Medicines Adverse Reactions Committee

Meeting date	10/06/2021	Agenda item	3.2.1
Title	**Boron-containing excipients and fertility concerns**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Affected products See Table 2: Approved medicines with boron content that may exceed 1 mg B/day and Annex 1: Approved medicines with boron content that may exceed 1 mg B/day but are contraindicated in children under two years of age and approved medicines with boron content that is unlikely to exceed 1 mg B/day			
PHARMAC funding	Chlorafast, Tobrex and Isopto Carpine are fully subsidised.		
International action	In 2017, the European Medicines Agency (EMA) added boric acid and borates to its guidance on excipients and requirements for patient information leaflets (see section 2.3.1). In April 2021, the Royal College of Ophthalmologists (UK) released a safety alert in response to the above EMA guidance, with a focus on chloramphenicol eye drops (see section 2.3.2).		
Classification	Chloramphenicol 0.5% eye drops are Pharmacist Only Medicines. However, supply of these medicines by pharmacists is restricted to adults and children over two years of age. Tobrex (tobramycin) 0.3% eye drops are a Prescription Only Medicine. Clear Eyes (naphazoline) 0.01% eye drops are a Pharmacy Only Medicine Isopto Carpine (pilocarpine) 4% eye drops are a Prescription Only Medicine.		
Usage data	Number of people who received a dispensing from a community pharmacy at least once during 2019 [1]: Tobramycin eye drops 0.3% 396 Chloramphenicol eye drops 0.5% 117,479 Isopto Carpine eye drops 4% 283		
Advice sought	**The Committee is asked to advise:** • Whether warnings/contraindications relating to boron content and fertility concerns in children should be added to the data sheets for any of the medicines discussed in this report • Whether any other changes should be made to these data sheets to mitigate this concern • Whether any other action is required.		

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1 PURPOSE

In 2017, the European Medicines Agency (EMA) added boric acid and borates to its guidance on excipients and requirements for patient information leaflets. The guidance requires a contraindication and warning about fertility concerns for children under 2 years of age for medicines that exceed the threshold of 1 mg B (boron)/day.

In April 2021, the Royal College of Ophthalmologists (UK) released a safety alert regarding the above EMA guidance. The statement noted that some manufacturers have added contraindications to their chloramphenicol eye drop products for children under two years of age due to the boric acid content. The College considered that when used appropriately, the benefits of chloramphenicol eyedrops in paediatric ophthalmic practice outweigh the possible risks posed by boron ingestion.

Following the statement from the Royal College of Ophthalmologists, Medsafe has received several queries from healthcare professionals regarding this potential safety concern. Some queries concerned whether chloramphenicol eye drops should continue to be used in children under two, or whether a boron-free alternative such as chloramphenicol eye ointment should be used instead.

As a result, a review of all medicines containing boric acid and borax has been carried out. The medicines with the highest daily boron dose at the maximum dose in the data sheet are included in Table 2. This includes antibiotic eye drops containing tobramycin and chloramphenicol as they may be dosed frequently in severe superficial eye infections.

A number of other medicines that contain these excipients are summarised in Annex 1. Some of these medicines may exceed the EMA threshold but are contraindicated in children, and others are unlikely to meet the EMA threshold.

The Committee is asked to advise whether the data sheets for any of these medicines should be changed to reflect fertility concerns due to boron-containing excipients or whether these should be changed in any other respect to mitigate this concern.

2 BACKGROUND

2.1 Systemic absorption of eye drops

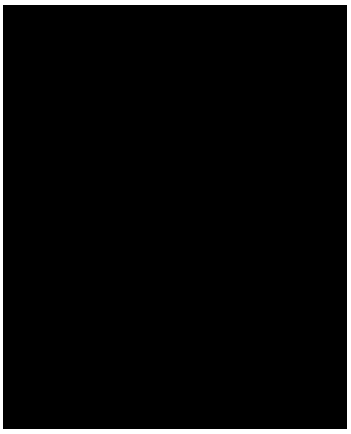
When eye drops are administered, several routes of absorption are possible and a significant proportion of the dose can be absorbed systemically (Figure 1a). A major route of systemic absorption of eye drops is via drainage through the nasolacrimal duct with subsequent absorption via the highly vascularised nasopharyngeal mucosa (Figure 1b) [2].

To limit absorption via this route, the 'Double DOT: digital occlusion of tear duct and don't open technique' is recommended. However, this requires keeping the eye closed with pressure on the lacrimal sac for one to two minutes and is likely to be impractical in children [3].

