9 October 2017
EMA/CHMP/735217/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on boric acid' (EMA/CHMP/619104/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Weleda AG
2	German Pharmaceutical Industry Association (BPI e.V.)
3	Novartis Pharma AG
4	AESGP
5	Sandoz
6	Medicines Evaluation Board in the Netherlands
7	ECI-EEIG
8	Reckitt Benckiser Healthcare (UK) Limited

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Boric acid and its salts are used in many ophthalmic products as a buffer or for isotonisation. The quantity of boron in these kinds of products is very low: E.g. for buffering purposes a concentration of approximately 0.02 % boron is used. The choice of the borate-buffer is suitable and based on experience. It is well-known in the production of eye drops. Its compatibility with other excipients, with drug substances, and with the packaging material is also shown. One drop has approximately a volume of 50 µl. The maximum amounts that can be accommodated by the anterior parts of the eye are 10 – 20 µl (Deutsche Apotheker Zeitung Nr. 32, 2015). The surplus runs off quickly. Consequently by each instillation of one eye drop 20 µl (comparable to 20 mg) are applied, corresponding to an amount of approximately 0.004 mg of boron. Thus 0.04% of the PDE (10 mg boron per day) are instilled with each drop. Assuming a daily dose of 5 drops and the treatment of both eyes 0.04 mg boron/day are applied corresponding to 0.4% of the PDE. Furthermore, it is questionable how much of this amount comes in fact to a systemic effect. Taking into account the theoretical amount of 50 µl per drop, this corresponds to 0.01 mg of boron. Considering a maximum daily posology of 5 drops for each eye, i.e. 10 drops for both eyes, the amount of boron will reach 0.10 mg/day, which is still much lower than the threshold of 1 mg/day. In the „Besonderheitenliste des Bundesinstituts für Arzneimittel und	Zero threshold: The Q&A was updated. For human medicinal products inducing an exposure of < 1 mg B/day, the inclusion of an information on the toxicological effects of boric acid and borates in the PL is no more requested taking into account) the lack of risk at this exposure level as acknowledged in the document and ii) the confusion that might cause the proposed wording to patients.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Medizinprodukte (BfArM) / Version 1-11, März 2015 auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen“ is stated that ophthalmic preparations – among others - are excluded from the German „Stufenplan-Bescheid“ from 25 July 1983, in which it is stated that the marketing authorisations for drug products containing boric acid, boric acid salts and esters had to be withdrawn. Prerequisite for these products was that under normal conditions of use, the supplied amounts of boric acid shall not exceed the limits set for drinking water (2.5 mg boron at a daily water intake of 2.5 L) and that children under the age of three years are excluded from the treatment. In the publication of the BfArM from 20 May 2005 “Kontraindikationen/Warnhinweise in den Produktinformationen von Ophthalmika, die Borverbindungen enthalten” it was stated that, due to a new assessment taking into account current literature, warnings and contraindications regarding boric acids and its salts are not required and that an adjustment in the information of the Besonderheitenliste has been done. We suggest exempting ophthalmic preparations containing boron just for pH adjustment completely from the obligation to inform patients in the package leaflet. Indeed, the small amount of boron contained in these preparations (much lower than 1 mg/day) cannot impair fertility. Information for the package leaflet would be necessary from 1 mg/day of boron and more which is never reached by ophthalmic preparations using boron as buffer.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	The German Pharmaceutical Industry Association (BPI e.V.) thanks for the opportunity to give comments on the above mentioned Q&A paper on boric acid which is prepared in context of the revision of the Guideline on the “Excipients in the label and package leaflet of medicinal products for human use” BPI wants to give the following comments: **The necessity to give information in the package leaflet regarding boric acid and borates containing preparations should be exempted for ophthalmic preparations** The toxicological consideration stated in the Q&A paper is based on the oral intake of Boron containing products. Due to this fact the oral Permitted Daily Exposure (PDE) for boron has been calculated to 10 mg B/ day. Based on this PDE (based on the oral intake of the product) the thresholds for the requirements of different information to be included in the package leaflet have been established. But especially, the topic route of administration, which is the case for ophthalmic preparations (e.g. eye drops) cannot be included to this principle. Boric acid and Borate containing products were subject to a national referral procedure in Germany and the national competent authority BfArM has released a decision on 25.07.1983 containing a rejection of a marketing authorisation for Boric acid and borate containing products. Ophthalmologic preparations, containing boric acid /borate as a buffer or isotonisation system were exempted from the decision. The Drug Commission of the German Medical Association (AKdÄ) published in November 1999 information about boric acid containing preparations. The use of boric acid was considered as harmful and was	As mentioned above, information in the PL is no more requested for human medicinal product inducing an exposure to less than 1 mg B/day.