfactant production and in blocking afferent nerves, leading to a local anaesthetic activity (Mucoangin®)

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Bromhexine and Ambroxol

The cumulative patient exposure until March 31st 2014 worldwide for the mono-products:

- Mucosolvan: 31,881,769 patient-years
- Mucoangin: 364,223 patient-years
- Bisolvon: 20,737,760 patient-years

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WHAT WAS THE TRIGGER?
An in depth reevaluation of the benefit-risk balance of ambroxol hydrochloride in all its currently approved indications seems to be necessary. As this conclusion results from a pharmacovigilance assessment (signal detection and PSUR) conducted by the lead Member State and the P-RMS of ambroxol and involves the interests of the Union, a safety driven referral may be initiated. As the urgency criteria outlined in the article 107i(1) are not met, the re-examination of the benefit-risk balance of ambroxol hydrochloride containing products under the article 31 of the Directive 2001/83/EC should be considered.

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- Identification of immediate and delayed-type hypersensitivity issues
  → significant impact on safety profile
- Negative outcome of the re-evaluation of the B/R balance of ambroxol in the indication in all paediatric populations below 6 years of age

**Conclusion from BE:** B/R balance of Ambroxol (AX) is questionable in all its currently approved indications and thorough re-evaluation of B/R balance of AX containing products is necessary

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**Scope of referral was extended to Bromhexine (BX) containing products as AX is a metabolite of BX**

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Main topics under discussion:

- SCAR causally related to intake of AX/BX products?
- Limitation of age groups
- Limitation of indications
- Benefit/Risk profile (positive or negative?)

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HOW TO ORGANISE A RESPONSE WITHIN THE GIVEN TIMELINES?
Which thoughts would have come to YOUR mind?

We need a strategy today...
...and Senior Management approval tomorrow

We need a deadline extension!

Let's build a core project team!

This has absolute priority!

Who can help from outside BI?

What if we lose these products?

Which products have to be included?

What does Pharmacovigilance say?

How should our response document be set up?

Whom else do we need internally?

Let's build a core project team!

Representatives:
- Global Pharmacovigilance
- Medicine
- Regulatory Affairs
- Corporate Communication
- Legal
- Marketing
- Business Development
- Commercial Management

For CHC and RX functions!

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We need a strategy today…

- Basic Core Team proposal prepared within days
- Projects Timelines considered review cycles for Management Review
- Final approval of response at the level of Board of Managing Directors

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Which products have to be included?

- 3 main brands:
  - Mucosolvan
  - Mucoangin
  - Bisolvon

- 2 combination products
  - Spasmo-Mucosolvan
  - Bisolvomycin

Dr. Petra Kammann
Which products have to be included?

<table>
<thead>
<tr>
<th>EU country</th>
<th>Bromhexine</th>
<th>Ambroxol</th>
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<tbody>
<tr>
<td></td>
<td>Mono products</td>
<td>Combination products</td>
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<td>Norway (NO)</td>
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Number of MAs in the EU (+ NO and IS): 77 | 113 | 51 | 6

Whom else do we need internally?

- Colleagues in the local affiliates
- PV Writing
- Archiving
- Administrative support

Several Sub-Teams + ad hoc Working Teams
Who can help from outside BI?

- Legal Experts
- Regulatory Affairs Experts
- Scientific and medical support for PV questions
- Support in ICSR evaluation
- Key Opinion Leaders in the local affiliates

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We need a deadline extension!

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<th>Procedural step</th>
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<th>Comments</th>
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<td>Start of procedure/notification</td>
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<td>List of questions (LoIs)</td>
<td>10.04.2014</td>
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<tr>
<td>Submission of response to LoIs</td>
<td>23.06.2014</td>
<td>No deadline extension accepted, less than 3 months to reply</td>
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</table>

Clarification of several aspects of the Questions needed to be addressed with the PRAC

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How should our response document be set up?

- Create a shareroom for the 5 modules of the response document
- A summary response to cover the main aspects in a short version
- Format needed to be archivable

What does Pharmacovigilance say?

- Ad-hoc preliminary assessment on the topics to be prepared within days
- Comprehensive Data Analysis plan needed
- Workload not manageable in house:
  - Contact with external experts on immunology to be set up
  - CRO for the causality assessment of ISCRs on severe allergic reactions needed

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What if we lose these products?

- AX/BX product portfolio one of the most important Brands for BI CHC
- Contingency plan to be set up
- Operational aspects to be worked-out in case immediate label-changes would be required

WHAT WERE THE CHALLENGES OF THE LIST OF QUESTION?

A flavour of complexity
Example: Question 1b

In question 1b of the PRAC List of Questions the MAH is requested to provide sales figures and estimated patient exposure for **ambroxol and/or bromhexine and combination products**, if possible stratified by **age**, by **member state** and by **indication**.

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What does that mean for Ambroxol?

- Approved in 18 EU countries
- For 4 indications

Member states x indications = subsets of exposure

\[18 \times 4 = 72\]
Mucosolvan formulations

- Ampoule 15mg/2ml
- Ampoule 30mg/4ml
- Infusion sol. 1000mg/50ml
- Contr. Rel. capsule
- Drops 15mg/ml
- Effervescent tab. 60mg
- Filmcoated tab. 60mg
- Inhalat. Liquid 7.5mg/ml
- Lozenge 15mg
- Syrup 15mg/5ml
- Syrup 30mg/5ml
- Tablet 30mg
- Sachet powder 15mg
- Sachet powder 30mg
- Sachet powder 60mg
- Adult Supp. 60mg
- Paed. Supp. 15mg
- Paed. Supp. 30mg

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Mucosolvan exposure datasets

72 subsets of exposure data × 18 formulations = 1296 total exposure subsets

...not yet considering the different age groups

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Example Question 3

For this purpose, all the MedDRA Preferred Terms (PTs) within the SMQ Hypersensitivity (broad), reported for the selected suspected or interacting ambroxol and/or bromhexine–containing products should be provided. Causality assessment should be performed for serious cases.