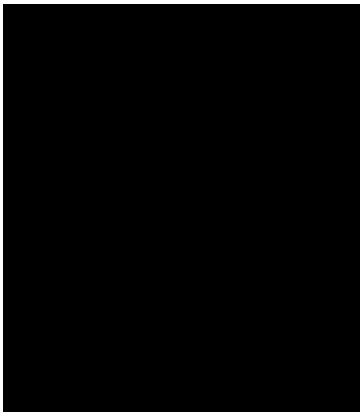
The volume of drops dispensed can vary from 25-50 µL, which exceeds the conjunctival sac capacity of 10-20 µL. Some of the drop may be squeezed out of the eye onto the eyelids and cheeks. Blinking also forces tears (and eye drops) into the nasolacrimal duct via the lacrimal pump (Figure 1c) [2, 4].

There are physical differences in the eyes of children compared with adults that may impact systemic absorption but this has not been quantified. The eye of a newborn is roughly two thirds of its adult size, which is reached at three or four years of age. Membranes in the eyes of infants are thinner, and permeation and absorption may be greater. The absorptive corneal area of a new-born is approximately 70% of the adult area. Tear volumes are reported to be 0.5 µL for newborns, 2.5 µL for older infants, and 6 µL in adults [2].

Figure 1 (a): Possible absorption pathways of a medicine administered into the eye [2]



(b) Lacrimal drainage system [3]



(c) The lacrimal pump [4].

Comments
The extent of absorption of boric acid through the eye, particularly via the nasopharyngeal mucosa, is unknown. It is unknown how systemic absorption of boric acid from eye drops in children may differ from that of adults. Systemic absorption can be minimised by using a finger to press on the tear duct, but this may be impractical in children.

2.2 What is boron and why is it used in eye drops?

Boron widely occurs in nature in the form of borates in oceans, sedimentary rocks, coal, shale, and some soils. It is found in the environment primarily combined with oxygen as borates and is never found as the free element. Intake of boron from food and water is estimated by the European Food Safety Authority to be 1.2 mg B/day and 0.2-0.6 mg B/day, respectively. B is the chemical symbol for boron, and here represents the equivalent amount of boron contributed by various boron compounds [5, 6].

Some boron compounds are used as excipients in medicines. The compounds that are in currently registered medicines in New Zealand are boric acid and borax (sodium tetraborate), which are primarily used as antimicrobial and pH buffering agents in eye drops [6, 7].

2.3 Fertility concerns with boric acid and borates

Boric acid has been associated with developmental and reproductive toxicity in animal studies, as outlined in the EMA guidance discussed below. As a result, warnings statements are required by the EMA for medicines with boron content greater than 1 mg B/day. The UK Royal College of Ophthalmologists has also issued guidance on this issue as it relates to chloramphenicol eye drops.

2.3.1 European Medicines Agency guidance on boric acid/borates and product information

In 2017, the European Medicines Agency (EMA) added boric acid and borates to the guidance document 'Excipients and information for the package leaflet'. This document is an annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' which sets out the way excipients in medicinal products must be declared [7, 8].

The guidance lists the required warning statements relating to the presence of certain excipients in medicinal products above a threshold. The threshold is expressed as the quantity of excipient in the maximum daily dose of the medicinal product, as indicated in the summary of product characteristics (data sheets) [7].

The EMA considered that appropriate warnings for boric acid and borates should be added to the document because these compounds are categorised as toxic to reproduction [6].

Table 1 describes the thresholds for boric acid and borates and the corresponding warnings statements listed in the guidance. These warnings are applicable to all dosage forms.

Table 1: Boric acid and borate thresholds and package warnings required by the European Medicines Agency

Name	Route of administration	Threshold	Information for package leaflet	Comments
Boric acid (and borates)	All	1 mg B/day*	Do not give to a child less than 2 years old as this medicine contains boron and may impair fertility in the future.	* 1 mg B is equivalent to 5.7 mg boric acid or 8.8 mg borax. See Q&A document (EMA/CHMP/619104/2013) for further calculations. Amount of boron per age group which may impair fertility if exceeded: Age: Safety limit < 2 years: 1 mg B/day < 12 years: 3 mg B/day < 18 years: 7 mg B/day** ≥ 18 years: 10 mg B/day** ** This amount may also cause harm to the unborn child.
		3 mg B/day*	Do not give to a child less than 12 years old as this medicine contains boron and may impair fertility in the future.	
		7 mg B/day*	Do not give to a child less than 18 years old as this medicine contains boron and may impair fertility in the future. If you are pregnant, talk to your doctor before taking this medicine as it contains boron which may be harmful to your baby.	

Source: Adapted from European Medicines Agency guidance document 'Excipients and information for the package leaflet' (EMA/CHMP/302620/2017 Rev. 1) [8].

The safety concerns with boric acid and borates are summarised in a supplementary document, 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use' [6] (Annex 2).

Fertility studies in animals have demonstrated the reproductive toxicity of boric acid. Inorganic borates, at low concentrations, are converted to boric acid prior to absorption. Therefore, animal studies with boric acid are also relevant to borates [6].