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	not recommended to use. But even in this recommendation, the use of boric acid, salts and esters used to buffer or isotones ophthalmologic preparations was exempted and considered not as harmful. In the publication of the BfArM from 20 May 2005 “Kontraindikationen/Warnhinweise in den Produktinformationen von Ophthalmika, die Borverbindungen enthalten” it was stated that, due to a new assessment taking into account a current literature, warnings and contraindications regarding boric acids and its salts are not required and that an adjustment in the information of the “Besonderheitenliste” (national implementation of Excipients Guideline in Germany) has been done. Ophthalmic preparations containing boric acid, salts or esters as a buffer, are widely used in the EU. Most of these preparations have been authorised and marketed for over 25 years. No signals or ADR have been observed so far that would lead to the fact to include information in the package leaflet and there are no new scientific cognitions compared to the outcome of the national referral and the recommendations that would justify changing the labelling. The publication of Scalli AR, Bone JP, Brüske-Hohlfeld I, Culverd BD, Li Y, Sullivan FM (2010): An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers, Reprod; Toxicol 29: 10-24 came to the results, while boron has been shown to adversely affect male reproduction in laboratory animals, there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers. The publication of Robbins WA, Xin L, Jia J, Kennedy N, Elastoff DA, Pinge L (2010): Chronic boron exposure and human semen parameters; Reprod Toxicol 29:184-190 gives the conclusion that in	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	their investigations no significant correlations between blood or urine boron and adverse semen parameters were found. Furthermore, it should be considered that even in some ophthalmic medicinal products the use of these eye drops is limited to a short time of about 14 days as stated in the SmPC and the package leaflet. These eye drops are prescription drugs and include only 5 ml of the preparation.. The toxicological risk of the use of boric acid or boric salts and esters as a buffer in eye drops has not changed and can be regarded as appropriate with regard to the benefit of a stable and isotone eye preparation. The considerations between " possible toxicological effects from animal tests, which could not be verified in human beings" and the uncertainty for patients/parents and children which is associated with these labelling information in the package leaflet lead to the opinion that the inclusion of the planned information concerning boric acids and borates should not be included in the package leaflet. **According to BPIs opinion, the requirement to include information on the toxicological effects of boric acid and borates is not justified for ophthalmic preparations. Ophthalmic preparations, especially containing boric acid just for pH-adjustment should be excluded from this requirement.**	
4	The proposed wording for the amendment of the guideline on excipients should be specified in order to address the issue more precisely: a) It should be clearly stated that the given thresholds refer to the amount of boron derived from boric acid and borates contained in the medicine. The current wording only gives values in mg/day. Together with column 1 stating "boric acid (and borates)" this could be misleading in that way, that the	a) The comment is endorsed, and the table was clarified to avoid any misinterpretation. b) Age categories are clearly reported in the table. c) The zero threshold is no more proposed (see above).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	amount of boric acid or borates is meant. b) The proposed wording could be misleading in that patients and caregivers could fear that fertility might also be impaired in children and adults above the given age limit. It should be clarified that the effect on fertility is limited to patients in the given age group. c) It should be clarified whether the proposed introductory text for threshold zero ("This medicinal product contains <X mg boron> per <dose>.") should be stated **in addition** to the proposed wording for higher thresholds which is reasonable in our view. AESGP proposes the following wording to be included in the guideline on excipients in order to address the above mentioned issues (see table below in section 2).	
4	Boric acid and its salts are used in many ophthalmic products as a buffer or for isotonisation. The quantity of boron in these kinds of products is very low: e.g. for buffering purposes a concentration of approximately 0.02 % boron is used. The choice of the borate-buffer is suitable and based on experience. It is well-known in the production of eye drops. Its compatibility with other excipients, with drug substances, and with the packaging material is also shown. One drop has approximately a volume of 50 µl. The maximum amounts that can be accommodated by the anterior parts of the eye are 10 – 20 µl (Deutsche Apotheker Zeitung Nr. 32, 2015). The surplus runs off quickly.	See above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Consequently, by each instillation of one eye drop 20 µl (comparable to 20 mg) are applied, corresponding to an amount of approximately 0.004 mg of boron. Thus 0.04% of the PDE (10 mg boron per day) are instilled with each drop. Assuming a daily dose of 5 drops and the treatment of both eyes 0.04 mg boron/day are applied corresponding to 0.4% of the PDE. Furthermore, it is questionable how much of this amount comes in fact to a systemic effect. Taking into account the theoretical amount of 50 µl per drop, this corresponds to 0.01 mg of boron. Considering a maximum daily posology of 5 drops for each eye, i.e. 10 drops for both eyes, the amount of boron will reach 0.10 mg/day, which is still much lower than the threshold of 1 mg/day. In the „Besonderheitenliste des Bundesinstituts für Arzneimittel und Medizinprodukte (BfArM) / Version 1-11, März 2015 auf Basis der Excipients-Guideline (CPMP/463/00 Final, Juli 2003), der Arzneimittel-Warnhinweisverordnung sowie umgesetzter nationaler Stufenplanmaßnahmen“ is stated that ophthalmic preparations – among others - are excluded from the German „Stufenplan-Bescheid“ from 25 July 1983, in which it is stated that the marketing authorisations for drug products containing boric acid, boric acid salts and esters had to be withdrawn. Prerequisite for these products was that under normal conditions of use, the supplied amounts of boric acid shall not exceed the limits set for drinking water (2.5 mg boron at a daily water intake of 2.5 L) and that children under the age of three years are excluded from the treatment. In the publication of the BfArM from 20 May 2005 “Kontraindikationen/Warnhinweise in den Produktinformationen von Ophthalmika, die Borverbindungen enthalten” it was stated that, due	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	to a new assessment taking into account current literature, warnings and contraindications regarding boric acids and its salts are not required and that an adjustment in the information of the Besonderheitenliste has been done. We suggest exempting ophthalmic preparations containing boron just for pH adjustment completely from the obligation to inform patients in the package leaflet. Indeed, the small amount of boron contained in these preparations (much lower than 1 mg/day) cannot impair fertility. Information for the package leaflet would be necessary from 1 mg/day of boron and more which is never reached by ophthalmic preparations using boron as buffer.	