- For Mucosolvan alone, 256 cases required a causality assessment

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Example Question 5

“Please provide a benefit/risk balance evaluation of ambroxol and/or bromhexine-containing medicinal products, in each of their licensed indications. Based on the responses to the above questions, this should consider how the benefit risk balance may differ according to age, separating the populations of 0-6 years old, 6-12 years old and 12 years of age and older.“

Example Mucosolvan

- 3 indications
  - Secretolysis
  - Infant respiratory distress syndrome
  - Prophylaxis of post-operative complications

- 3 age groups

9 sub-sections of Benefit/Risk assessment

Prerequisite: stratification of both efficacy and safety data according to these sub-groups
....for one single indication

Response in a nutshell

The result of the analysis of the safety-related aspects revealed no new or undue risks to patients.

The benefit/risk balance was considered positive for all products, indications and age groups.

Clinical data were transparently described, including the given limitations for studies from the pre-ICH/GCP era.

It was pointed out that post-Marketing experience was considered an essential part of the available data.

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AFTER SUBMISSION WITHIN THE GIVEN TIMELINE...

Assessment of the Rapporteur and Co-Rapporteurs

**AT:** positive position; acknowledged the situation for these mature registered products

**BE:** negative position concerning all products independently from indications and age groups

**PT:** position in between but tendency more in favour with certain limitations (e.g. age groups, labelling)

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List of outstanding issues, 11 Sep 2014

[35]

- ...provide further justification supportive of a positive benefit risk in the secretolytic indication in each of the paediatric sub-populations i.e. 0-2, 2-6 and 6-12 years of age...

- ... provide proposals and justifications for further risk minimisation measures for each of the approved indications..

- Plus various detailed questions around the SCAR topic

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Timetable

[36]

<table>
<thead>
<tr>
<th>Procedural step</th>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>PRAC List of outstanding issues (1st LoOIs)</td>
<td>15.09.2014</td>
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<td>PDCO opinion</td>
<td>10.10.2014</td>
<td>On safety + efficacy for paediatric use → based on request from PRAC</td>
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<tr>
<td>Submission of response to 1st LoOIs</td>
<td>20.10.2014</td>
<td></td>
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</tbody>
</table>

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Why did we ask for this meeting?

Topics:

- SCARs - Relationship to AX & BX use
- Post-operative Pulmonary Complications (PPC) in adults - Positive benefit/risk of AX
- Secretolytic indication – Paediatric use
- Efficacy and safety of AX/BX
- Proposed Risk Minimisation Measures

7 BI participants and 1 external expert (on SCAR)

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At the EMA

Procedural aspects

Welcome + explanations by Chairperson of the PRAC (Dr. June Raine) how the meeting will be held
- Introduction of the company's participants
- Presentation: 20 minutes (our presentation was a few minutes longer)
- Q&A section: 10 minutes (actually it took 1 hour in our case)

After the Meeting
- Administrative person will bring you back to the waiting room

Debriefing session with (Co-)Rapporteurs:
- Outcome in our case not yet conclusive
- SCARs: discussion still ongoing but rather in the direction that it must be included as side effect
- Age groups/indications: still under discussion

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Information about PRAC Referral to the public


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Press reactions

Ambroxol/Bromhexin: EMA vertagt auf 2015


**PRAC recommendation - Conclusions**

- There is a reasonable possibility of a risk of SCARs associated with ambroxol and bromhexine.
- Ambroxol and bromhexine are associated with an increased risk of hypersensitivity reactions.
- Risk of SCARs should be addressed by its inclusion in the product information, accompanied by a warning in order for patients and caregivers to recognise the prodromes of SCARs and discontinue treatment immediately in the event of such signs.
- The available data were insufficient to justify new age restrictions.

The Committee ... concluded that the benefit-risk balance of ambroxol- and bromhexine-containing medicinal products remains favourable ... (22 of 31 votes)

**CMDh position - Conclusions**

The CMDh ... agrees with the overall scientific conclusions by the PRAC and reached the position that the marketing authorisations for ambroxol- and bromhexine-containing medicinal products should be varied.

Position reached by a majority of 19 out of 28 votes. Icelandic + Norwegian CMDh members agreed with position.

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Status today...

Lessons learned

General
- Don’t underestimate the enormous pressure on the organisation
- Large resource and financial impact
- Everything will take more time than you expected

Project Management
- Get started immediately
- Assign clear responsibilities and leadership roles
- Perform regular weekly Core Team meetings
- Make sure you get the resources you need
- Strategy first!

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Lessons learned (cont’d)

Internal Communication/ Information
- Immediately involve all people you might need
- Inform your colleagues in the countries regularly on the status

External Communication
- Prepare Q&A papers + reactive press statements
- Establish a good communication channel with EMA contact person

Lessons learned (cont’d)

Administrative aspects
- Train the authors to avoid unnecessary work afterwards (e.g. references to be filled in the eTOC)
- Install a dedicated Shareroom for handling of huge data packages, work on the same documents
- Consolidation of draft documents by one person
- Plan enough time for Management Review and submission process
Lessons learned (cont’d)

Oral Explanation Meeting

- Time is precious: focus on the most important topics
- Consider already upfront any possible questions that the PRAC may have and be prepared to answer
- Pre-define the roles of active participants and perform rehearsals with all speakers
- Bring paper copies of all response documents

Efforts in numbers

- 35,158 pages
- 771 documents
- 72 colleagues
- 27 Functions
- 9 months of work

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