Reversible changes to testicular histology and sperm parameters were observed after a single oral exposure in the rat. After repeated oral dosing in the male mouse and rat, impairment of spermiation (sperm release) and sperm quality was observed with a resulting reduction in fertility or sterility, depending on the dose. Following oral administration in female rats, a decrease in ovulation was observed with resultant decrease in reproductive performance at high doses. Effects on fertility occurred at doses without other toxic effects. The No Observed Adverse Effect Level (NOAEL) for fertility effects in the rat was equivalent to 17.5 mg B/kg/day [6].

Boric acid was found to be foetotoxic and foetolethal at high doses in the mouse, rat and rabbit, causing costal and cardiovascular abnormalities. The NOAEL for developmental effects in the rat was equivalent to 9.6 mg B/kg/day [6].

Available epidemiological studies in workers exposed to boron were insufficient to demonstrate an effect or an absence of effect on fertility [6].

A permitted daily exposure (PDE) of 10 mg B/day for adults was established by the EMA based on:

- The Minimum Risk Level (MRL) of 0.2 mg B/kg/day for acute duration of exposure set by the Agency for Toxic Substances and Disease Registry (ATSDR) [9]
- The tolerable upper intake level (UL) of 10 mg B/day for adults (including pregnant and breastfeeding women), set by the Scientific Committee on Consumer Safety (SCCS) of the European Commission Directorate-General for Health and Consumers [10].

PDE = 0.2 mg B/kg/day x 50 kg = 10 mg B/day

The SCCS also extrapolated ULs for children based on body surface area, and a similar approach was taken by the EMA to define thresholds for warnings and contraindications.

Comments
The extent of absorption and effects of non-oral routes of exposure (eg, ocular exposure) are not discussed. The EMA guidance applies to all routes of administration. This was discussed during the consultation process for establishing the guidance, where it was stated that deriving the thresholds from the oral PDE was a worst-case scenario and was considered applicable to all routes of administration due to a lack of robust evidence showing significantly lower absorption by other routes [11].

2.3.2 Royal College of Ophthalmologists (UK) statement

In April 2021, the Royal College of Ophthalmologists issued a safety alert outlining the EMA requirements for boron-containing excipients, with a focus on chloramphenicol eye drops (Annex 3). The alert came after a number of chloramphenicol eye drop products in the UK added the EMA contraindication and warning for children under two years.

The College considered that the benefits of chloramphenicol eye drops outweigh the risks in children when used appropriately with conventional regimens. The following points were made:

- Chloramphenicol has a long history of use in children without documented effects on fertility.
- There are situations where chloramphenicol eye drops are preferable to ointment, and alternative antibiotic eye drops may not be a suitable replacement or should be reserved for severe infections.
- Given that the maximum volume that can be accommodated in the conjunctival sac is 10-20 µL, a typical regime of one drop to either eye four times daily would result in a daily exposure well below 1mg B/day, even if 100% absorption is assumed.
- It is unlikely that chloramphenicol eye drops will be reformulated to remove boron-containing excipients.
- There is a risk that second- or third-line antibiotic eye drops will be prescribed instead of chloramphenicol and encourage the development of microbial resistance [12].

2.3.3 Registered medicines that contain boric acid and/or borax

A number of medicines in New Zealand contain boric acid and/or borax. Table 2 and Annex 1 list the products, boron content per mL and maximum boron dose contained in the maximum daily dose listed in the data sheet. Table 2 lists products that may exceed the EMA threshold for boron content if used at the maximum dose listed in the data sheet. Annex 1 lists products that are unlikely to exceed the threshold or are contraindicated in children under two years of age.

The boron doses have been calculated using a standard droplet size of 30 µL, however the actual droplet size depends on the individual product container. A calculation using a volume of 20 µL has also carried out to reflect the maximum volume that can be accommodated by the conjunctival sac.

Vaccines are excluded as they are administered as single doses and have very low boron content.

Section 2.3.3.1 to 2.3.3.4 describes the individual eye drops listed in Table 2.