5	Boric acid can be found in products such as • *Ophthalmic preparations, containing boric acid or its salts used as buffer and/or isotonicity agents,* • *Ears drops, 45* • *Homeopathic dilutions containing boric acid, its salts and esters.* For deriving the PDE there is no differentiation made to consider differences in absorption resulting from the different routes of administration. What is the rational?	Boric acid is readily absorbed from the GI tract (≥92% in humans). Therefore, deriving a PDE from the oral route represents a worst-case scenario. This PDE is relevant for other routes of administration unless robust data shows a significantly lower absorption. Such data were not found.
5	The aspect that there are other sources such as cosmetics and food appears not to have been considered. It is mentioned that the limit is consistent with the Scientific Committee on Consumer Safety opinion on Boron compounds which is set the Upper Intake Level (UL) in food for at 10 mg boron/person/day (lines 89-94)- this, de facto, means that one can have a maximum exposure for an adult of 10 mg/day	The Permissible Daily Intake use many safety factors and has been consider very conservative and it has been consider for each source by many authorities.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	(from food, cosmetics and other sources) and 10 mg/day from pharmaceutical preparations which actually would result in 20 mg/day. This appears to be in contradiction to the definition of a PDE value. What is the rational?	
6	Please find enclosed the comments of the Medicines Evaluation Board in the Netherlands. The MEB highly supports the revision of the Excipients guideline and the immediate provision of information through question and answer documents. The MEB is of the opinion that the SmPC should include a warning as well. Any information considered relevant for health care professionals should be included in the SmPC, and hence reference to the SmPC should be included in the Q&A document. The MEB does not have any comments to the scientific information in the Q&A, however it feels that the wording of the Table can be improved in order to better inform health care professionals, patients and caregivers on the risks, if any, of using boron containing products. In addition, the MEB would raise the question whether a contraindication will be applicable when exceeding the limit of 1 mg/day in the specific age groups. This is not clear from the document.	The Q&A document aims at supporting the revision of the Annex of the guideline “Excipients in the label and package leaflet of medicinal products for human use (CPMP/463/00 Rev. 1) for boric acid and borates. Stating on a warning to be included in the SmPC of human medicinal products containing boric acid or borates is out of the scope of this document. The document mentions explicitly that “The threshold is a value, equal to or above which it is necessary to provide the information stated for the package leaflet. This threshold is not a highest acceptable limit” (section 6).
7	Members of the ECI-EEIG welcome the opportunity to give comments on the above mentioned Q&A paper on boric acid which is prepared in context of the revision of the Guideline on the “Excipients in the label and package leaflet of medicinal products for human use” The ECI-EEIG endorses the comments of the German industry	See above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	association BPI which have been generated in co-operation with the ECI-EEIG managers: **The necessity to give information in the package leaflet regarding boric acid and borates containing preparations should be exempted for ophthalmic preparations** The toxicological consideration stated in the Q&A paper is based on the oral intake of boron containing products. Due to this fact the oral Permitted Daily Exposure (PDE) for boron has been calculated to 10 mg/day. Based on this PDE (based on the oral intake of the product) the thresholds for the requirements of different information to be included in the package leaflet have been established. However, the topical administration, which is the case for ophthalmic preparations (e.g. eye drops), cannot be treated in the same way. Boric acid and borate containing products were subject to a national referral procedure in Germany and the national competent authority BfArM has released a decision on 25.07.1983 containing a rejection of a marketing authorisation for boric acid and borate containing products. Ophthalmologic preparations, containing boric acid /borate as a buffer or for isotonicity were exempted from the decision. The Drug Commission of the German Medical Association (AKdÄ) published in November 1999 information about boric acid containing preparations. The use of boric acid was considered as harmful and was not recommended for use. But even herein, the use of boric acid, its salts and esters for buffering or adjusting isotonicity of ophthalmologic preparations was exempted and considered not to be harmful. In the publication of the BfArM from 20 May 2005 “Kontraindikationen/Warnhinweise in den Produktinformationen von	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Ophthalmika, die Borverbindungen enthalten" it was stated that, taking into account current literature, warnings and contraindications regarding boric acids and its salts were not required and that information given in the "Besonderheitenliste" (national implementation of Excipients Guideline in Germany) were modified, accordingly. Ophthalmic preparations containing boric acid, its salts or esters