23 July 2015
EMA/CHMP/765436/2012
Committee for Human Medicinal Products (CHMP)

# Background review for the excipient 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)

Draft report published in support to the Q&A document.
*For information only*

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# Background review for the excipient boric acid

## Executive summary

Boric acid is very well absorbed following oral administration. Cutaneous absorption is negligible if the skin is intact. However, cutaneous barrier crossing by boric acid applied to damaged skin has been demonstrated, particularly in children. In the body, boric acid diffuses into body fluids. Animal studies have nonetheless shown potential accumulation of boron in bone. Boric acid is not metabolised. However, it is to be noted that, at low concentrations, inorganic borates are metabolised to boric acid at physiological pH in the aqueous layer on the surfaces of the mucosa pre-absorption. Therefore, systemic effects observed in animal studies with boric acid are relevant also for inorganic borates. That is why, dose levels are also expressed as mg boron/kg (mg B/kg). Over 90% of the boric acid dose administered is excreted in the urine, irrespective of the administration route.

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 from 2200 to 4000 mg/kg. In the repeated-dose studies in the mouse and rat, the testes were the target organ. The rat is the most sensitive species. The NOAEL of boric acid was 100 mg/kg/day in the 2-year rat study. The testicular toxicity was confirmed by the fertility studies. The latter showed, after a single oral exposure in the rat, testicular histopathological changes and changes in the spermatozoid parameters (reversible effects for dose levels up to 2000 mg/kg). 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. In female rats, following oral administration, a decrease in ovulation was observed and resulted in a decrease in reproductive performance at high dose levels. The effects on fertility occurred at dose levels not inducing any other marked toxic effects. In the rat, the NOAEL is 100 mg/kg.

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. In the rat, the developmental NOAEL was 55 mg/kg/day (9.6 mg boron/kg/day).

No genotoxic or carcinogenic potential of boric acid was evidenced. The compound is neither a skin irritant nor a skin sensitizer in the rabbit. It is not classified as an eye irritant according to EU or GHS guidelines, in contrast to other boron compounds (disodium tetraborate pentahydrate, disodium tetraborate decahydrate, and disodium tetraborate anhydrous).

The most sensitive effect seen in the toxicological studies is considered developmental toxicity in rats, for which a NOAEL of 9.6 mg B/kg/day was determined. On this basis, a permitted daily exposure (PDE) was calculated for adult patients. Since paediatric patients may be exposed to medicinal products containing boric acid or borates, PDE values were derived for paediatric patients by extrapolating from the adult PDE on a body surface area basis. Overall, the PDE for boron compounds is set at 1, 3, 7, and 10 mg B/day for patients aged 0–2, 2–12, 12–18, and >18 years, respectively.

## Introduction

Boron, which is the characteristic element of boric acid, is a widely occurring chemical 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.

Boron compound may be used as excipients in some human medicinal products, and were classified as to toxic to reproduction (CMR Repr. cat. 2). Therefore, it was considered necessary to review the most adequate data to provide information to be included in the package leaflet of boron compound-containing medicines.
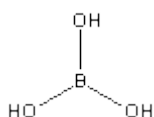
# Scientific discussion

## 1. Characteristics

### 1.1. Formula, structure, characteristics and function

Molecular formula: $H_3BO_3$

Structure:



Molecular weight: $M_r$ 61.8

Appearance: white or almost white, crystalline powder, colourless, shiny plates greasy to the touch, or white or almost white crystals. *Solubility*: soluble in water and in ethanol (96 per cent), freely soluble in boiling water and in glycerol (85 per cent). *pH of 3.3% aqueous solution:* 3.8 – 4.8 (Ph. Eur. 01/2008:0001 corrected 6.0).

### 1.2. Use

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 of tonicity-adjusting agent.