Table 2: Approved medicines with boron content that may exceed 1 mg B/day

Product	Active ingredients	Sponsor	Total boron (mg/mL)	Max daily dose (drops)	Max boron dose (mg B/day) – if 20 µL retained in eye	Max boron dose (mg B/day) – 30 µL avg droplet size	Notes	Dosage
Tobrex Eye drops, solution, 0.3% (Prescription)	Tobramycin	Novartis New Zealand Ltd	[redacted]	[redacted]	[redacted]	[redacted]	Based two drops dosed hourly during waking hours*. Data sheet states safety in children below one year not established.	Instil one or two drops into the affected eye(s) every four hours. In severe infections, instil two drops into the eye(s) hourly until improvement.
Chlorsig Eye drops, solution, 0.5% (Restricted)	Chloramphenicol	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	[redacted]	[redacted]	[redacted]	[redacted]	Based on two drops in each eye every two hours during waking hours*. Indicated for children over two years but can be used under two on medical advice.	Instil 1 or 2 drops in the affected eye(s) every two to six hours for up to 5 to three days. The interval between applications may then be increased.
Chlorafast Eye drops, solution, 0.5% w/v (Restricted)	Chloramphenicol	Teva Pharma (New Zealand) Limited	[redacted]	[redacted]	[redacted]	[redacted]	Based on two drops in each eye every two hours during waking hours*. No lower age limit.	Instil 1 or 2 drops in the affected eye(s) every two to six hours for two to three days. Treatment should be continued for at least 48 hours after the eye appears normal.

Product	Active ingredients	Sponsor	Total boron (mg/mL)	Max daily dose (drops)	Max boron dose (mg B/day) – if 20 µL retained in eye	Max boron dose (mg B/day) – 30 µL avg droplet size	Notes	Dosage
Minims Chloramphenicol Eye drops, solution, 0.5% w/v (Restricted)	Chloramphenicol	Bausch & Lomb (NZ) Ltd	[redacted]	[redacted]	[redacted]	[redacted]	Based on dosing both eyes six times daily - although the data sheets that dosing more frequently may be required (up to every 15 mins initially). No lower age limit.	1-2 drops applied to affected eye(s) up to 6 times daily or more frequently if required. (Severe infections may require 1-2 drops every 15-20 mins initially, reducing gradually as infection is controlled).
Clear Eyes Eye drops, solution, 0.01% w/v (Pharmacy only)	Naphazoline	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	[redacted]	[redacted]	[redacted]	[redacted]	No lower age limit on label.	Instil 1 or 2 drops into each eye up to 4 times a day.
Isopto Carpine Eye drops, solution, 4 % (Prescription)	Pilocarpine	Novartis New Zealand Ltd	[redacted]	[redacted]	[redacted]	[redacted]	No lower age limit.	Instil two drops topically in the eye(s) up to three or four times daily. Under selected conditions, more frequent instillations may be indicated. Individuals with heavily pigmented irides may require larger doses.

Conversion factors: dose of boric acid × 0.175 = equivalent dose of boron; dose of borax × 0.113 = equivalent dose of boron
*Waking hours refers to 16 hours per 24 hours.

2.3.3.1 Tobrex (tobramycin) 0.3% w/v eye drops

Indications

Tobrex (tobramycin) eye drops are indicated for the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Tobrex should not be used in children under one year of age, as safety and efficacy have not been established in this population [13].

Role in clinical practice

In general, chloramphenicol is the medicine of choice for superficial eye infections, with framycetin (partial subsidy) and fusidic acid listed as alternatives for adults and children in the BPAC antibiotics guide [14]. The New Zealand Formulary for Children states that tobramycin has a broad spectrum of activity and is effective for treatment of superficial eye infections caused by *Pseudomonas aeruginosa* [15].

Starship guidelines for paediatric bacterial conjunctivitis (outside of neonatal age group) recommend chloramphenicol eye drops 0.5% administered four times daily for 5 days. No alternative medicines are named [16].

[redacted]

Local and international data sheets

The Tobrex New Zealand data sheet does not include fertility concerns in children under two years of age due to boric acid content. The product indication does not specifically include a lower age limit for use, but the data sheet states that safety and effectiveness in children below the age of 1 year have not been established. There is no instruction to apply pressure to the tear duct to minimise systemic absorption.

The data sheets for Tobrex in Australia, Canada and the United States do not list this concern.

Comments
Given low usage and that ocular tobramycin does not feature in clinical guidelines for superficial eye infections, the role of tobramycin eye drops in paediatric practice appears to be limited. There is an eye ointment available that does not contain boric acid or borates.

2.3.3.2 Chloramphenicol 0.5% w/v eye drops

Three brands of chloramphenicol 0.5% w/v eye drops are currently approved in New Zealand: Chlorsig, Chlorafast and Minims Chloramphenicol.

Indications

Chloramphenicol 0.5% w/v eye drops are indicated for treatment of bacterial conjunctivitis and other superficial ocular infections caused by chloramphenicol-sensitive organisms [17].

Role in clinical practice

Chloramphenicol is the medicine of choice for superficial eye infections in children [15].

Starship guidance recommends chloramphenicol 0.5% eye drops four times daily for five days for bacterial conjunctivitis outside of the neonatal period. During the neonatal period, treatment should be targeted to the

causative organism, but chloramphenicol eye drops remain a recommended broad-spectrum treatment [18, 19].

Chloramphenicol ointment is a suitable alternative to eye drops that does not contain boron and has a longer eye contact time.

