Annex II

Scientific conclusions

Scientific conclusions

A type II variation application was submitted under the mutual recognition procedure for Lorazepam Macure (lorazepam) 4 mg/ml, solution for injection on 19 August 2022 to update the product information in line with that of the reference medicinal product: Xilmac 4 mg/ml solution for injection. The scope of the variation (C.I.z) is an update of the product information for Lorazepam Macure in all concerned member states (CMS) following a repeat use procedure (RUP). The variation included the addition of a new indication *'for the control of status epilepticus in adults, adolescents, children and infants from 1 month of age'*, in line with the reference medicinal product. The reference Member State (RMS) is The Netherlands (NL). The CMS are Austria (AT), Belgium (BE), Denmark (DK), Finland (FI), Germany (DE), Ireland (IE), Italy (IT), Norway (NO), Slovenia (SI), Sweden (SE).

Since major issues raised by SE remained unresolved on non-clinical and clinical aspects related to the potential risk of metabolic acidosis in children below 12 years old, the procedure was referred by NL to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 13(1), paragraph 1 of Regulation (EC) No 1234/2008 on 27 July 2023. As no agreement could be reached, the procedure was referred to the CHMP.

On 01 February 2024, the RMS NL therefore triggered a referral under Article 13(2) of Regulation (EC) No 1234/2008. This refers to SE's objections pertaining to the potential risks resulting from metabolic acidosis in children below 5 years old, known to have immature alcohol dehydrogenase (ADH) metabolic capacity, in the treatment of status epilepticus, considered to be a potential serious risk to public health (PSRPH).

Overall summary of the scientific evaluation by the CHMP

The issue raised in this CHMP referral procedure under Article 13 of Commission Regulation (EC) No 1234/2008 is on whether the marketing authorisation of the medicinal product Lorazepam Macure could be varied to include, amongst other, the addition of a new indication *'for the control of status epilepticus in adults, adolescents, children and infants from 1 month of age'* considering the potential adverse effects resulting from the potential risk of metabolic acidosis in children below 5 years old following the accumulation of the alcohol excipients (benzyl alcohol, propylene glycol, and polyethylene glycol (PEG 400; also known as macrogol 400)) combined in the medicinal product, as these are all substrates of ADH, a limiting step of the metabolism.

Following the review of the available data and responses from the MAH in relation to the objections raised as a PSRPH as well as the Non-Clinical Working Party (NcWP) and the Paediatric Committee (PDCO) responses provided in the context of the CMDh referral procedure, the CHMP considered that amendments where required to the product information in order to adequately minimise the risks resulting from metabolic acidosis associated with the combination of excipients in young children. The CHMP considered that clinical monitoring is not feasible in the medical emergency of status epilepticus where the full medicinal product dose is administered within a timeframe of 10-15 minutes. Therefore, the CHMP agreed that the exposure to the excipients should be kept below any toxic levels. Hence, the maximum dose of Lorazepam Macure should not be repeated within 24 hours in children below 5 years of age, in order to prevent potential toxicity due to the accumulation of excipients. In addition, the CHMP was of the view that Lorazepam Macure should be contraindicated in neonates due to the vulnerability of the population, and the immaturity of their renal and metabolic capacity. Moreover, warnings on the risks resulting from metabolic acidosis associated with the combination of the excipients should be added due the greater risk of toxicity resulting from their accumulation in children from 4 weeks of age until 5 years of age.

As a consequence, the CHMP considered the variation to the marketing authorisation of Lorazepam Macure adding, amongst other, the new indication *'for the control of status epilepticus in adults, adolescents, children and infants from 1 month of age'* approvable, subject to the agreed

amendments to the product information to minimise the risks resulting from metabolic acidosis associated with the possible combined accumulation of excipients substrate of ADH in Lorazepam Macure (lorazepam) in children from 4 weeks of age until 5 years old.

It was noted that Lorazepam Macure contains the same combination of excipients (benzyl alcohol, propylene glycol and polyethylene glycol) as its reference medicinal product indicated in the same target population. The CHMP recommends by extrapolation that all medicinal products containing at least two of the alcohol excipients present in Lorazepam Macure (benzyl alcohol, propylene glycol and polyethylene glycol), indicated for the control of status epilepticus in children below 5 years of age and currently authorised in the EU or subject to future authorisation procedures include the product information amendments resulting from the scientific evaluation of the current procedure.

Grounds for the CHMP opinion

Whereas,

- The Committee considered the referral under Article 13 of Regulation (EC) No 1234/2008.
- The Committee considered the totality of the data submitted by the MAH in relation to the objections raised as a potential serious risk to public health (PSRPH). In addition, the Committee considered the responses from the Non-Clinical Working Party (NcWP) and the Paediatric Committee (PDCO) provided in the context of the CMDh referral procedure.
- The Committee considered that the risks resulting from metabolic acidosis associated with the possible combined accumulation of excipients substrate of alcohol dehydrogenase (ADH) in Lorazepam Macure (lorazepam) in children from 4 weeks of age until 5 years old, should be further minimised.
- Therefore, the Committee concluded on the amendments of the product information to reflect that the maximum dose should not be repeated within 24 hours in children below 5 years of age, that the medicinal product is contraindicated in neonates in the indication of status epilepticus, as well as to warn about the risks resulting from metabolic acidosis associated with the combination of the excipients in this patient population.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I of the CHMP opinion subject to the agreed amendments to the proposed wording of the product information as set out in Annex III of the CHMP opinion.