### 1.3. Regulatory status

**Regulatory status in medicinal products**

In Germany the marketing authorisations for drug products containing boric acid, boric acid salts (disodium tetraborate, zinc borate) and esters were withdrawn (Stufenplan-Bescheid from 25.07.1983, pharmacovigilance action). However, the following drug product types were exempted from the withdrawal:

- Medicinal waters and salts thereof

- Ophthalmic preparations, containing boric acid resp. the salts as buffer and/or isotonicity agents

- Homeopathic dilutions with boric acid, boric acid salts and esters

- Drug products with phenylmercuric borate or phenylmercuric (II) dihydrogene borate.

When used as intended, the uptake of boron should not exceed the amount calculated for drinking water (2.5 mg boron derived from the limit for boron laid down for water for human consumption and a consumption of 2.5 l drinking water per day).

For medicinal waters and salts thereof, the SPC and the package leaflet have to contain a contraindication not to use the drug product in infants and children up to 3 years as well as a warning that the excipient can cause toxic reactions in infants and children up to 3 years.

In addition to the drug product types exempted from the withdrawal (see above), an ear drops preparation containing boric acid as excipient was approved a few years ago.

### Regulatory status in food

According to Regulation (EC) No 1333/2008 and Commission Regulation (EC) no. 1129/2011, boric acid and disodium tetraborate are only allowed as food additives for sturgeons' eggs (caviar) with a maximum level of 4000 mg/kg, expressed as boric acid.

### Regulation of boron (B) in drinking water

Council Directive 98/83/EC on the quality of water intended for human consumption (amended) contains a limit of 1.0 mg/l for boron. The German regulation on water for human consumption (Trinkwasserverordnung) includes the same limit.

### Regulatory status in cosmetics

According to Commission Regulation (EC) no. 1223/2009 the use of boric acid, borates and tetraborates in cosmetics is restricted (see table below).

# Table 1: restriction of use of boric acid, borates and tetraborates in cosmetics (Commission Regulation (EC) no. 1223/2009)

*ANNEX III*

**LIST OF SUBSTANCES WHICH COSMETIC PRODUCTS MUST NOT CONTAIN EXCEPT SUBJECT TO THE RESTRICTIONS LAID DOWN**

| Reference number | Substance identification | | | | Restrictions | | | Wording of conditions of use and warnings |
|---|---|---|---|---|---|---|---|---|
| | Chemical name/INN | Name of Common Ingredients Glossary | CAS number | EC number | Product type, body parts | Maximum concentration in ready for use preparation | Other | |
| a | b | c | d | e | f | g | h | i |
| 1a | Boric acid, borates and tetraborates with the exception of substance No 1184 in Annex II | Boric acid | 10043-35-3/ 11113-50-1 | 233-139-2/ 234-343-4 | (a) Talc | (a) 5 % (as boric acid) | (a) Not to be used in products for children under 3 years of age<br><br>Not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1,5 % (as boric acid) | (a) Not to be used for children under 3 years of age<br><br>Not to be used on peeling or irritated skin |
| | | | | | (b) Oral products | (b) 0,1 % (as boric acid) | (b) Not to be used in products for children under 3 years of age | (b) Not to be swallowed<br><br>Not to be used for children under 3 years of age |
| | | | | | (c) Other products (excluding bath products and hair waving products) | (c) 3 % (as boric acid) | (c) Not to be used in products for children under 3 years of age<br><br>Not to be used on peeling or irritated skin if the concentration of free soluble borates exceeds 1,5 % (as boric acid) | (c) Not to be used for children under 3 years of age<br><br>Not to be used on peeling or irritated skin |
| 1b | Tetraborates, see also 1a) | | | | (a) Bath products | (a) 18 % (as boric acid) | (a) Not to be used in products for children under 3 years of age | (a) Not to be used for children under 3 years of age |
| | | | | | (b) Hair products | (b) 8 % (as boric acid) | | (b) Rinse well |

# 2. Pharmacokinetics

## 2.1. Absorption

Boric acid is readily absorbed from the gastrointestinal tract in rats and humans. At least 92% of a single oral dose of boric acid was recovered in the urine of human volunteers [11, 14].

