LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bevione
(thiamine hydrochloride)

SE/H/2406/01/DC

This module reflects the scientific discussion for the approval of Bevione. The procedure was finalised on 2024-10-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bevione, 50 mg/mL, Solution for injection.

The active substance is thiamine hydrochloride, thiamine. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Bevione, 50 mg/mL, solution for injection, is a well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

For an application according to Article 10a, Well-Established Use (WEU), the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

Potential similarity with orphan medicinal products
Not applicable

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of thiamine hydrochloride are well known. As thiamine hydrochloride is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bevione is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Conclusions on studies:
The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, thiamine hydrochloride is not expected to pose a risk to the environment.

There are no objections to approval of Bevione provided that the level of impurities is satisfactory and in accordance with the ICH Q3B Guideline.

IV. CLINICAL ASPECTS

Pharmacokinetics
Absorption and distribution
Because of its essential function in the carbon metabolism thiamine is localised in all organs and tissues. It also passes the blood/brain-barrier. The liver contains the highest concentration of thiamine. In blood, 90% of thiamine is incorporated in blood cells, only 10% thiamine is localised in the serum where it is mainly bound to albumin. In blood and tissues, thiamine is present in its free form and in mono-, di- (pyro)-, and triphosphorylated forms, which are interconvertible.

Transport of thiamine into tissues requires, at low concentrations, an active transport mechanism. However, high concentrations of thiamine are absorbed into tissues by passive diffusion. There are two well-characterized transporter proteins that are specific for free thiamine and some of its analogues; these are designated ThTr1 and ThTr2, respectively. In the hepatocytes also OCT-1 is capable of transporting thiamine.

Metabolism and elimination
Thiamine is quickly converted to the diphosphate and to a smaller extent the triphosphate esters in the tissues. Excess thiamine and its metabolites are excreted in the urine. The level of unchanged thiamine in the urine increases as intake increases.

Special populations
The influence of renal and hepatic impairment on the pharmacokinetics of thiamine has not been evaluated. No dose adjustment is recommended, but caution is advised when treating these patients. The influence of age, gender, race and weight on the PK of thiamine has not been evaluated.

The lack of data is reflected in Section 5.2 of the SmPC.

Interactions
A very limited discussion has been provided, proposing 5-Fluorouracil (and his derivatives) as well as diuretics as interacting substances, without support of adequate original references. Still there are several reports of 5-FU and loop diuretic induced thiamine deficiency in the public domain and the issue not further pursued.

Pharmacokinetics discussion and overall conclusion
In a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. For iv and im formulations the Guideline on the Investigation of Bioequivalence issued by the Committee for Medicinal Products for Human use (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) states that bioequivalence studies are not required for aqueous solutions containing the same concentration active substance and comparable excipients as long as it can be demonstrated that these have no impact on viscosity. Bevione is an aqueous solution with 50 mg/mL thiamine hydrochloride and sodium hydroxide is the sole excipient, used to adjust the pH. The absence of a BE-study is therefore acceptable.

The basic ADME-properties of thiamine has been briefly described. Some reviews and summary documents have been included in the dossier and while original references are usually expected the occasional referring to more general documents is accepted due to the well-established knowledge of this endogenous vitamin. Several original references have been provided in support of key pharmacokinetic data.

Approval can be recommended from a pharmacokinetic point of view.

Pharmacodynamics
The mechanism of action of thiamine is well known and comprehensively described in the clinical overview.
The principal physiological role of thiamine is as a coenzyme in carbohydrate metabolism, where thiamine pyrophosphate (TPP) is required for several stages in the breakdown of glucose to provide energy. Thiamin is also essential for neurotransmitter production.

Clinical efficacy
The applicant has provided a comprehensive overview on the use of thiamine in treatment of thiamine deficiency of various origin. The overview adequately describes a well-established use of thiamine in these pathologies.
The indications applied for is beriberi and Wernicke-Korsakoff syndrome associated with alcohol use disorder.
In the overview of efficacy, beriberi is described as the classical form of thiamine deficiency.
Wernicke- Korsakoff syndrome (WKS) or Wernickes encephalopathy is another thiamine deficiency disease associated with alcohol abuse and a number of references are given supporting the use of thiamine for this condition.
In addition to the two indications applied for literature data is also provided showing efficacy for use in other conditions with thiamine deficiency, e.g neuro-sensory disorders and congenital heart failure. Thiamine deficiency can also be caused by malnutrition, bariatric surgery, refeeding and more.

As there are several aetiologies of thiamine deficiencies, and the medicinal product under assessment is a thiamine solution for injection, it is expected that it could be used to treat thiamine deficiency of any aetiology.

In the proposed SmPC from the first round prevention and treatment is mentioned. The wording ‘prevention of vitamin B1 deficiency’ in the indication could be misinterpreted that this product could be used for prevention of thiamine deficiency in the general population, when it should rather be used to prevent symptomatic thiamine deficiency in asymptomatic high-risk patients. The indication has been re-written to reflect that.

Thiamine is an established treatment for thiamine deficiency in patients with WKS. But it is clear from the literature data provided that there are no universally accepted guidelines with regard to the optimal dose to be used.
In the studies described in the clinical overview doses from a single dose of 100 mg to >500 mg two to three times a day are described. Even though it is stated that high-dose thiamine appears safe, there are also data showing no clear benefit of high doses over intermediate and low doses.
Considering that the active substance is a vitamin that has been used for decades with no apparent consensus regarding posology, it is deemed acceptable that treatment should be based on individual clinical assessment.
Rapid and adequate thiamine replacement is necessary to avoid worsening of symptoms or progression to largely irreversible brain damage. Given that absorption in the gut is a relatively slow process, parenteral administration is generally the only option in acute cases. In maintenance treatment however, oral supplementation is an acceptable alternative. This is reflected in the SmPC.
No literature data is available that suggest that dose adjustments are needed in elderly patients or in patients with hepatic or renal impairment.
From the data provided there seems to be limited experience in children and adolescents.

Clinical safety
The safety profile of thiamine is well known and thoroughly described in the overview with supportive literature data.

The main concerns are hypersensitivity and anaphylactic reactions, mainly after parenteral administration. Therefore, it is recommended that parenteral administration should only be used when essential and replaced by oral administration when possible. To reduce the risk of anaphylactic shock and reactions at the injection site intravenous injection must be administered slowly. In addition, emergency medical equipment for treating anaphylactic shocks must be available.

A contraindication is included in section 4.3 of the SmPC for hypersensitivity to the active substance or any of the excipients.

The proposed warnings in section 4.4 and description of adverse events in section 4.8 of the SmPC is supported by the submitted literature data.

Risk Management Plan
The MAH has submitted an updated risk management plan following the LoQ, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bevione.

Part II Safety specification

Summary of safety concerns	
Important identified risks	- None
Important potential risks	- None
Missing information	- None

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.
Issue resolved

The submitted Risk Management Plan, version 2.0 signed 27th of March 2024 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

A comprehensive overview with literature data on the use of thiamine in treatment of thiamine deficiency of various origin has been submitted. The overview adequately describes a well-established use of thiamine in these pathologies and supports the efficacy for the indications and doses in the SmPC.
The safety profile of thiamine is well known and thoroughly described in the overview with supportive literature data. An acceptable RMP has been submitted.

The benefit risk balance of this product is considered positive and it is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

Not applicable

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Not applicable

VII. APPROVAL

The decentralised procedure for Bevione, 50 mg/mL, solution for injection was positively finalised on 2024-10-01.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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