

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Icalziss 340 mmol/L solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Calcium Chloride dihydrate 50 g/l

Calcium, Ca⁺⁺ 340 mmol/l

Chloride, Cl⁻ 680 mmol/l

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

The solution is clear and colourless.

Theoretical osmolarity: 1020 mOsm/l

pH ≈ 5.5 – 7.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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

4.2 Posology and method of administration

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.

Posology

Icalziss should be administered as prescribed by a physician experienced in citrate anticoagulation for specific treatment with CRRT and/or TPE.

This medicine is used as a calcium replacement solution and must be administered through a separate central venous access line or through the return-line of the extracorporeal blood circuit.

Do not add supplementary medication.

Administration rate must be adjusted to maintain systemic ionized calcium levels in the normal physiological range between 1.0 – 1.3 mmol/L to avoid complications associated with hypocalcaemia or hypercalcaemia. Systemic ionized calcium level must not fall below 0.9 mmol/L.

Monitoring of the post-filter blood ionized calcium (iCa), systemic blood iCa, and total blood calcium levels in conjunction with other laboratory and clinical parameters are essential to guide appropriate Icalziss dosage based on the desired level of anticoagulation during extracorporeal therapies with RCA.

Systemic ionized calcium levels should be evaluated at baseline, during the first hour of therapy initiation or dose adjustment until stable, and then at least every 6 hours. Monitoring the systemic total calcium levels every 12 to 24 hours is recommended.

The amount of calcium chloride required to maintain systemic ionized calcium levels within the desired range depends on a number of factors, such as:

- The amount of calcium required to compensate the effects of citrate entering the systemic circulation and patient's citrate metabolism
- The calcium concentration in the replacement fluid
- Any calcium present in other medications / infusions the patient is taking (e.g., calcium in total parenteral nutrition)

- Any intended change of the baseline systemic calcium concentration
- Any impact on the patient's ionized calcium concentration by other medicinal interventions (e.g., chemotherapy, radiation therapy)
- Other medical conditions that may predispose the patient to hypocalcaemia or hypercalcaemia (e.g., hypoparathyroidism, hyperparathyroidism, malignancy, liver failure, rhabdomyolysis, severe pancreatitis, post-tumour lysis, and toxic shock syndromes)

When determining the appropriate amount of calcium replacement during CRRT, several factors must be considered, such as:

- Prescribed flow rates, especially the effluent flow rate
- Adherence to a standardized protocol or algorithm, which simplifies and facilitates the prescription for calcium replacement and helps decrease errors and variability
- Filter membrane permeability for calcium and calcium-citrate complexes

Adult and adolescent population:

In RCA-CRRT a typical calcium dose is 1.7 mmol per Liter of effluent volume (4-6 mmol/h) for adults and adolescents.

A maximum dose of 340 mmol of calcium per day is recommended, which is equivalent to 1 L of Icalziss. This medicine is not intended for chronic use.

Paediatric population:

The recommended dosage of Icalziss for neonates and children (0 to 11 years and above 8 kg) is similar to adults and adolescents.

The maximum hourly calcium infusion rate to body weight ratio is 0.3 mmol/h/kg, which is equivalent to a maximum hourly volume infusion rate of 0.88 ml/h/kg. Due to the generally lower prescribed effluent flows in children, correspondingly lower absolute flows of this medicine will result. Protocols developed for the smallest age groups should be carefully designed based on the context for the local facilities.

Method of administration

Adjust or stop calcium infusion according to physician's prescription when citrate anticoagulation is stopped.

Infuse only with an extracorporeal blood purification device intended for the infusion of calcium chloride solution and includes an appropriate balance of flow volumes.

Infuse only into the extracorporeal circuit or, if recommended in the instructions for use of the extracorporeal blood purification device, via a separate central venous access. Icalziss is not intended for intramuscular or subcutaneous use.

The instructions for use from the manufacturer of the extracorporeal blood purification device, from the manufacturer of the extracorporeal circuit set and the intravenous line must be followed.

4.3 Contraindications

- Hypercalcaemia (see section 4.4).
- Hyperchloremia (see section 4.4).
- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- Concomitant administration of calcium-containing solutions and ceftriaxone is contraindicated in premature neonates and neonates (≤ 28 days of age), due to the risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream, even if separate infusion lines are used (see sections 4.5 and 6.6).

4.4 Special warnings and precautions for use

Cardiovascular effects

Administration of digitalis glycosides after calcium chloride can lead to potentially life-threatening digitalis-induced cardiac arrhythmias. Patients intoxicated with or treated with digitalis glycosides may show signs of digitalis overdose after the application of calcium containing solutions.

Icalziss may be administered to patients intoxicated with or being treated with cardiac glycosides for the treatment of severe, immediate life-threatening symptoms of hypocalcaemia if safer alternatives are not available, and an oral administration of calcium is not possible (see section 4.5).

