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Comments should be provided using this template. The completed comments form should be sent to excipients@ema.europa.eu

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Questions and answers on boric acid in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

1. Background

Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) [1], a multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP, BWP and BPWP was created in 2011.

The objective of this group is to update the labelling of selected excipients listed in the Annex of the above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their safety. The main safety aspects to be addressed were summarised in a concept paper published in March 2012 [2].

Draft questions and answers (Q&A) documents on excipients are progressively released for public consultation. They include proposals for new or updated information for the label and package leaflet. The corresponding background report supporting the review is published for information only.

When one or several Q&As have been finalised, the new information in the package leaflet will be included in a revised annex of the guideline.

For more information see the Excipients labelling webpage on the EMA website.

2. What is boric acid and why is it used as an excipient?

Boron, which is the characteristic element of boric acid, is a widely occurring element found mainly in minerals in sediments and sedimentary rock. It is found in the environment primarily combined with oxygen in compounds called borates, and is never found as the free element. Common borate compounds include boric acid, salts of boric acid (e.g., sodium tetraborate, also referred to as borax), and boron oxide [3].

Boric acid is used as an antimicrobial preservative and is used as a buffering agent to control the pH. Additionally, it can have the function as tonicity-adjusting agent.

3. Which medicinal products contain boric acid?

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,
- Homeopathic dilutions containing boric acid, its salts and esters.

4. What are the safety concerns?

Metabolism of inorganic borates by biological systems is not feasible owing to the excessive energy required to break the boron-oxygen bond. Inorganic borates, in low concentrations, convert to boric acid at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption. This is supported by the evidence in both human and animal studies, where more than 90% of the administered dose of borate is excreted as boric acid [4]. Therefore, systemic effects observed in animal studies with boric acid are relevant for inorganic borates. That is why, dose levels are also expressed as mg boron/kg (mg B/kg).

Following single-dose administration, the target organs identified in the mouse, rat and dog were the kidneys (glomerular and tubular lesions) and nervous system (cerebral cortex, spinal marrow). In the mouse and rat the oral LD_{50} ranges approximately from 2200 to 4000 mg/kg (400–700 mg boron/kg) [4]. These data are consistent, from a qualitative point of view, with the neurological toxicity suggested for boric acid after analysis of the pharmacovigilance cases over a 10-year period. In the repeated-dose studies in the mouse and rat (90 days, 2 years), the testes were the target organ [5, 6]. The rat is the most sensitive species. The NOAEL of boric acid was 100 mg/kg/day in the 2-year rat study [6].

The testicular toxicity was confirmed by the fertility studies. The latter showed, after a single oral exposure in the rat, reversible changes in testicular histology and sperm parameters [7]. Following repeated oral dosing in the male mouse and rat, impairment of spermiation and sperm quality was observed and resulted in a partial reduction in fertility or complete sterility, depending on the dose [6, 8, 9]. In female rats, following oral administration, a decrease in ovulation was observed and resulted in a decrease in reproductive performance at high dose levels [6]. The effects on fertility occurred at dose levels not inducing any other marked toxic effects. In the rat, the NOAEL is 100 mg/kg [6].

No genotoxic or carcinogenic potential of boric acid was evidenced. The compound is not a cutaneous or ocular irritant in the rabbit. The compound does not induce cutaneous sensitisation in an appropriate test in the guinea pig.

In the mouse, rat and rabbit, boric acid administered during gestation was fetotoxic and fetolethal (at high doses). Malformations were reported in the 3 species, particularly costal malformations. In the rabbit, cardiovascular abnormalities were observed in the heart and main vessels. In the rat, the most sensitive species, fetotoxic and teratogenic effects were evidenced at dose levels not inducing maternal toxicity [10–12]. In the rat, the fetal NOAEL was 55 mg/kg/day (equivalent to 9.6 mg B/kg/day) [10, 11].

There are several epidemiological studies in workers. Boron exposure data were measured in the workplace and in biological samples [13, 14] the Scientific Committee on consumer Safety concluded that the design of such studies are insufficient to demonstrate an effect or an absence of effect on fertility [15].

Based on the above reprotoxicity study, and taking into account the modifying factors according to the procedures for setting exposure limits in pharmaceuticals [16], the method adopted by the IPCS for Assessing Human Health Risk of Chemicals [17] and also in ICH Q3C, the oral Permitted Daily Exposure (PDE) for boron is:

$$PDE = 9.6 \text{ mg B/kg/day} \times 50 \text{ kg} / 5 \times 10 \times 1 \times 1 \times 1 = 9.6 \text{ mg B/day} \sim 10 \text{ mg B/day}$$

This 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 in adults and consider that this UL also applies to pregnant and lactating women. The SCCS UL values for children were derived by extrapolating from the UL for adults on a body surface area basis, giving values (mg/day) of 3, 4, 5, 7, and 9 mg boron/person/day for children aged 1–3, 4–6, 7–10, 11–14 and 15–17 years of age, respectively. These UL values apply only to the intake of boron as boric acid and borates [15].

5. What are the reasons for updating the information in the package leaflet?

There is currently no information in the package leaflet. Boron compounds are classified as toxic to reproduction (CMR Repr. cat. 2) [18, 19]. Therefore, it is considered necessary to include appropriate information in the package leaflet of boron-containing medicinal products especially for the most sensitive populations, i.e. pregnant women and children.

6. Proposal for new information in the package leaflet

<table>
<tr><th>Name</th><th>Route of Administration</th><th>Threshold*</th><th>Information for the Package Leaflet</th><th>Comments</th></tr>
<tr><td rowspan="4">Boric acid (and borates)</td><td rowspan="4">All routes</td><td>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 rowspan="4">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 years</td><td>1mg/day</td></tr><tr><td>< 12 years</td><td>3 mg/day</td></tr><tr><td>< 18 years*</td><td>7 mg/day</td></tr><tr><td>> 18 years*</td><td>10 mg/day</td></tr></table>* This amount may also cause harm to the unborn child.</td></tr>
<tr><td>1 mg/day</td><td>Do not give to your child less than 2 years old as it may impair fertility in the future.</td></tr>
<tr><td>3 mg/day</td><td>Do not give to your child less than 12 years old as it may impair fertility in the future.</td></tr>
<tr><td>7 mg/day</td><td>Do not give to your child less than 18 years old as it may impair fertility in the future.

If you are pregnant talk to your doctor before taking this medicine as it contains boron which may harm your baby.</td></tr>
</table>

Note:

* 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 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].

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