LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Icalziss
(calcium chloride dihydrate)

SE/H/2455/01/DC

This module reflects the scientific discussion for the approval of Icalziss. The procedure was finalised on 2024-10-03. 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 Icalziss 340 mmol/L solution for infusion.

The active substance is 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.

The application for Icalziss 340 mmol/L solution for infusion is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK as concerned member states (CMS).

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.

The active substance is not considered a new active substance.

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, containing well-known active substances, no further studies are required, and Applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Icalziss 340 mmol/L solution for infusion 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, calcium chloride dihydrate is not expected to pose a risk to the environment.

There are no objections to approval of Icalziss 340 mmol/L solution for infusion from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
The pharmacokinetic properties of calcium provided via infusion of Icalziss 340 mmol/L solution for infusion are considered to be identical to those of calcium found endogenously in the systemic circulation and resulting from the physiological regulation of blood calcium.

A bridge to the products used in the literature used to support efficacy and safety is expected for a WEU application. For aqueous intravenous solutions containing the same active substance, BE-studies are not required according to the BE guideline unless there are excipients interacting with the drug substance (e.g. complex formation). In this case, the product applied for contains only water for injections as excipient, thus there is no excipient interacting with the active substance. The literature data referred to also concern intravenous administration of calcium, mainly as aqueous solutions of either calcium chloride or calcium gluconate. There is thus no need for a BE-study to provide a bridge between the product applied for and the literature. Any differences in composition and biopharmaceutical properties between the product applied for and the formulations used in the literature are not considered critical considering that the products are given intravenously, as long as instructions for administration and monitoring instructions for calcium, other electrolytes and pH are followed.

Pharmacodynamics
The product's primary pharmacological effects and mechanism of action align with calcium and chloride physiology. Differences in metabolism between calcium chloride and calcium gluconate, such as hyperosmolality and hyperchloremia associated with calcium chloride, are regarded as known aspects of clinical practice. This is particularly relevant during therapeutic plasma exchange (TPE) conducted without concomitant CRRT, when excess electrolytes are not dialysed.
Monitoring and adjusting systemic ionized calcium levels before, during and after CRRT or TPE with RCA and calcium substitution is necessary to minimize adverse events. Adjustments for specific patient categories is considered as part of prescribers clinical management.

Clinical efficacy
The product benefits from over 20 years of clinical use of calcium chloride solutions. The efficacy of Icalziss (340 mmol/L) is comparable to other calcium chloride replacement solutions.

Adult population
The bibliography includes critically ill ICU patients with one or more organ failures. Hence, comorbidities are expected to contribute to complications, adverse events with a substantial overall mortality rate. RCTs support the different CRRT modalities — continuous venovenous hemofiltration [CVVH], continuous venovenous hemodialysis [CVVHD] and continuous venovenous hemodiafiltration [CVVHDF]. RCA-CRRT as non-inferior compared to no anticoagulation or heparin with longer filter lifespan, lower rates of bleeding and transfusions. The incidences of adverse events due to electrolyte and metabolic disturbances were low. Additional observational studies support efficacy and include patients with comorbidities and high risk of bleeding due to general surgery, cardiac surgery or trauma. In addition, dosing protocols in different patient categories and under various circumstances are improved in supportive studies. Efficacy for calcium chloride substitution during Therapeutic Plasma Exchange is supported.

Pediatric population
Efficacy is supported in all pediatric age groups and CRRT modalities, CCVH, CVVHD and CVVHDF are represented.

The efficacy for therapeutic plasma exchange (TPE) in children is based on observational studies. Due to the rarity of the indication, large-scale studies are not anticipated. As TPE is frequently a lifesaving intervention, the available data are considered sufficient to support efficacy for the indication outlined in SmPC Section 4.1 for children above 1 year of age. Additionally, the combination of the presented studies and extrapolation from older children supports the efficacy of TPE in children below 1 year of age or with a body weight under 10 kg.

The final wording of 4.1 are as follows:

> *Icalziss is indicated for calcium replacement during extracorporeal therapies with Regional Citrate Anticoagulation (RCA) provided during Continuous Renal Replacement Therapy (CRRT) and Therapeutic Plasma Exchange (TPE), either as single treatment or in combination.*
>
> *Icalziss is indicated in adults and children of all ages (above 8 kg)*

With a clarifying in section 4.2 as follows:

> *The weight limit of >8 kg in the indication is not due to the safety or efficacy characteristics of the medicinal product but is based on the characteristics of the monitoring devices offered by the marketing authorisation holder*.

Information to ensure safe administration in the paediatric age groups are provided in the SmPC section 4.2 – 4.4.

Clinical safety
Patients undergoing RCA-CRRT and/or TPE are critically ill, which inherently increases the risk of serious adverse events. The indication and risks must always be carefully assessed weighted against each other.

During CRRT/TPE with RCA, calcium is chelated to the citrate complexes which is lost in the effluent. Monitoring of ionized and total calcium serum levels aim to maintain calcium concentration within a physiological range to avoid serious complications related to hypo- and hypercalcemia and to prevent citrate accumulation. Other electrolyte disturbances should be monitored as needed.

The information in the SmPC section 4.3 – 4.9 are described and supported by relevant references.

For pediatric population, see details above.

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 Icalziss.

Summary of Safety specification
from RMP Part II: Module SVIII Version 0.3 Issued 11 Sep 2024.

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
From the RMS perspective the submitted Risk Management Plan, version 0.3 signed 11 sept 2024 is 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 PlL was English. 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

The benefit for calcium replacement during RCA CRRT is valid for all ages. Bibliographic data has been provided to support the proposed indications: calcium replacement during extracorporeal therapies with Regional Citrate Anticoagulation (RCA) provided during different modalities of Continuous Renal Replacement Therapy (CRRT) and Therapeutic Plasma Exchange (TPE), either as single treatment or in combination.

Icalziss is indicated in adults and children of all ages (above 8 kg).

Efficacy is supported in all age groups for CRRT and TPE, even though the documentation for TPE in pediatric patients aged < 1 year or with a body weight < 10 kg documentation is sparse and extrapolation from older children is needed.

Safe use and risk limitation should be ensured with altogether adequate information for administration, dosage, monitoring and risk management in the SmPC, sections 4.2 – 4.4.
No literature support for the risk of increased osmolality due to calcium chloride substitution was identified in the literature, but the physiological risk is now sufficiently addressed, as well as the risk for hyperosmolality.

The applicants' amendment regarding the weight limit of 8 kg is related to the applicant's monitoring device and not to quality aspects of the product, and in order to avoid confusion among prescribers and administrating HCP it is accepted with a justification and clarifying amendment in 4.2.

An acceptable Risk Management Plan has been submitted.

Furthermore, the provided quality documentation is considered acceptable.

The benefit/risk 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

The decentralised procedure for Icalziss 340 mmol/L solution for infusion was positively finalised on 2024-10-03.

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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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