Framycetin (partial subsidy) and fusidic acid are listed as alternative antibacterials for adults and children in the BPAC antibiotics guide [8].

[redacted]

Local and international data sheets

Table 3 describes the information contained in New Zealand and international chloramphenicol eye drop data sheets that pertains to boric acid/borax and fertility concerns. The New Zealand data sheets do not currently contain any information relating to boric acid/borax and fertility concerns in children under two years of age. All data sheets include an instruction to apply pressure to the tear duct to avoid systemic absorption.

Four of the eight products with published data sheets in the UK include contraindications and warnings not to give to children under the age of two due to the boric acid/borax content. Both of the products with published data sheets in Ireland include this warning.

Canada, Australia and the US do not appear to have published data sheets for currently registered chloramphenicol eye drop products. [redacted]

Table 3: New Zealand and international data sheet information pertaining to boric acid/borax and fertility concerns in children under two years

Product	Indicated age	Contra-indication	Precaution
New Zealand			
Chlorafast	Adults and children	N	N
Chlorsig	Adults and children > 2 years*	N	N
Minims Chloramphenicol	Adults and children	N	N
UK			
Boots Pharmacy Antibiotic Eye Drops	Adults and children > 2 years	N	N
Brochlor	Adults and children > 2 years	N	N
Chloramphenicol (Martindale Pharmaceuticals)	Adults and children > 2 years	N	N
Chloramphenicol (FDC International Ltd)	Adults and children > 2 years	Y	Y
Clorogen	Adults and children > 2 years	Y	Y
Eykappo	Adults and children	Y	Y

Product	Indicated age	Contra-indication	Precaution
Minims Chloramphenicol	Adults and children	N	N
Optrex Infected Eye Drops	Adults and children > 2 years	N	Y
Ireland			
Chloromycetin	Adults and children > 2 years	Y	Y
Minims Chloramphenicol	Adults and children > 2 years	N	Y

*Can be used in children under two on medical advice

Comments

Chloramphenicol ointment is a suitable alternative to eye drops that does not contain boric acid or borax. Chloramphenicol eye drops are also funded for use in the ear for bacterial infection in otitis externa (unapproved indication), but this is not mentioned in the BPAC Antibiotics Guide.

As stated by the Royal College of Ophthalmologists (UK), use of alternative antibacterial agents may be at odds with principles of antimicrobial stewardship and there are differences in susceptibility.

The recommended dose in Starship guidelines does not exceed the EMA threshold. Introduction of a paediatric dose is one approach that would limit boron exposure, while being compatible with local guidelines and the position of Royal College of Ophthalmologists (UK) that the benefits of chloramphenicol eye drops outweigh the risks when using conventional regimens.

2.3.3.3 Clear Eyes (naphazoline) 0.01% eye drops

Indications

Clear Eyes (naphazoline) 0.01% eye drops are an over the counter product used to treat eye redness.

Role in clinical practice

Ocular naphazoline should not be used in children under 12 and red eye in children should be assessed by a healthcare professional [20].

[redacted]

Product information

There is no published data sheet for this over the counter medicine and there is no package insert. The packaging for this product does not indicate a lower age limit for use.

Comments

Naphazoline eye drops should not be used in children under 12. The lack of a lower age limit on this over the counter medicine is not appropriate.

2.3.3.4 Isopto Carpine (pilocarpine) 4% w/v eye drops

Three strengths of Isopto Carpine are registered in New Zealand: 1%, 2% and 4%.

Indications

Isopto Carpine (pilocarpine) eye drops are indicated as a miotic to control intraocular pressure. It may be used in combination with other miotics, beta blockers, carbonic anhydrase inhibitors, sympathomimetics, or hyperosmotic agents [21].

The New Zealand Formulary for Children states that it is used pre- and postoperatively in goniotomy and trabeculotomy, and is used occasionally for aphakic glaucoma [22].

Role in clinical practice

Glaucoma is rare in children and is always managed by a specialist. Control of intra-ocular pressure in children is usually achieved with surgery, with medicines playing a supportive role. However, topical medicines may be used first-line in aphakic glaucoma [23-25].

Pilocarpine eye drops are a miotic used pre- and postoperatively in goniotomy and trabeculotomy, and are occasionally used for aphakic glaucoma. The dose listed in the New Zealand Formulary for Children for raised intra-ocular pressure is one drop of the 1% solution three times daily. Information on paediatric dosing is not included in the New Zealand data sheet, as discussed below [22, 26].

[redacted]

Local and international data sheets

The New Zealand data sheet does not list fertility concerns in patients under two and does not contain information on use in paediatric patients. The data sheet includes an instruction to apply pressure to the tear duct to minimise systemic absorption.

