EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2024
EMA/390606/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 13 of Regulation (EC) No 1234/2008

Invented name: Lorazepam Macure

INN/active substance: lorazepam

Procedure number: EMEA/H/A-13/1536

Note: Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure 3

2. Scientific discussion 3

2.1. Introduction 3

2.2. Assessment of the issues raised as a potential serious risk to public health 5

3. Benefit-risk balance 6

4. Risk minimisation measures 7

5. Grounds for Opinion 8

1. Information on the procedure

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 includes 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).

The names and the marketing authorisation holder (MAH) of this medicinal product currently authorised are listed in Annex I of the CHMP opinion.

The type II variation procedure (NL/H/4353/001/II/004) started on 19 August 2022.

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. The CMDh 60-day procedure was initiated on 04 December 2023.

Day 60 of the CMDh procedure was on 01 February 2024. As no agreement could be reached, the procedure was referred to the CHMP.

On 01 February 2024, NL as RMS 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 in the treatment of status epilepticus, considered to be a potential serious risk to public health (PSRPH).

2. Scientific discussion

2.1. Introduction

Lorazepam belongs to the class of benzodiazepines. Lorazepam Macure is authorised as a 4 mg/ml solution for injection under the legal basis of Article 10.1 of Directive 2001/83/EC, via mutual recognition procedure. It is indicated in adults and adolescents above 12 years of age as a premedication before surgical procedures or prior to diagnostic procedures; and for the symptomatic treatment of pathological anxiety and tension in patients who, for some reason, are unable to take oral medication. Each ml contains 21 mg benzyl alcohol, 840 mg propylene glycol (E1520) and 189 mg polyethylene glycol (PEG 400; also known as macrogol 400).

The MAH of Lorazepam Macure submitted a type II variation application to include (amongst other) a new indication *'for the control of status epilepticus in adults, adolescents, children and infants from 1 month of age'*, in line with that authorised for the reference medicinal product.

SE raised a PSRPH in view of the possible adverse effects resulting from the risk of metabolic acidosis in children below 12 years of age. The potential risk of metabolic acidosis relates to the three alcohol

excipients, namely benzyl alcohol, propylene glycol, and polyethylene glycol combined in the medicinal product, that are all substrates of alcohol dehydrogenase (ADH), when administered to young children known to have immature ADH metabolic capacity.

Benzyl alcohol is a preservative commonly found in a range of drugs and parenteral formulations. In neonates, especially premature babies, overexposure to benzyl alcohol can lead to a set of distinct symptoms, commonly termed as 'gasping syndrome'. This emerges from metabolic acidosis due to the accumulation of its metabolite, benzoic acid, which can further result in neurological toxicity manifesting as seizures. In extreme scenarios, this might progress to liver or kidney failure, potentially resulting in death.

Propylene glycol is a solvent frequently used in medicines administered by the oral, topical and intravenous routes. It metabolises into lactic acid, pyruvic acid, and glycerol. However, in neonates, especially preterm infants, due to their less efficient metabolism and elimination because of their underdeveloped enzymatic systems, accumulation can lead to central nervous system (CNS) depression and cardiac arrhythmias. This is accompanied by hyperosmolarity due to hypernatremia and metabolic acidosis.

Polyethylene glycol does not affect newborns unless given in excess, which might lead to osmotic overload.

NL as the RMS considered the variation application approvable as the addition of this indication was previously approved in March 2022 for the reference medicinal product for the same target population and both medicinal products contain the same combination of excipients in very similar quantities. Additionally, the amount of each individual excipient does not exceed the established acceptable daily intake (ADI) as per the 'Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use' (EMA/CHMP/508188/2013) and the 'Questions and Answers on propylene glycol used as an excipient in medicinal products for human use' (EMA/CHMP/704195/2013) (see table 1).

Table 1. Lorazepam Macure excipient composition compared to the ADI

	Benzyl alcohol	Propylene glycol	Polyethylene glycol
Lorazepam Macure 4m/ml, solution for injection	21 mg/ml	840 mg/ml	189 mg/ml
Posology in status epilepticus	0.1 mg/kg intravenously. Maximum 4 mg/dose. A maximum of 2 doses may be administered.		
Volume of solution corresponding to 0.1 mg lorazepam / kg bodyweight	0.025 ml		
Calculated amount of excipient per kg bodyweight	0.525 mg	21 mg	4.725 mg
Calculated amount of excipient per kg bodyweight per day if dose is repeated (2 doses)	1.05 mg	42 mg	9.45 mg
ADI	5 mg/kg/day	50 mg/kg/day (children less than 5 years of age)	N/A

In the context of the CMDh referral procedure, the Non-Clinical Working Party (NcWP) and the Paediatric Committee (PDCO) were consulted. In the NcWP responses, the working party highlighted that the maturation profile of ADH varies through developmental stages and is notably lower during prenatal and early paediatric stages. The systematic review of pharmacovigilance cases and literature related to the use of medications in paediatric emergency care unit containing these excipients reveals that poisoning is largely due to a lack of awareness about the amounts of these excipients present in the prescribed medications. Several injectable pharmaceutical formulations are compounded with a combination of benzyl alcohol, propylene glycol, polyethylene glycol, and ethanol, all of which are contraindicated in patients under 4 weeks of age but may be used with caution in older patients. The Annex of the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) mandates the inclusion of information on the exact quantities of excipients in pharmaceutical preparations and their potential associated risks, especially regarding metabolic interactions. From a non-clinical perspective, the working party considered that the use of the excipient combination in paediatric patients over 4 weeks of age does not raise safety issues, provided monitoring is possible, subject to PDCO's position on the clinical monitoring aspects. As a result, the PDCO was also consulted. The PDCO concluded that the risks resulting from metabolic acidosis related to such combination of excipients in this particular medicinal product administered in hospital setting are not considered to impact the benefit-risk profile of the product in children over 4 weeks of age to the extent that an age restriction of the indication would be recommended.

