Annex III

Amendments to the relevant sections of the Product information

Note:

This product information is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to the relevant sections of the Product Information

The valid product information is the final version achieved during the Coordination group procedure with the following amendments (marked as {to be filled in}, **insertion** or ~~deletion~~ of the text as appropriate) to reflect the agreed wording as provided below:

SUMMARY OF PRODUCT CHARACTERISTICS

4.1. Therapeutic indications

{(Invented) name} is indicated in adults, adolescents, children and infants from 1 month of age:

- for the control of status epilepticus ~~in adults, adolescents, children and infants from 1 month of age~~.

4.2. Posology and method of administration

Status epilepticus

[…]

Due to the potential risk of toxicity from accumulation of excipients the maximum dose of {(Invented) name} should not be repeated within 24 hours in children under 5 years of age (see section 4.4).

Paediatric population

The use of {(Invented) name} in children under 12 years is contraindicated, except for the indication status epilepticus **where it is contraindicated in neonates** (see sections 4.1, 4.3 and 4.4).

4.3. Contraindications

{(Invented) name} is contraindicated in children under 12 years of age, except for the indication status epilepticus **where it is contraindicated in neonates.**

4.4. Special warnings and precautions for use

Information on excipients

{(Invented) name} contains benzyl alcohol, polyethylene glycol and propylene glycol.

Risk of excipient accumulation and toxicity in paediatric patients less than 5 years of age and other special populations

All these excipients are substrates of alcohol dehydrogenase and may saturate metabolism and increase the risk of excipient accumulation that can lead to toxicity. Paediatric patients less than 5 years of age are particularly vulnerable due to immature renal and metabolic capacity.

The risk also includes patients with impaired hepatic or renal function, pregnant or breast-feeding women (see section 4.6), as well as patients with an impaired alcohol and aldehyde dehydrogenase enzyme system.

It is important to take into account the combined daily metabolic burden of co-administration with other substrates of alcohol dehydrogenase (e.g. ethanol). Particular caution should be taken when repeated doses are given.

Further risks for each individual excipient are outlined below.

Propylene glycol

This medicine contains 840 mg propylene glycol in each ~~vial~~ **ampoule**, which is equivalent to 840 mg/ml.

[…]

~~Prolonged administration of products containing propylene glycol, as well as co-administration with other substrates of alcohol dehydrogenase (e.g., ethanol), increase the risk of propylene glycol accumulation and toxicity, especially in patients with impaired hepatic or renal function.~~ The population predisposed to propylene glycol accumulation and associated potential adverse events also include patients ~~with an impaired alcohol and aldehyde dehydrogenase enzyme system, including paediatric patients less than 5 years of age, pregnant women, patients with severe kidney or liver disease and those~~ being treated with disulfiram or metronidazole.

Benzyl alcohol

This medicine contains 21 mg benzyl alcohol in each ~~ml solution for injection~~ **ampoule, which is equivalent to 21 mg/ml**.

[…]

Intravenous administration of benzyl alcohol has been associated with serious adverse events and deaths in neonates ("gasping syndrome"). **Premature and low birth weight neonates are more likely to develop toxicity. Medicinal products containing benzyl alcohol should not be used for more than 1 week in children under 3 years of age, unless necessary.** Although normal therapeutic doses of this product usually release amounts of benzyl alcohol significantly lower than doses reported in association with gasping syndrome, the minimum concentration of benzyl alcohol at which toxicity may occur is unknown.

~~Premature and low birth weight neonates are more likely to develop toxicity. Medicinal products containing benzyl alcohol should not be used for more than 1 week in children under 3 years of age, unless necessary.~~

~~If the use of {(Invented) name} is necessary, it is important to take into account the combined daily metabolic burden of benzyl alcohol from all sources, especially in patients with impaired hepatic or renal function, as well as in pregnant or breast-feeding women, due to the risk of accumulation and toxicity (metabolic acidosis).~~

PACKAGE LEAFLET

2. What you need to know before you use {(Invented) name}

Children

Children under 12 years old are not allowed to use <{(Invented) name}> except for the control of status epilepticus. **For status epilepticus, {(Invented) name} must not be used in neonates.**

[…]

{(Invented) name} contains benzyl alcohol, propylene glycol and polyethylene glycol.

{(Invented) name} contains 21 mg benzyl alcohol, 840 mg propylene glycol and 189 mg polyethylene glycol in each ml.

~~This medicine contains 840 mg propylene glycol per ampoule, equivalent to 840 mg/ml.~~

~~This medicine contains 189 mg polyethylene glycol per ampoule, equivalent to 189 mg/ml.~~

~~This medicine contains 21 mg benzyl alcohol per ampoule, equivalent to 21 mg/ml.~~

Ask your doctor or pharmacist for advice if your child is below 5 years of age, if you have liver or kidney disease or if you are pregnant or breast-feeding. This is because the excipients may cause side effects. Your doctor may need to adjust the dose if you or your child use other medicines that contain benzyl alcohol, propylene glycol or alcohol.

[…]

~~Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build up in your body and cause side effects (called "metabolic acidosis").~~

~~Ask your doctor or pharmacist for advice if you have liver or kidney disease. This is because large amounts of benzyl alcohol can build up in your body and may cause side effects (called "metabolic acidosis").~~

~~If your child is less than 5 years old, talk to your doctor or pharmacist before giving this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.~~

3. How to use {(Invented) name}

3. Status epilepticus

If the epileptic seizure lasts longer than 10-15 minutes, the doctor may decide to administer one more dose. A maximum of 2 doses may be administered.

Your child should not be given more than two repeated doses on a single day, if your child is below 5 years of age.

Use in children

{(Invented) name} should not be used in children under 12 years except for the control of status epilepticus ~~(see also section 2)~~. **For status epilepticus, it should not be used in neonates (see also section 2)**.