The US prescribing information does not include fertility concerns. The dosage information specifies that the 1% strength should be used at a dosage of one drop three times daily for children under 2 years of age, which would not exceed the EMA threshold.

There is no published data sheet for this product in the UK or Ireland. The data sheets for similar products state that concentrations up to 2% may be safely used in paediatric populations, and that treatment should be started with the lowest available dose and strength in patients under 18 years of age.

The Australian and Canadian data sheets do not include any information about fertility concerns or use in paediatric populations.

Comments
The use of pilocarpine in children appears to be extremely limited and would occur only under specialist treatment. However, the New Zealand Isopto Carpine data sheet lacks information on paediatric use. The US Isopto Carpine data sheet indicates that the lowest strength and a reduced dosing regimen should be used in children under the age of two. This paediatric dose would not result in a boron dose that exceeds the EMA threshold. This lower dosage is reflected in the New Zealand Formulary for Children, but not the New Zealand data sheet.

3 SCIENTIFIC INFORMATION

The EMA report on 'Boric acid and borates used as excipients', published in support of the 'Questions and answers' document (see section 3.1.1), is a comprehensive summary of available toxicological evidence relating to boron compounds. A review article was also identified that summarises recent epidemiological studies relating to environmental and occupational exposure to boron.

3.1 Published literature

3.1.1 Boric acid and borates used as excipients – European Medicines Agency, 2017

This report was published by the European Medicines Agency (EMA) in support of the 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use'. The report (Annex 4) summarises the pre-existing regulations, and the available pharmacokinetic, toxicology and clinical safety data for boric acid and borates [27].

Regulatory status

After pharmacovigilance action Germany in 1983, the marketing authorisations were withdrawn for medicinal products containing boric acid or boric acid salts and esters. The exceptions to this were medicinal waters and the salts thereof, ophthalmic products with boric acid as a buffer/isotonicity agent, homeopathic dilutions and medicines containing phenylmercuric borate or phenylmercuric (II) dihydrogene borate.

The exempted product types were required to comply with an exposure limit of 2.5 mg boron per day when used as intended. This limit was set in accordance with the amount calculated for drinking water. Medicinal waters and salts thereof were contraindicated in children under three years of age, with a warning about toxic reactions required. An ear drop containing boric acid has since been approved in Germany.

European food regulations only allow use of boric acid or borax as food additives in caviar. The European limit for boron in drinking water is 1 mg/L. The use of boric acid and borates in cosmetics is restricted.

Pharmacokinetics

Boric acid is readily absorbed from the gastrointestinal tract in humans and animals. Cutaneous absorption is negligible, but systemic penetration has been demonstrated on damaged skin.

A distribution study in rats administered 68 mg B/kg/day orally for 7 days showed similar boron concentrations across the tissues examined, which were three to 20 times higher than controls. Steady state (12-30 mg B/kg) was achieved after three to four days. Bone concentrations were higher than other tissues (47 mg B/kg) and increased throughout the study.

Metabolism of inorganic borates does not occur due to excessive energy required to break the boron-oxygen bond. At low concentrations, inorganic borates are converted to boric acid in the aqueous layer overlying mucosal surfaces prior to absorption. Human and animal studies have demonstrated that over 90% of the administered borate dose is excreted as boric acid. Boric acid does not undergo metabolism.

Clearance of boron acid is similar in humans and animals. More than 90% of the dose is excreted via the urine. Excretion is relatively rapid, with a half-life of 24 hours or less. A study in rats found that the elimination of boron from the bone compartment is different from that of other tissues. The bone concentration decreased gradually after stopping boron administration and remained higher than in controls at week 32.

Toxicology

In single-dose studies, the oral LD_{50} of boric acid in the mouse and rat was equivalent to 400-700 mg B/kg. In the guinea pig, an LD_{50} of 210 mg B/kg was reported. The LD_{50} in the dog, rabbit and cat ranged from 250 to 350 mg B/kg. The symptoms included incoordination, hypothermia, convulsions and violet-red colour of the

skin and mucosa. In the kidneys, glomerular and tubular lesions were seen and increased small dark cells (probably microglia) were found in the brain cortex and spinal cord.

Animal studies consistently show that the male reproductive tract is a target of toxicity. Testicular lesions have been seen in mice, rats and dogs. Histopathologic changes in repeated dose studies range from reduced spermiation, to degeneration of seminiferous tubules, to absence of germ cells resulting in transient or irreversible infertility. The No Observed Adverse Effects Level (NOAEL) for fertility effects in the rat was 17.5 mg B/kg/day.

Foetotoxic, foetolethal and teratogenic effects have been observed in mice, rats and rabbits. The most notable malformations were costal and cardiovascular abnormalities. The rat was the most sensitive species, with effects on embryofoetal development seen at levels not causing maternal toxicity. The NOAEL for embryofoetal development in rats is 9.6 mg B/kg/day.