However, SE as CMS did not consider that the PSRPH related to the potential adverse effects resulting from the combination of the excipients (benzyl alcohol, propylene glycol, and polyethylene glycol) was resolved in children below 5 years of age with immature metabolic capacity. As all three excipients are substrates of ADH, a limiting step of the metabolism, SE considered there is a risk of accumulation that can lead to toxic effects in those children. Therefore, SE was of the view that further changes to the product information (sections 4.1, 4.2, 4.3, 4.4 and 4.5 of the summary of product characteristics (SmPC) and corresponding sections of the package leaflet) were warranted in order to adequately minimise this risk.

As no agreement could be reached within the CMDh referral procedure, the procedure was referred to the CHMP. The CHMP considered all available data in relation to the safety concerns related to non-clinical and clinical aspects. A summary of the most relevant information is included below.

2.2. Assessment of the issues raised as a potential serious risk to public health

The potential risks resulting from metabolic acidosis relate to the accumulation of three alcohol excipients benzyl alcohol, propylene glycol and polyethylene glycol (PEG 400) combined in the medicinal product when administered to young children with immature metabolic capacity that can lead to toxic effects. The clinical experience of toxicity from benzyl alcohol and propylene glycol mainly stems from cases in neonatal intensive care, where these excipients are administered continuously over time and acid-base status routinely monitored over time. The development of a persistent metabolic acidosis is a key indicator of toxicity, and usually, the appropriate measure to address this is to discontinue exposure to these alcohol-related excipients.

The CHMP considered that the risks resulting from metabolic acidosis associated with the combination of excipients with known safety concerns in young children in a vulnerable target population from 4 weeks of age were not adequately addressed and minimised in the proposed product information. Although the NcWP and the PDCO responses confirmed that the use of the medicinal product in status epilepticus is safe as monitoring is possible in hospital setting, the CHMP did not consider that such

clinical monitoring is feasible in the medical emergency of status epilepticus where the full medicinal product dose is administered within a timeframe of 10-15 minutes. Due to the nature of the condition, repeated administration may occur, and this represents a further medical emergency which is not a predictable event. Acid-based measuring is not considered feasible in a complex clinical situation where timeliness of treatment is essential. In addition, this would not lead to reliable results due to the generalised muscle contractions and respiratory compromise induced by the seizure activity. Moreover, treatment of the acidosis (by buffering) does not have a key role in the management strategy and no direct impact on toxicity. Therefore, the CHMP agreed the excipient exposure should be kept below any toxic levels.

The CHMP was of the view that the risk was greater in young children with immature renal and metabolic capacity. While it was noted that the medicinal product was only proposed to be indicated in children and infants from 1 month of age for the control of status epilepticus, the CHMP considered that it should also not be used in neonates taking into account their vulnerability. In line with the ICH E11(R1) guideline on clinical investigation of medicinal products in the paediatric population (EMA/CPMP/ICH/2711/1999), neonates include term, post-term and preterm newborn infants. The neonatal period for term and post-term newborn infants is defined as the day of birth plus 27 days. The neonatal period for preterm newborn infants is defined as the day of birth through the expected date of delivery plus 27 days. Therefore, the CHMP considered that no amendments were needed to the section of the SmPC on therapeutic indication to exclude the preterm newborn infants during their neonatal period from the indication, but that a contraindication should be added in neonates for the indication of status epilepticus.

Due to the potential risk of toxicity from accumulation of excipients, the CHMP considered that the maximum dose should not be repeated within 24 hours in children under 5 years of age. It was considered that this should be specified under the section on posology and method of administration.

Regarding the description of the risks resulting from metabolic acidosis related to the excipients and to the co-administration of other ADH substrates, the CHMP considered that although the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) refers to warnings for the individual excipients of propylene glycol and benzyl alcohol, the NcWP responses specify that poisoning with such excipients is largely due to a lack of awareness about the amounts of these excipients present in the prescribed medication. Therefore, the CHMP considered that the risks resulting from metabolic acidosis related to the combination of excipients should be reflected in the product information to best warn about them. As patients experiencing status epilepticus are in a vulnerable situation, urgent treatment is essential. Given that the full (excipient) dose is to be administered within a timeframe of 10-15 minutes, the CHMP concluded that the specific clinical emergency setting linked to the condition requires clear information on the accumulation of the alcohol-related excipients. Therefore, the CHMP agreed on amendments of the section on special warnings and precautions for use of the SmPC. It is noted that the included wording is compliant with the Annex of the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'.

3. Benefit-risk balance

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, among other things, 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)) combined in the medicinal product.

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 NcWP and the PDCO responses provided in the context of the CMDh referral procedure, the CHMP considered that amendments were 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.

4. Risk minimisation measures

The CHMP considered that routine risk minimisation measures in the form of updates to the product information are necessary in order 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.

Section 4.2 of the SmPC is to be updated to specify that the maximum dose 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.

Section 4.3 of the SmPC is to be updated to include that the medicinal product is contraindicated in neonates in the indication of status epilepticus.

Section 4.4 of the SmPC is also to be updated to reflect the risks resulting from metabolic acidosis associated with the combination of the excipients that are all substrates of alcohol dehydrogenase (taking into account co-administration of other substrates), and to specify that paediatric patients less than 5 years of age are particularly vulnerable due to immature renal and metabolic capacity.

Further minor editorial amendments are implemented to ensure consistency in the SmPC.

The package leaflet is amended accordingly.

5. Grounds for 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.

To the extent that other 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 by the Member States, the CHMP recommends that the Member States concerned take due consideration of the scientific conclusions of this procedure.