as part of the buffering system are widely used in the EU. Most of these preparations have been authorised and marketed for more than 25 years. No signals or ADRs have been reported so far that would suggest to include specific statements in the package leaflet and there are no new scientific cognitions that would justify changing the labelling. The publication of Scalli AR, Bone JP, Brüske-Hohlfeld I, Culverd BD, Li Y, Sullivan FM (2010): An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers, Reprod; Toxicol 29: 10-24 came to the results, while boron has been shown to adversely affect male reproduction in laboratory animals, there would be no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers. The publication of Robbins WA, Xin L, Jia J, Kennedy N, Elastoff DA, Pinge L (2010): Chronic boron exposure and human semen parameters; Reprod Toxicol 29:184-190 concludes that in their investigations no significant correlation between blood or urine boron and adverse semen parameters were found. The toxicological risk of the use of boric acid or its salts and esters in eye drops has not changed since and can be regarded as acceptable with regard to the benefit of a stable and isotonic eye preparation. Considering "possible	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	toxicological effects from animal tests, which could not be verified in human beings" and the uncertainty for patients/parents and children which is associated with the proposed warnings in the package leaflet, members of the ECI-EEIG recommend not to include such wording in the package inserts of ophthalmic preparations. **The ECI-EEIG advises, not to include information on the toxicological effects of boric acid and borates in the package inserts of ophthalmic preparations. Ophthalmic preparations, especially containing boric acid just for pH-adjustment should be excluded from this requirement.**	
8	Will the text in the 'Comments' column (Line 101) be required to be added to the SmPC?	No. Stating on a wording to include in the SmPC of boric acid- or borate-containing human medicinal products is out of the scope of the Q&A document.
8	What is the expected timeline for the implementation of the wording?	The timeline should be implemented in the core text of the guideline on excipients in the labelling and package leaflet of medicinal products for human use.
8	AESGP have queried whether the status of the source of boron in ophthalmic formulations is relevant to this legislation, namely whether a low level excipient is used as a buffering agent should qualify. Could the PRAC comment on this inclusion criteria? We would like to align our position to that of the AESGP: "We suggest exempting ophthalmic preparations containing boron just for pH adjustment completely from the obligation to inform patients in the package leaflet. Indeed, the small amount of boron contained in these preparations (much lower than 1 mg/day) cannot impair fertility. Information for the package leaflet would be necessary from 1 mg/day	See above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	of boron and more which is never reached by ophthalmic preparations using boron as buffer.”	
8	Please can the PRAC confirm whether the calculations for the exposure to boron have been made on the basis of chronic dietary intake, taking into consideration boron exposure from environmental sources such as drinking water? If the above assumption is correct and taking into consideration that some products contain very low level amounts of boron and are intended only for short term use, are the guidelines intended to apply to OTC products intended for extremely limited and transient exposure only? **Comments:** Exposure calculations appear to have been made on a chronic dietary intake calculation, deriving boron exposure from environmental sources such as drinking water. However, some products containing only very low level amounts of boron are intended only for short term use. Are the guidelines intended to apply to OTC products intended for extremely limited and transient exposure only?	The guideline applies to all human medicinal products, irrespective of their prescription status. The PDE was derived from an embryofetal toxicity studies reporting embryotoxic and/or teratogenic effect at non-maternotoxic doses. Therefore, any waiver based on the duration of treatment is not considered as appropriate. This is especially the case for OTC products whose dispensing is less controlled than medicinal products subject to prescription.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 43	2	**Comments:** Ophthalmic preparations should be excluded (see justification above). **Proposed change:** Deletion of ophthalmic preparations, containing boric acids or its salts.	Partly accepted. The “zero threshold” was deleted, therefore an information in the PL is no more required for any human medicinal product inducing an intake of less than 1 mg B/day.
Line 43	7	**Comments:** Ophthalmic preparations should be excluded (see justification above). **Proposed change:** Deletion of ophthalmic preparations, containing boric acids or its salts.	Partly accepted. Ophthalmic preparations remain in the scope. The “zero threshold” was deleted, therefore an information in the PL is no more required for any human medicinal product inducing an intake of less than 1 mg B/day. If this threshold is exceeded for any human medicinal product, including ophthalmic preparations, then the appropriate labelling should be included in the PL.
Line 84-88	3	**Comments:** The PDE was calculated on the basis of the rat reprotox study where fetal toxicity was seen in the absence of maternal toxicity. According to the ICH Q3C PDE calculation (which is cited as reference), in case of fetal toxicity in the absence of maternal toxicity, an uncertainty factor of 5 should be used. It would make sense to explain why F4 = 1 was used or apply the more conservative F4 = 5.	The method used to set the oral PDE for boron was changed since it is now derived from the oral MRL of 0.2 mg B/kg/day determined by the ATSDR, taking into account as point of departure developmental toxicity endpoints in rodents. The resulting PDE value is the same as that determined previously, i.e. 10 mg B/day.
Lines 91-	8	**Comments:**	The ULs were determined by the CHMP and SCCS for each