Cutaneous absorption through the intact skin was negligible in all the species studied, including, in particular, the rat, rabbit and humans (adults and children). On damaged skin, systemic penetration of boric acid has been demonstrated. In infants aged 1.25 to 10 months, application of talc containing 5% boric acid 7 to 10 times daily for 1 month resulted in daily exposure to 2.33 g of boric acid [11].

## 2.2. Distribution

Boric acid is distributed in body fluids [11].

The most complete distribution study was conducted in male rats (30/group) by administration of 9000 ppm in the diet, equivalent to intake of 68 mg of boron/kg/day for 7 days. The controls received feed containing less than 20 ppm of boron. Six animals per group were sacrificed on D1, D2, D3, D4 and D7. The study showed that the boron concentrations were similar in all the tissues studied[1] with a steady state (12–30 mg of boron/kg of tissue) being achieved in 3–4 days. The concentrations were 3- to 20-fold higher than those in the controls. It is to be noted that the bone boron concentration was higher (47.4 mg/kg of tissue) and increased throughout the study [11, 12].

## 2.3. Metabolism

Metabolism of inorganic borates by biological systems is not feasible owing to the excessive energy required to break the boron-oxygen bond (523 kJ/mol). 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 [11].

## 2.4. Excretion

Boric acid clearance is similar in animals and humans. Over 90% of the dose administered is excreted in the urine, independently of the administration route. The maximum elimination half-life is 24 hours.

In a study conducted in male rats, it was shown that the boron elimination profile from the bone compartment was different from that for plasma or soft tissue. Intake ranging from 1.4 to 6.8 mg of boron/kg/day (by administration of 3000–9000 ppm of boric acid in the diet) for 9 weeks resulted in a dose-dependent increase in the bone boron concentration. The concentration fell off gradually post-treatment and remained higher than that measured in the controls at week 32 post-treatment discontinuation [2, 11].

## 2.5. Conclusion

The available pharmacokinetic data show that boric acid is very well absorbed following oral administration. Absorption by the cutaneous route is negligible if the skin is intact. In contrast, boric acid has been shown to cross the cutaneous barrier when applied to damaged skin, particularly in

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[1] Of which: plasma, liver, kidneys, muscles, colon, brain, testes, epididymes, seminal vesicles, prostate and adrenal glands.

infants. In the body, boric acid is distributed via body fluids. Animal studies have nonetheless shown the potential accumulation of boron in the bone.

Boric acid is not metabolised. However, it is to be noted that at low concentrations inorganic borates are metabolised to yield boric acid at physiological pH in the aqueous layer on the surface of the mucosa pre-absorption. 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).

Over 90% of the boric acid dose administered is excreted in the urine, independently of the administration route.

# 3. Toxicology

## 3.1. Single-dose toxicity

The oral $LD_{50}$ of boric acid in the mouse and rat is of the order of 400–700 mg of boron/kg (i.e. 2200–4000 mg of boric acid/kg). In the guinea pig, an $LD_{50}$ of 210 mg B/kg (1200 mg $H_3BO_3$/kg) has been reported. In the dog, rabbit and cat, the $LD_{50}$ ranged from 250 to 350 mg B/kg (1430–2000 mg $H_3BO_3$/kg) [11].

In the mouse, rat and guinea pig, the symptoms reported consisted in ataxia, seizures, hypothermia, violet-red colour of the skin and mucosa. In the dog (200–2000 mg $H_3BO_3$/kg), similar effects were reported together with rigidity of the paws and shock syndromes.

Histopathological changes have been reported in the mouse, rat and dog in relation to:
- the kidneys: changes in glomerular capillary permeability, vacuole formation and loss of tubule cells;
- the nervous system: increase in the proportion of probably microglial cells in the spinal marrow and in the cerebral cortex grey matter.

A study in the rabbit consisting in cutaneous application to damaged skin for 24 hours is available. No death occurred during the observation period (14 days). The $LD_{50}$ of boric acid is greater than 2000 mg/kg [21].

