THE PAEDIATRIC SOCIETY OF NEW ZEALAND

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PHARMAC
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Dear An-Ruo

Lasix® Oral Solution (furosemide 10 mg/mL) 30 mL - New Formulation

On behalf of the Paediatric and Therapeutics Special Interest Group of the NZ Paediatric Society and with support of paediatric cardiologists across New Zealand, we would like PHARMAC to consider funding furosemide 20mg tablets as an alternative formulation to use in children.

As you are aware, Sanofi announced in September 2015 that the formulation of Lasix® was changing from containing 0.04% ethanol to 10% w/v ethanol (equivalent to 12.5% v/v). Ethanol is used as a solvent to improve drug solubility[1]. This has enabled the formulation to be stored at room temperature and increase the in-use shelf life to 8 weeks.

There has been much discussion amongst prescribers and pharmacists both in New Zealand and Australia regarding the safety of a liquid containing 10 % ethanol for children. While we are aware of other oral liquid medicines which contain ethanol such as ranitidine, it is in the clinical setting of repeated doses in neonates and pre-term infants needing long-term therapy which holds the most concern using the new Lasix oral solution formulation. Furosemide is not readily replaceable with an alternative product.

In neonates and very young infants, the enzyme alcohol dehydrogenase (ADH), which is responsible for breaking down ethanol, is not mature. 'ADH activity is reported to be present in neonates and infants from age 9 days to 2 months, but it accounts for <20% of adult enzymatic activity… and 'does not reach adult levels until about age 5 years'[1]. This means the clearance of ethanol is reduced leading to more CNS side effects. 'It is important to note that the effect of long term exposure to even low levels of ethanol in medicines on the health and development of children has not been evaluated'[2] Neonates and young infants being treated with furosemide usually have comorbidities: usually cardiac or respiratory conditions. These children will have a decreased ability to tolerate ethanol.

There is currently little data to indicate the safe level of ethanol products used for children. There are also no regulatory guidelines available to guide ethanol use in children under the age of two.

The European Medical Authority (EMA) recommendation is that medicines for children 2-6 years should contain no more than 6mg/kg/dose of ethanol[2]. The most recent document from EMA in 2014[2] states that 'Ethanol should not be included in medicinal products unless justified…as part of the justification for the use of ethanol there should be discussion of why other excipients cannot fulfil the functions of ethanol in the formulation. Where ethanol use is necessary, measures to minimise ethanol exposure should be discussed'. The same document suggests wording for package inserts around the amount of ethanol a product contains, which we suggest is applied for New Zealand products. Currently there is no information included with the product to indicate the amount of ethanol in the product. The only statement is in fine print stating "contains alcohol".

The UK patient information leaflet for Frusol® oral liquid states 'this medicinal product contains 10% v/v ethanol (alcohol), ie up to 0.4 g per 5 ml dose'.…This should also be taken into account in…children and high risk groups'[4]. This would equate to 0.08 g (80 mg) per 1 mL dose.

Example: a 5 kg child receiving 2 mg/kg/ dose twice a day (datasheet recommends 2-6 mg/kg/dose in infants and children), would receive 2 ml daily of the 10 mg/ml Frusol® solution. This equates to 0.16 g (160mg) ethanol/day, equivalent to 4ml beer per day or 1.6ml wine per day. The Lasix® formula registered in New Zealand states it is 10% w/v which equates to 12.5% v/v giving an even higher amount of ethanol.

The Federal Drug Administration (FDA) recommends not including ethanol in medicinal products for use in children. If necessary, the amount of ethanol should not produce a blood alcohol concentration (BAC) of greater than 0.25g/L (25 mg/100 mL). The World Health Organisation (WHO) proposes to limit the ethanol content on over-the-counter products to less than 0.5% for children less than 6 years, less than 5% in children aged 2 to 6 years and less than 10% for children over 6 years. However, these limits do not consider the dose actually given.

The American Academy of Pediatrics suggest any single medicine should not result in a BAC of greater than 25 mg/100 mL in a child after one dose. The EMA are more conservative and propose a limit of 1 mg/100mL rise in BAC in children 2-6 years and of 12.5 mg/100 mL in children greater than 6 years[1].

While this new Lasix® oral liquid is registered in the USA and Australia. In Australia, discussions are occurring in regard to alternatives to this formulation which include the use of Syrspend® SF Alka solution to extemporaneously manufacture an alternative oral suspension. In the UK they have Frusol® solution with an equivalent amount of ethanol but they have access to centrally manufactured 'specials' formulations[6] as well.

We have discussed the options available to us. These include:

- Using the current Lasix formulation containing 10% w/v ethanol for all paediatric patients.
- Having access to a furosemide 20mg tablet, which is available in Australia. With access to this smaller dose tablet, we could quarter the tablets and dose in 5mg increments, as has previously been the case with spironolactone tablets and continues to be the case with bumetanide. Furosemide tablets disperse but do not dissolve in water. Dispersing the 40 mg tablet currently registered, in a known volume of water and taking an aliquot for the dose, will not give an accurate dose due to the uneven dispersion. Dose-banding in 5mg increments could be a solution to those children falling between the 5kg weights using a 20 mg tablet. They could then use ¼, ½ tablet etc so the whole volume it is dispersed in would be given.

- Continue to investigate the possibility of Biomed manufacturing a furosemide solution and then obtaining funding for this.
- Asking one of the universities to begin stability testing of a furosemide solution in Ora or other products to see if this could be a future option if funding was available.
- Further investigate the possibility of importing and funding the Syrspend®SF Alka product, which has published stability data available for an extemporaneous furosemide suspension. However, this is not a preferred option as there is potential for confusion with Ora® products leading to errors in compounding.
- NICU's around NZ could use the injection orally however the pH is 8-9.3[5] which could pose some problems.

None of these options are ideal but we would ask that the process around registering and funding a 20mg furosemide tablet is expedited so that our paediatric population requiring this medicine are not disadvantaged in regard to an appropriate and safe formulation.

Yours sincerely

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