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td>94</td><td></td><td>The upper intake levels (ULs) of boron as boric acid or borates, given by the Scientific Committee on Consumer Safety (SCCS), are cited as the baseline toxicological data, presented as follows compared with the current PRAC proposed thresholds:

SCCS proposed upper intake levels
<table><tr><th>Age (Years)</th><th>Upper Intake Level (mg B/day)</th></tr><tr><td>1-3</td><td>3</td></tr><tr><td>4-6</td><td>4</td></tr><tr><td>7-10</td><td>5</td></tr><tr><td>11-14</td><td>7</td></tr><tr><td>15-17</td><td>9</td></tr></table>PRAC proposed
<table><tr><th>Age (Years)</th><th>Upper Intake Level (mg B/day)</th></tr><tr><td>< 2</td><td>1</td></tr><tr><td>< 12</td><td>3</td></tr><tr><td>< 18*</td><td>7</td></tr><tr><td>> 18*</td><td>10</td></tr></table>Whilst it is understood these are being transposed from an age range to an age threshold, the proposed values appear</td><td>patient age category by extrapolating from the UL for adults based on body weight and body surface area, respectively. The adult UL was the same, i.e. 10 mg B/day. Therefore, two factors may explain the apparent discrepancy between the ULs determined by each institution

a) The use of different age categories:

The CHMP classified paediatric patients into 3 age categories, according to ICH E11 guideline: newborns/infants/toddlers (<2 years), children (<12 years), and adolescents (<18 years). Since the aim of the Q&A document is to update the PL of human medicinal products containing boric acid/borates, this is considered the most adequate and practicable approach for purpose;

b) An impact of extrapolating according to either BW or BSA:

The UL values were not significantly different according to the method used, as shown below.
<table><tr><th rowspan="2">Age (Years)</th><th rowspan="2">BW (kg)</th><th rowspan="2">BSA (m^2)</th><th colspan="2">Upper Intake Level (mg B/day) - extrapolation based on</th></tr><tr><th>BW</th><th>BSA</th></tr><tr><td>0-2</td><td>5</td><td>0.25</td><td>1</td><td>1.5</td></tr><tr><td>2-11</td><td>15</td><td>0.56</td><td>3</td><td>3.3</td></tr><tr><td>12-17</td><td>35</td><td>1.28</td><td>7</td><td>7.5</td></tr><tr><td>> 18</td><td>50</td><td>1.70</td><td>10</td><td>10</td></tr></table></td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to differ significantly from the SCCS recommended values. Could the PRAC provide a rationale for the discrepancies in proposed threshold values?	
Line 101	2	**Comments:** Threshold: Zero A threshold of zero implicating to include information is not appropriate at all. Even to label information that "a small amount of boron in the medicine will not be harmful if used as recommended by your doctor or pharmacist" might cause confusion to patients. The correct use of the preparation is stated in the package leaflet and approved during marketing authorisation with regard to safety and efficacy. Further information is not needed, especially if the threshold is zero. **Proposed change:** Specify < 1 Delete the sentence: The small amount of boron contained in this medicine will not be harmful if used as recommended by your doctor or pharmacist. No information on the package leaflet is required.	Partly accepted. The "zero threshold" was deleted (see above), therefore it is not required to indicate "<1".
Line 101 Table 1	6	**Comments:** This table may be subject to confusion with respect to the text mentioned for the zero threshold. It does not clearly take into consideration that 1) the maximum daily dose of a medicine may depend on	Not accepted since a) The zero threshold was deleted (see above) b) As regards the 1, 3, and 7 mg thresholds: the labelling as originally proposed appears as suitable since it should be elaborated taking into account the maximal daily dose

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the indication and user group. 2) a medicine can be marketed in a range of medicinal products. Products may differ in their type of dosage form, strength, composition, other formulation characteristics, packaging, dosing device or user instruction. A certain medicinal product may be directed to the use by a specific patient population. 3) that single doses may be given different times a day; Therefore, the information in the package leaflet should be specific for a certain medicinal product (i.e. a medicine in a certain dosage form, with a particular strength / volume per dose, with other particular formulation characteristics such as taste and colour, with a particular formulation, packaging and user instruction) rather than the medicine as such. Also multiple boron containing products may be used concurrently. **Proposed changes:** <u>Zero threshold</u>: From: “This medicinal product contains <X mg Boron> per <dose>. The small amount ……” Into: “One single dose <add the amount of the maximum single dose in SmPC, where relevant> of this <unique reference to dosage form, strength and formulation of the medicinal	recommended in the SPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product> contains <x mg> boron. The small ……" <u>1 mg / 3 mg / 7 mg threshold</u> Add the following sentence prior to the warning One single dose <add the amount of the maximum single dose in SmPC, where relevant> of this <unique reference to dosage form, strength and formulation of the medicinal product> contains <x mg> boron".	
Line 101	7	**Comments:** Threshold: Zero A threshold of zero implicating to include information is not appropriate at all. Even to label information that "a small amount of boron in the medicine will not be harmful if used as recommended by your doctor or pharmacist" might cause confusion to patients. The correct use of the preparation is stated in the package leaflet and approved during marketing authorisation with regard to safety and efficacy. Further information is not needed, especially if the threshold is zero. **Proposed change:** Specify < 1 Delete the sentence "The small amount of boron contained in this medicine will not be harmful if used as recommended by your doctor or pharmacist." No information on the package leaflet is required.	Partly accepted. The "zero threshold" was deleted (see above), therefore it is not required to indicate "<1".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 101	8	**Comments:** Would the inclusion of weight ranges to support the age ranges proposed be appropriate?	When extrapolating the adult PDE to paediatric patients, the lower body weight values was used for each age category (see the table above comparing extrapolation according to either BW or BSA). Therefore, a conservative approach was used. If BW ranges was added to age ranges in the PL, it might cause unnecessary confusion.
Line 101	8	**Comments:** If the amount of boron in the product formulation triggers a warning in an age range in which the product is not indicated, will it be necessary to add the warning to the product labelling?	In principle, it will not be necessary.
Line 101-102	1	**Comments:** Normally, a threshold corresponds to an upper limit, which is not the case here. Furthermore, we have to write in the title, that it must be expressed in boron **Proposed change:** Clarification of thresholds: change the threshold values into ranges expressed in boron, e.g. see below. Zero (>0 - <1mg/day): Exemption of ophthalmic preparations containing boron just for pH adjustment completely from the obligation to inform patients in the package leaflet.	Not accepted a) The threshold as expressed in the table is a (upper) limit value below which an effect on fertility is not expected to occur. This is considered to be in line with the common use of the term “threshold” for risk assessment purposes. Since a threshold is given, it cannot be expressed as a range of boron intake; b) Exemption of ophthalmic preparation is not endorsed, as detailed above.
101-102	4	**Comments:** Normally, a threshold corresponds to an upper limit, which is not the case here. Furthermore, it should be written in	Not accepted. See above.