Overall, the target organs in the mouse, rat and dog after a single dose were the kidneys (glomerular and tubular lesions) and the nervous system (cerebral cortex, spinal marrow). The clinical findings are consistent with these microscopic changes with, in particular, the emergence of seizures. Although boric acid was administered by the oral route in these studies, the effects reported can be extrapolated to the cutaneous route since the preparations containing boric acid are intended for application to damaged skin.

## 3.2. Repeat-dose toxicity

Ninety-day and 2-year oral toxicity studies were conducted in mice and rats. The main findings are summarised in **Table 2**.

The NOAEL of boric acid in the rat is 149 mg/kg/day and 100 mg/kg/day following oral administration for 90 days and 2 years, respectively.

In both species, testicular atrophy was reported after treatment for either 90 days or 2 years. In rats, this was associated with atrophy of the seminiferous epithelium and decreased size of seminiferous tubules. In the 2-year mouse study, interstitial cell hyperplasia was observed at 1150 mg/kg/day, as well as loss of spermatogonia and spermatogenesis impairment.

With regard to testicular toxicity, the NOAELs were:
- Mouse: 405 and 446 mg/kg/day after treatment for 90 days and 2 years, respectively;
- Rat: 149 and 100 mg/kg/day after treatment for 90 days and 2 years, respectively.

The 2-year studies will be re-discussed in section 3.4. .

With regard to the therapeutic use of boric acid, only one cutaneous route study was identified [5] but the original article could not be obtained.

**Table 2: summary of repeat-dose toxicity studies**

| Species | Dose<br><br>mg/kg/d<br>(boric acid) | Duration | Observations and Remarks | Ref. |
|---|---|---|---|---|
| B6C3F1 mouse 10/sex/group | Males: 0, 194, 405, 811, 1623, 3246<br>Females: 69, 560, 1120, 2240, 4480 | 90 d | GLP: no data<br>Doses at lowest two levels well tolerated. At 3246 mg/kg eight out of 10 males died. At 4480 mg/kg six out of 10 females died before the end of the study. Significant dose-related decrease in body weight gain of males and females at the three highest doses. Symptoms at high doses included dehydration, hunched posture, foot lesions and scaly tails. Testicular atrophy observed at 811 mg/kg in males and dose-related incidence of minimal to mild extramedullary hematopoiesis of the spleen in males and females at all doses. | National Toxicology Program 1987 [15]<br><br>Dieter 1994 [4] |
| Sprague-Dawley rat 10/sex/group | 0, 15, 50, 149, 500, 1490 | 90 d | GLP: no data<br>All the animals at the top dose had died by week 6. Animals at the top two doses displayed rapid respiration, inflamed eyes, swollen paws and desquamated skin on paws and tail. These animals exhibited reduced food consumption and body weight gain. At 500 mg/kg reduced weight for liver, spleen and testes or ovaries were observed in addition to reduced weight of kidney and adrenal observed only in males. All the male rats at 500 mg/kg had atrophied testes and histologically complete atrophy of the spermatogenic epithelium and a decrease in the size of the seminiferous tubules. Animals treated with 149 mg/kg bw and lower doses exhibited no adverse effects | Weir and Fisher 1972 [23] |
| Sprague-Dawley rat 35/sex/group | 0, 33, 100, 334 | 2 y | GLP: no<br>At 334 mg/kg/d reduced food consumption during the first 90 days, suppressed growth throughout the study, coarse hair coats, | Weir and Fisher 1972 [23] |