Boron compounds were not genotoxic in animal and microbiological studies. Carcinogenicity was not seen in mice although testicular interstitial cell hyperplasia was observed at high doses. Likewise, carcinogenicity was not seen in rats although not all tissues were examined.

The boron compounds of interest to this report are not classified as skin irritants or skin or respiratory sensitisers. However, ocular irritation of boron oxide dust and sodium perborate monohydrate solution has been seen in animals. Inhalation exposure to boron compounds is known to cause respiratory irritation in humans. Borax, but not boric acid, is classified as an irritant to eyes under EU guidelines and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Clinical safety data

Reproductive toxicity in association with boric acid as an active ingredient has not been reported to the WHO adverse drug reaction database.

Epidemiological studies in humans based on workplace exposures and biological samples were reviewed by the European Commission Scientific Committee on Consumer Safety (SCCS) and were considered insufficient to demonstrate the absence of an adverse effect on human fertility.

Risk assessment and threshold

A Minimum Risk Level (MRL) of 0.2 mg B/kg/day for acute duration of exposure was set by the Agency for Toxic Substances and Disease Registry (ATSDR). This was calculated by dividing the estimated benchmark dose associated with a 5% reduction in foetal body weight ($BMDL_{05}$) of 10.3 mg B/kg/day by an uncertainty factor of 66. The uncertainty factor is intended to account for extrapolation of animal toxikinetics and toxidynamics to humans, and account for human variability of toxikinetics and toxidynamics. The estimated $BMDL_{05}$ of 10.3 mg B/kg/day is similar to the NOAEL of 9.6 mg B/kg/day.

The permitted daily exposure for boron for adults is 0.2 mg B/kg/day x 50 kg = 10 mg B/day. This is consistent with the SCCS opinion on boron compounds which set an Upper Intake Level (UL) in food for at 10 mg B/person/day in adults, including pregnant and lactating women. The ULs for children were extrapolated on the basis of body surface area:

Age (years)	UL (mg B/day)
1-3	3
4-6	4
7-10	5
11-14	7
15-17	9

The EMA considered that as boron compounds are classified as toxic to reproduction, appropriate information on boron-containing excipients should be included in the patient information leaflet. This information is required for all routes of administration. Thresholds for the inclusion of contraindications/warnings for children were extrapolated based on body surface area, which were determined from EC Scientific Committee for Food reported values for mean body weight and height.

Age (years)	Threshold (mg B/day)
< 2	1
< 12	3
< 18	7*
≥ 18	10*

*This amount may also cause harm to the unborn child.

Comments

The extent of absorption and effects of non-oral routes of exposure (eg, ocular exposure) are not discussed. The EMA guidance applies to all routes of administration. During the consultation process for establishing the guidance, deriving the thresholds from the oral PDE was stated to be a worst-case scenario and was considered applicable to all routes of administration due to a lack of robust evidence showing significantly lower absorption by other routes [11].

3.1.2 Effects of boron compounds on human reproduction - Bolt et al, 2020

This review article considers the available epidemiological studies assessing the effects of human exposure to boron on reproductive and developmental effects (Annex 5). The article also attempts to reconcile the results of these studies with animal studies that established a NOAEL 17.5 mg B/kg/day for fertility effects in male rats and 9.6 mg B/kg/day for developmental effects in female rats [28].

The reviewed studies were carried out in boron rich geographical areas: China's Liaoning province, the Argentinian Andes and Western Anatolia/Turkey.

A study in China compiling information on men and women working in boron mining or processing included individual assessments of boron exposure, interviews on reproductive experience and data on semen analysis. Boron workers (n=75) had a mean daily intake of 31.3 mg B/day, and a subset of heavily exposed workers (n=16) had an estimated mean daily intake of 125 mg B/day. Reproductive outcomes in the wives of boron workers were not significantly different from those of the wives of background control men after adjustment for potential confounders. There were no statistically significant differences in semen characteristics between exposure groups, except for reduced sperm Y:X ratio in boron workers which was not correlated with blood levels of boron within the exposed group.

A study in Argentina examined a possible link between boron exposure and low birth weights in a community exposed to elevated boron concentrations in drinking water. The study found that serum boron concentrations above 80 µg/L were associated with decreased length and weight of newborns. However, lithium exposure and high altitude may have confounded the effect.

A number of studies have been carried out in boron-rich areas of Turkey. One study investigated possible reproductive effects of boron exposure in workers employed in a boric acid production plant. The mean daily exposure of the highly exposed subgroup was 14.45 mg B/day. Effects on sperm parameters and male reproductive hormones were not observed. An extension of this study did not consider there was a significant correlation between boron exposure and DNA-strand breaks in sperm cells.