<table>
<tr><th>Line no.</th><th>Stakeholder no.</th><th>Comment and rationale; proposed changes</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>the title that the limit must be expressed in boron.

Proposed change:

Clarification of thresholds: change the threshold values into ranges expressed in boron, e.g. see below.

Zero (>0 - <1mg/day):

Exemption of ophthalmic preparations containing boron just for pH adjustment completely from the obligation to inform patients in the package leaflet.</td><td></td></tr>
<tr><td>Line

104-105</td><td>1</td><td>Comments:

When clear ranges are given (see comment above) the footnote can be omitted.</td><td>Not accepted.

The table is in line with the methodology used in the context of the revision of the guideline on excipients in the label and the package leaflet of medicinal products for human use. Therefore, a threshold has to be determined. In addition, it is considered that the footnote provides some relevant information which could also be applied to dose ranges (e.g. that the limit proposed is not an acceptable limit).</td></tr>
<tr><td>104-105</td><td>4</td><td>Comments:

When clear ranges are given (see comment above) the footnote can be omitted.</td><td>Not accepted. See above.</td></tr>
<tr><td>101-105</td><td>4</td><td>See additional proposed changes in the table below.
<table><tr><th>Name</th><th>Route of Administration</th><th>Threshold limit</th><th>Information for the package leaflet</th><th>Comments</th></tr><tr><td>Boric acid (and borates)</td><td>All routes</td><td>< 1 mg boron per day Zero</td><td>This medicinal product contains <X mg Boron> per <dose>. The small amount of boron contained in this medicine will not be harmful if used as recommended by your doctor or pharmacist.</td><td>Amount of boron per age group which may impair fertility if exceeded:<table><tr><td>Age</td><td>Safety limit</td></tr><tr><td>< 2</td><td>1</td></tr></table></td></tr></table></td><td>Not accepted. See above.</td></tr>
</table>

Line no.	Stakeholder no.	Comment and rationale; proposed changes					Outcome
				1 – 3 mg boron per ~~/~~day	This medicinal product contains <X mg boron> per <dose>. Do not give this medicine to children~~your child~~ less than 2 years old as it may impair fertility in the future if given below the age of 2 years.	years / mg/day < 12 years / 3 mg/day < 18 years* / 7 mg/day > 18 years* / 10 mg/day * This amount may also cause harm to the unborn child.	
				3 – 7 mg~~/~~ boron per day	This medicinal product contains <X mg boron> per <dose>. Do not give this medicine to children~~your child~~ less than 12 years old as it may impair fertility in the future if given below the age of 12 years.		
				7 – 10 mg~~/~~ boron per day	This medicinal product contains <X mg boron> per <dose>. Do not give this medicine to ~~your child~~ children and adolescents less than 18 years old as it may impair fertility in the future if given below the age of 18 years. If you are pregnant talk to your doctor before taking this medicine as it contains boron which may harm your baby.		
		~~* The threshold is a value, equal to or above which it is necessary to provide the information stated for the package leaflet. This threshold is not a highest acceptable limit. A 104 threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product [1].~~					