| Species | Dose mg/kg/d (boric acid) | Duration | Observations and Remarks | Ref. |
|---|---|---|---|---|
| | | | hunched position, swollen paws and inflamed bleeding eyes, as well as changes in hematologic parameters were observed. Shrunken scrotum and atrophic testes were observed with atrophied seminiferous epithelium and decreased tubular size in the testes at 334 mg/kg/d. No effects were observed at 33 and 100 mg/kg bw/d. | |
| B6C3F1 mouse 50/sex/group | 0, 446, 1150 | 2 y | GLP: no<br>Method: NTP Protocol<br>Reduced survival in all dose groups including control. In the males the final survival was 82%, 64%, 44% with increasing dosage which may have reduced the sensitivity of the study. Final survival in females was 66%, 66%, 74% for 0, 446, and 1150 mg/kg bw/d respectively, which was adequate for assessment of the study. Mean final body weights were 7% and 13% below control values for exposed males and 7% and 20% below control values for females. No chemically related clinical signs were reported. The histopathological findings showed no significant dose-related increase in neoplasms.<br>At top dose, an increased incidence of testicular atrophy (3/49 control; 6/50 low dose; 27/47 high dose) and interstitial cell hyperplasia (0/49; 0/50; 7/47) was observed in male mice. There was variable loss of spermatogonia and various stages of spermatogenesis from the seminiferous tubules. | National Toxicology Program 1987 [15] |

## 3.3. Genotoxic potential

Boric acid was not mutagenic in Salmonella typhimurium with or without rat or hamster S9 fraction or in mouse lymphoma cells with or without rat liver S9. Borax was not mutagenic in Salmonella with or without rat liver S9. Refined borax, crude borax ore, and kermite ore were not mutagenic in V79 Chinese hamster cells. Other tests showed that boric acid did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells [15]. Existing data suggest that genotoxicity is not an area of concern following exposure to boron compounds in humans [11].

Overall, boric acid and inorganic borates can be considered as devoid of genotoxic potential.

## 3.4. Carcinogenic potential

As mentioned in section 3.2. , 2-year studies were conducted in rodents. There was no evidence of carcinogenicity in mice, but testicular interstitial cell hyperplasia was observed at 1150 mg/kg/day. In rats, no neoplastic lesion was reported, however this study was not specifically designed for the study of carcinogenic effects.

## 3.5. Reproduction toxicity

### 3.5.1. Fertility

Studies aiming at assessing the impact of boric acid on fertility were performed in rodents after either a single or repeat doses as summarised in **Table 3** and **Table 4**.

After a single oral dose, testicular histopathological changes and changes in spermatozoid parameters (morphology, count, motility) were observed in rats. The effects were reversible at up to 2000 mg/kg, the highest dose tested.

After repeated oral exposures, impaired spermiation (spermatozoid release into the lumina of the seminiferous tubules at end spermiogenesis) and quality of sperm were reported in male mice and rats, resulting in a partial reduction in fertility or even complete sterility - depending on the dose. In female rats, boric acid caused a decrease in reproductive performance at the high doses induced by decreased ovulation. The effects occurred at dose levels not inducing other marked toxic effects. In the rat, the NOAEL is 100 mg/kg.

**Single dose studies**

**Table 3: summary of fertility studies with single dose regimen**

| Species | Route<br><br>Dose<br>mg/kg<br>(boric acid) | Observation period | Observations and remarks | Ref. |
|---|---|---|---|---|
| Sprague-Dawley male rat 6/ group | Oral (gavage) 0,2000 | 2, 14, 28, 57 days post exposure | GLP: no data<br>type of study: time-response study<br>Histopathological changes in the testis and epididymis appeared from day 14 after exposure: disturbed sperm maturation in the tubules and testicular debris in the epididymis. Recovery occurred from day 28 onwards but was not yet complete at termination of the recovery period (57 days post-exposure) since 2 out of 6 animals had still some retention of spermatids in the tubules. Abnormalities in sperm heads and tails and in sperm head counts were observed from day 14 and changes in spermatozoa motility were noted. By day 57 all sperm parameters had returned to control levels. The observed effects on sperm parameters were reversible at 2 000 mg/kg bw. | Linder, Strader and Rehnberg [13] |

| Sprague-Dawley male rat 8/group | Oral (gavage) 0, 250, 500, 1000, 2000 | 14 days | GLP: no data type of study: dose-response study Histopathological changes in the testes, and changes in sperm parameters consistent with the previous time-response study were observed in animals exposed to 1000 and 2000 mg/kg bw. No significant effect on serum hormones was found at any exposure level. | Linder, Strader and Rehnberg [13] |