Another study in boron workers calculated a mean exposure of 47.17 (range: 7.95–106.8) mg B/day in an 'extreme exposure' subset (n=98). Effects on sperm parameters and male reproductive hormones were not observed.

A study in females residing in a boron-rich area calculated a mean exposure 24.67 (range: 10.47–57.86) mg B/day in the 'high exposure' group (n=27). Effects on induced abortion, miscarriage, stillbirth, infant/neonatal death, preterm birth, congenital anomalies, sex ratio and birth weight of newborns were not observed. A related study did not find an adverse effect of DNA damage in the lymphocytes and buccal cells of the women.

A study of shifts in sex ratios at birth did not find a difference in Y:X sperm ratios. An extension to this study found no significant increase in the DNA damage in blood, sperm and buccal cells in those exposed to boron both occupationally and environmentally.

Table 4 summarises the mean exposure levels and blood concentrations of boron in human studies, compared with animal studies used as the basis for NOAELs in rats. The subsets of highly exposed people were in each case fewer than 100 people. Some of the people in these groups were exposed to levels below the accepted PDE of 10 mg B/kg/day. The authors note that blood boron concentrations seen in humans were much lower than seen in the rat studies and take this to mean that toxic levels of exposure are not reached through normal exposure and handling. The authors considered that the classification of boron as toxic to reproduction should be reconsidered.

Table 4: Summary of human and rat exposures to boric acid/borates and associated boron blood levels (means or median and range) [28].

4 DISCUSSION AND CONCLUSIONS

The European Medicines Agency has set guidance requiring a warning about the fertility concerns associated with boron-containing excipients and a contraindication for children under two if the medicine exceeds a threshold of 1 mg B/day. Medicines that exceed thresholds of 3 and 7 mg B/day require contraindications for people under 12 and 18 years of age, respectively. The UK Royal College of Ophthalmologists has also released a statement on chloramphenicol eye drops, stating that the benefit-risk profile is considered to be positive when conventional regimens are used.

These changes to the EMA guidance are based on animal studies showing developmental toxicity in female rats and effects on fertility in male rats. Human studies to date have not found a correlation between environmental boron exposure and fertility or developmental effects, and do not provide information on reversibility of any potential effects. However, the authorities responsible for setting safety limits for boron exposure did not consider the body of human evidence sufficient to discount the possibility of boron being a reproductive toxin in humans.

As a result of several queries from healthcare professionals, a review of all medicines containing boric acid and borates has been undertaken. The calculation used an average droplet size of 30 µL and the maximum dose listed in the data sheet. Another set of calculations used a 20 µL as the maximum volume that can be accommodated by the conjunctival sac. The calculations found that Tobrex 0.3% eye drops, several chloramphenicol 0.5% eye drops, Clear Eyes 0.01% eye drops and Isopto Carpine 4% eye drops may exceed the EMA thresholds when used at the maximum dose.

Some other medicines, listed in Annex 1, may also exceed the threshold of 1 mg B/kg/day but are contraindicated in children under two years of age.

Ocular tobramycin appears to have a limited role in the treatment of paediatric eye infections as it does not appear in clinical guidelines and has low usage in New Zealand. There is an eye ointment available that does not contain boric acid or borates.

Chloramphenicol eye drops have a long history of use for the treatment of superficial eye infections, including in children under two years of age. Starship guidelines recommend a dose of one drop in the affected eye(s) four times daily which would not exceed the boron threshold, but this is not reflected in the data sheet. Chloramphenicol ointment is a suitable alternative to eye drops that does not contain boric acid or borax.

Clear Eyes (naphazoline) eye drops should not be used in children under 12 years of age but this is not reflected on the product label.

Pilocarpine eye drops have an extremely limited role in the treatment of paediatric glaucoma and this would always occur under specialist supervision. However, the data sheet lacks information on paediatric use while this information is reflected in the New Zealand Formulary and international data sheets.

A number of chloramphenicol data sheets in the United Kingdom and Ireland have been updated to include a contraindication for children under two and a warning about fertility concerns. [redacted]

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether warnings/contraindications relating to boron content and fertility concerns in children should be added to the data sheets for any of the medicines discussed in this report
- Whether any other changes should be made to these data sheets to mitigate this concern
- Whether any other action is required.

6 ANNEXES

Annex 1: Approved medicines with boron content that may exceed 1 mg B/day but are contraindicated in children under two years of age and approved medicines with boron content that is unlikely to exceed 1 mg B/day

Annex 2: Questions and answers on boric acid and borates used as excipients in medicinal products for human use (EMA/CHMP/619104/2013)

Annex 3: Safety alert: Boron additives in chloramphenicol drops; should ophthalmologists be concerned?

Annex 4: Boric acid and borate used as excipients (EMA/CHMP/619104/2013)

Annex 5: Bolt et al. 2020. Effects of boron compounds on human reproduction

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