LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Kalciumklorid Abboxia
(calcium, calcium chloride dihydrate)

SE/H/2596/001/MR

This module reflects the scientific discussion for the approval of Kalciumklorid Abboxia. The procedure was finalised on 2024-11-19. 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 Kalciumklorid Abboxia, 0,46 mmol/ml, Solution for injection.

The active substance is calcium, calcium chloride dihydrate. 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.

I.1 General comments on the submitted dossier

The application for Kalciumklorid Abboxia, 0.46 mmol/mL, Solution for injection, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

For an application according to Article 10a, 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.

Potential similarity with orphan medicinal products
N/A

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 calcium chloride dihydrate are well known. As calcium chloride dihydrate is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. The overview based on literature review is, thus, appropriate. The Applicant provided brief but acceptable data to support that calcium chloride is not considered to be genotoxic.

In conclusion, the well-established use of the product and the long clinical experience compensate for the non-clinical shortcomings.

Environmental Risk Assessment (ERA)
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, calcium chloride dihydrate is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
In normal physiology, calcium metabolism is regulated through hormonal control of a three-tissue axis of intestine, kidney, and bone to tightly control serum ionized calcium within a narrow range.

For this intravenous formulation of calcium chloride the bioavailability is per definition 100 %. In the body calcium exists in the skeleton (99%) and body fluids (1%). The calcium in the body fluids can exist in three forms: ionized (~50%), protein-bound (~40% mainly to albumin) and complexed with other anions (~10%). Calcium does not undergo any direct metabolism. Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Limited information regarding the PK of calcium in special populations has been provided by the Applicant. This is considered acceptable for this calcium product for which the patient is closely monitored for serum levels and side effects by healthcare professionals. There are several known interactions with calcium and other products where the absorption from the GI-tract is affected. These are not relevant as this is an iv-product. The SmPC describes the relevant pharmacokinetic interactions.

In a WEU application establishing a link between the applied for product and the literature data used to support efficacy and safety is crucial. Considering that the product is an aqueous intravenous solution with no special excipients there is no need for a BE study. Comparability of the formulation to the formulations used in the literature was discussed in the quality section and considered sufficient.

The pharmacokinetics of calcium has generally been sufficiently described and the occasional referring to more general documents can be accepted for very basic information of this endogenous substance, for more specific SmPC claims adequate references have been provided.

Pharmacodynamics

The overview, with published data, gives an extensive and adequate description of the pharmacology of the well-known substance calcium chloride, including the mechanism of action and pharmacodynamic drug interactions.
The provided literature supports the proposed text in 5.1 of the SmPC.

Clinical efficacy
Bibliographic data has been provided to support the proposed indication, *Hypokalcemi, toxicitet av kalciumkanalblockerare, hypermagnesemi eller hyperkalemi.*

Several studies are summarised where calcium chloride has been used to treat hypocalcaemia, raise Ca2+ during normocalcaemic state or as prophylactic strategy. There is data from both children and adults. The data are from both studies with active comparator or placebo and from non-comparative studies.
The summaries provided support the efficacy of calcium chloride to elevate calcium levels and treat **hypocalcemia.**
It is acknowledged that the dose needed depend on the level of hypocalcaemia and that careful monitoring is recommended in the SmPC to avoid creating a hypercalcaemia instead.

The data provided gives a weak support for the use of calcium chloride in treatment of **calcium channel blockers overdose**. Many references are case reports or case series.
The case reports support efficacy, with the limitations of observations in single patients.
Taken together, the support is weak, but all references point in the same direction and there is a possible mechanism described in the literature. Doses are not discussed at all in the clinical overview, but from the references some doses could be found that was in line with the dose proposed in the SmPC.

No bibliographic data on robust large studies have been provided for **hypermagnesemia,** only a review and a case study. However, in both these references there are results showing efficacy in the treatment of effects of hypermagnesemia.
The dose from the review is in line with the dose proposed in the SmPC.

The support for the efficacy of calcium chloride in treatment of **hyperkalaemia** is very limited. Case reports mainly discuss dialysis and other treatments, and maybe calcium as one part of a treatment with many different substances.
For cardiac arrythmias following hyperkalaemia calcium iv is mentioned, but only anecdotal and animal data exist.
It is mentioned in the literature that calcium salts are widely recommended to stabilize the myocardial cell membrane, but that additional research is necessary to establish criteria for use, dosages and preferred solutions.

It is acknowledged from clinical experience that calcium chloride may be a part of the treatment of hyperkalaemia, but for an application according to well established use all claims should be supported by bibliographic data. The indication hyperkalaemia was further justified by additional references from the applicant including treatment recommendations (where further literature references could be found).

Clinical safety
Summaries of studies and other scientific literature have been provided for calcium chloride. The safety profile for calcium is well known and the specific issues for iv administration of calcium chloride has been described and supported by data.

For an application according to well-established use all claims should be supported by relevant bibliographic data. However, for this well-known substance some of the wordings are common clinical knowledge.

Pharmacovigilance system
Proposed MAH: Abboxia AB
The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

Risk Management Plan
The MAH has submitted a risk management plan, 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 Kalciumklorid Abboxia.

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 submitted Risk Management Plan, version 0.2 signed 01.10.2024 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 package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was Swedish.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bibliographic data has been provided to support the proposed indication, *Hypokalcemi, toxicitet av kalciumkanalblockerare, hypermagnesemi eller hyperkalemi.* The overview adequately describes a well-established use of calcium chloride for these indications and supports the efficacy for the indications and doses in the SmPC.

Summaries of studies and other scientific literature have been provided for calcium chloride. The safety profile for calcium is well known and the specific issues for iv administration of calcium chloride has been described and supported by data.

An acceptable RMP has been submitted.

The benefit risk balance of this product is considered positive.

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

N/A

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

N/A

VII. APPROVAL

Kalciumklorid Abboxia, 0,46 mmol/ml, Solution for injection was approved in the national procedure on 2024-11-19.

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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
SE/H/2596/001/MR	Initial Mutual Recognition Procedure	Yes	2025-04-28	Approval	N/A

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

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