**Repeat-dose studies**

**Table 4: summary of fertility studies with repeat-dose regimen**

| Species | Route Dose mg/kg(bw)/d (boric acid) | Duration No. of generations exposed | Observations and remarks | Ref. |
|---|---|---|---|---|
| Swiss CD-1 mouse 10/group | Oral (gavage) 0, 120, 400, 1200 | Males: study days (sd) 3 to 20 Females Group A: sd 0 to 20 Group B: GD8-14 1 generation exposed | GLP: no data Short-term reproductive screening protocol Group A: mating occurred during sd 8 to 13. Group B: mating occurred on sd 0-3. No males showed adverse clinical signs. No treatment related effects on histopathological findings of liver and kidney sections. Reduction of testes weight at the two highest doses. Germ cell loss and tubular disruption at the highest dose in males. Group A females: Death in females at highest dose (3/10) and 2 out of 6 litters totally resorbed. Group B females: significantly reduced number of litters and number of live pups at highest dose. | Harris et al. 1992 [7] |
| Sprague-Dawley rat 35/sex/ group | Oral (diet) 0, 34, 100, 336, | 2 years 1 generation exposed | GLP: no Chronic feeding study Testicular degeneration: decreased testes weights, atrophied seminiferous epithelium and decreased tubular size at the highest dose at 6, 12, and 24 months. No significant histopathological alterations at the two lower doses. | Weir and Fisher 1972 [23] |

| Sprague-Dawley rat 8 males and 16 females | Oral (diet) 0, 34, 100, 336 | 14 w before mating 3 generations exposed | GLP: no 3-generation reproductive study Each generation was mated twice to produce two sets of offspring. Sterility in males at the highest dose (atrophied testes with no viable sperm). Evidence of decreased ovulation in the ovaries of females at the highest dose (336 mg/kg bw/d) and no litters after mating with controls. No adverse effects on reproduction at 34 and 100 mg/kg bw. No abnormalities were observed in the organs of the parents or weanlings from these dose groups. | Weir and Fisher 1972 [23] |
|---|---|---|---|---|
| CD-1-Swiss mouse | Oral (diet) 0, 152, 636, 1262 | 27 weeks 3 generations exposed | GLP: yes method: NTP continuous breeding protocol Sterility at highest dose of the parent mice (1262 mg/kg bw/d). Partial reduction in fertility in parental mice after 14 weeks at 636 mg/kg bw/d. For the first litter of the study the initial fertility index was not significantly affected at the two lower doses compared to controls. As the dosing period increased the fertility index declined during the study such that only 1/20 females from the mid-dose had a 4th litter. All other reproductive performance parameters were significantly decreased at the mid-dose. Cross over mating trials with control animals and mid-dose animals confirmed the males as the predominantly affected sex. Histopathological examination of the tissues from the parental animals revealed significant testicular effects in males at the two highest doses with a demonstrable dose response relationship. Sperm motility was lower than controls in all treatment groups although at the lowest dose no significant changes were noted in the testes. F1 animals at the lowest dose showed a slight but not significant decrease in sperm concentrations with no histopathological changes. F1 females at the lowest dose had significantly shorter estrus cycles than controls. Fertility was normal in the F1 animals of the low dose. F2 offspring showed a slightly lower adjusted mean body weight which was | Fail et al. 1991 [6] |

| | | | statistically significant (3% compared to controls). | |
|---|---|---|---|---|
| Male Fischer 344 rat 6 treated and 4 controls per time point | Oral (diet) 0, 348 | 28 d 1 generation exposed | GLP: no data Sacrifice on days 4, 7, 10, 14, 21, 28: a time dependent increase in the number of animals affected and severity of inhibition of spermiation was observed from 7-28 days with cell death and occluded tubular lumina beginning at day 21. By day 10 all animals sacrificed were affected. Lower serum basal testosterone level than controls from day 4, in the absence of selective accumulation of boron in the testis. Significant loss of spermatids at day 28. | Treinen and Chapin 1991 [21] |

## 3.5.2. Embryofetal development

The effects of embryo-fetal development could be evaluated based on studies performed in mice, rats, and rabbits (**Table 5**). In all species, fetotoxic (decreased body weight), fetolethal (at high doses), and teratogenic effects were reported. Malformations consisted notably in costal abnormalities as well as, in rabbits, cardiovascular abnormalities involving the heart and main vessels.

The rat is the most sensitive species since developmental toxicity was observed at a dose level not inducing maternal toxicity Therefore, the NOAEL has to be determined in this species. On the basis of the study published by Price, Strong, et al. 1996 [17], the maternal NOAEL is set at 143 mg/kg/day while the developmental NOAEL reached 55 mg/kg/day.

**Table 5: summary of embryo-fetal toxicity studies**

| Species | Route Dose mg/kg(bw)/d (boric acid) Duration | Observations and remarks | Ref. |
|---|---|---|---|
| Rabbit New Zealand white 30 animals per group | Oral (gavage) 0, 62.5, 125, 250 GD9-19 | GLP: yes method: NTP protocol Decreased food intake (30% compared to control) and vaginal bleeding on days 19-30 with no live fetuses at the highest dose. Also 90% implants per litter resorbed compared to 6% in controls. Average fetal body weight per litter reduced (92% of controls) at highest dose but not significant due to small number of fetuses. Increased incidence of malformed fetuses per litter at highest dose due primarily to cardiovascular defects (72% for major heart and/or great vessels; 3% in controls). Skeletal variation comparable among all groups (effect included extra rib on lumbar 1 and misaligned sternebrae) but with no dose response relationship. No maternal toxicity or definitive developmental effects at mid and low dose. | Price, Marr, et al. 1996 [16] |

| Sprague-Dawley rat 30/group (14/group at high dose level) | Oral (diet) 0, 78, 163, 330, 538 GD0-20 (high dose level: GD0-GD15) | GLP: yes<br>method: NTP protocol<br>Maternal rats exhibited increased relative liver and kidney weights at 3 highest doses and decreased weight gain at 2 highest doses. Average fetal body weight/litter reduced at all doses. Prenatal mortality increased at 539 mg/kg (36% resorption/litter; control group: 4%). Incidence of fetal malformations significantly increased at the 3 highest doses: enlarged lateral ventricles of the brain and agenesis or shortening of rib XIII. | Heindel et al. 1992 [8]<br><br>Heindel, price and Schwetz 1994 [9] |
|---|---|---|---|
| Swiss mouse 26-28 animals per group | Oral (diet) 0, 248, 452, 1003 GD0-17 | GLP: yes<br>method: NTP protocol<br>Mouse dams exhibited mild renal lesions (at all doses), increased water intake and relative kidney weight (at the highest dose) and decreased weight gain (at the highest dose). Reduction of fetal body weight (at mid and high doses) and increased incidence of resorptions and malformed fetuses per litter at the highest dose. Morphological changes included an increased incidence of short rib XIII and a decreased incidence of rudimentary or full rib at lumbar I (an anatomical variation). | Heindel et al. 1992 [8]<br><br>Heindel, price and Schwetz 1994 [9] |
| Sprague-Dawley rat (phase I) | Oral (diet) 0, 19, 36, 55, 76, 143 GD0-20 (sacrifice on GD20) | GLP: yes<br>method:<br>No evidence of maternal toxicity at any of the doses tested (except an increased relative kidney weight at 143 mg/kg). Reduction of fetal body weight and increased incidence of short rib XIII at the two highest doses.<br>Minor skeletal variations (wavy rib) at the two highest doses.<br>No effect at 55 mg/kg | Price, Strong, et al. 1996 [17] |
| Sprague-Dawley rat (phase II) | Oral (diet) 0, 19, 37, 56, 74, 145 GD0-20 (sacrifice on PND21) | GLP: yes<br>method<br>No evidence of maternal toxicity at any of the doses tested. No reduction in pup bw in any group compared to controls which indicates full recovery in the offspring. The minor skeletal variations (wavy rib) observed in the fetuses from phase I were not observed in any dose group in phase II. Increased incidence of short rib XIII at the highest dose. No effect at 74 mg/kg bw. | Price, Strong, et al. 1996 [17] |

## 3.6. Local tolerance

Boric acid, disodium tetraborate anhydrous, disodium tetraborate pentahydrate and disodium tetraborate decahydrate are not classified as skin irritants. They are neither skin nor respiratory sensitisers [18].

In animals, ocular instillation of 50 mg boron oxide (7.8 mg boron) dust resulted in conjunctivitis, while instillation of a sodium perborate monohydrate solution containing 6.3 mg boron into the eyes of rabbits caused mild irritancy of the epithelium and superficial stroma. The most clearly identified

effects in humans exposed to boron compounds are acute respiratory and ocular irritation from acute inhalation exposure to boron compounds [1]. Disodium tetraborate pentahydrate, disodium tetraborate decahydrate, and disodium tetraborate anhydrous are classified as eye irritant R36 under current EU guidelines (67/548/EEC) and as Category 2 Irritating to Eyes under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). No classification is indicated for boric acid under the current EU guidelines (67/548/EEC) or under the GHS guidelines [20].

# 4. Clinical safety data

Several local adverse reactions (e.g. pruritus, dermatis) with boric acid medicine, has been reported in the WHO ADR data base Therefore there is no reprotoxic effect reported. There are several epidemiological studies in workers. Boron exposure data were measured in workplace and in biological samples [18] the Scientific Committee on consumer Safety conclude that the design of such studies are insufficient to demonstrate an effect or an absence of effect on fertility [20].

# 5. Risk assessment and threshold

The most sensitive effect seen in the toxicological studies is considered developmental toxicity in rats. The NOAEL for developmental defects was set at 55 mg boric acid/kg/d, which is equivalent to 9.6 mg B/kg/day [17]. Taking into account the modifying factors according to the procedures for setting exposure limits in pharmaceuticals [3], and the method adopted by the IPCS for Assessing Human Health Risk of Chemicals [10] and also in ICH Q3C the oral 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 [20].

# 6. Recommendation for the guideline

There is currently no information in the package leaflet. Boron compounds were classified as toxic to reproduction (CMR Repr. cat. 2). Therefore, it is considered as necessary to include appropriate information in the package leaflet of boron-containing medicinal products especially because they may be used by the most sensitive populations, i.e. pregnant women and children.

In line with the SCCS, PDE values were derived for paediatric patients by extrapolating from the adult PDE on a body surface area basis calculated based on mean body weight and height values of European children reported by the SCF [19]. The age categories taken into account are consistent with ICH E11 guideline.

## 6.1. Information for the package leaflet as per 2003 guideline

There is no information about boric acid (or boron) in the Annex of the excipient guideline dated 2003.

## 6.2. Proposal for new information in the package leaflet

| Name | Route of Administration | Threshold | Information for the Package Leaflet | Comments |
|---|---|---|---|---|
| **Boric acid (and borates)** | All routes | Zero | This medicinal product contains <X mg Boron> per <dose>.<br><br>The small amount of boron contained in this medicine will not be harmful if used as recommended by your doctor or pharmacist. | Amount of boron per age group which may impair fertility if exceeded:<br><br><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><br>*This amount may also cause harm to the unborn child. |
| | | 1 mg/day | Do not give to your child less than 2 years old as it may impair fertility in the future. | |
| | | 3 mg/day | Do not give to your child less than 12 years old as it may impair fertility in the future. | |
| | | 7 mg/day | Do not give to your child less than 18 years old as it may impair fertility in the future.<br><br>If you are pregnant talk to your doctor before taking this medicine as it contains boron which may harm your baby. | |

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