This medicine should be used with caution in patients treated with digitalis-glycosides, and patients at risk for cardiac arrhythmias. Avoid intravenous calcium administration, or if necessary, administer in small amounts to avoid transient serum calcium levels higher than 7.5 mmol/L.

Patient calcium levels and intracellular calcium dynamics in cardiac cells have been identified as contributors for life threatening arrhythmias. Calcium administration should be carefully monitored according to baseline cardiovascular risks. Increased systemic calcium levels reaching the heart may increase the risk of cardiac syncope.

Electrolyte and Acid-Base Balance

Electrolyte and acid-base balance should be monitored and regularly controlled during citrate-anticoagulated extracorporeal blood purification treatments. Pre-existing hypocalcaemia, hypercalcaemia and hyperchloremia must be corrected prior to initiating the treatment. Alternatively, the adapted use of low-chloride infusion solutions may be considered.

Careful monitoring is required especially for hyperosmolality and hyperchloremia in patients undergoing RCA TPE therapy.

The risk for pH disturbances associated with hyperchloremia is increased in paediatric population.

Calcium Monitoring

Serum ionized calcium concentrations should be regularly monitored during administration of calcium chloride. The ratio of ionized calcium and total calcium should be monitored to assess citrate accumulation, this occurs when the ratio becomes > 2.25 (see section 4.2). If hypocalcaemia or hypercalcaemia occur during treatment, adjust dose of Icalziss accordingly. If treatment duration is prolonged or if citrate-anticoagulated treatments are repetitively applied, parathyroid hormone levels and other parameters of bone metabolism should also be evaluated.

Renal Calculi

Calcium chloride may increase the risk of symptomatic renal stones.

Extravasation

Intravenous administration of calcium salts may cause extravasation. Regularly inspect the infusion site for signs of extravasation. In the event of extravasation and infiltration, discontinue intravenous administration immediately. Regularly inspect the site of infusion for signs of locally developing clotting when Icalziss is being infused into the extracorporeal circuit, and if seen, a change of circuit should be considered.

Calcium or Citrate Metabolism and Excretion

Conditions affecting calcium or citrate metabolism and excretion may include, but are not limited to, nephrocalcinosis, hypercalciuria, cancer, hyperparathyroidism, hypoparathyroidism, rhabdomyolysis, and liver failure must be carefully considered when prescribing Icalziss. Dose adjustments may be needed and blood calcium levels should be carefully monitored.

After discontinuation of CRRT, a calcium rebound can be expected due to calcium release from the calcium-citrate complexes. Conditions affecting citrate metabolism may impact this effect. This medicine should be used with caution in patients with conditions affecting calcium metabolism and excretion.

Ceftriaxone treatment

In patients of any age, ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions even via different infusion lines or different infusion sites (see section 4.5 for details and 6.2).

Hypothermia

Moderate hypothermia, characterized by a body temperature of 30-34°C, can lead to intracellular calcium overload. Administration of Icalziss during hypothermic conditions may exacerbate hypercalcaemia.

Use only if the solution is clear and free from visible particles.

4.5 Interaction with other medicinal products and other forms of interaction

Additional applications of calcium due to other infusion solutions or medicinal products need to be considered for dosing.

Patients under treatment with digitalis glycosides may present with symptoms of digitalis overdose after the administration of solutions containing calcium (see section 4.4).

Medicinal products containing vitamin D and other vitamin D analogues can increase the risk of hypercalcaemia, and can result in a reduced anticoagulation effect.

Administration of Icalziss and calcimimetics, such as etelcalcetide and cinacalcet, can induce hypocalcaemia. It is recommended to consider withdrawing calcimimetics during treatment.

In patients of any age, ceftriaxone must not be mixed or administered simultaneously with any calcium-containing intravenous solutions even via different infusion lines or different infusion sites (see section 6.2).

Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described (see section 4.3).

However, in patients older than 28 days of age ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.

Sequential infusions of ceftriaxone and calcium-containing products must be avoided in case of hypovolaemia.

Thiazide diuretics decrease urinary calcium excretion. Caution is therefore required if such drugs are administered with this medicine.

The blood concentration of filterable/dialysable drugs may be reduced during treatment due to their removal by the extracorporeal filter. Corresponding corrective therapy should be instituted, if necessary, to establish the desired blood concentrations for drugs removed during treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or a very limited amount of data on the use of calcium chloride in pregnant patients. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Icalziss is not recommended during pregnancy unless there is a clear medical need of RCA, CRRT or TPE.

Breast-feeding

Calcium is excreted in breast milk. However, at therapeutic doses of Icalziss no effects on the breastfeeding child are anticipated. This medicine can be used during breast-feeding if the clinical condition of the mother allows so.

Fertility

There are no human data available regarding effects on fertility.

4.7 Effects on ability to drive and use machines

Icalziss is not known to affect your ability to drive or use machines.

4.8 Undesirable effects

Undesirable effects can result from the Icalziss. Special precautions for use have been described in section 4.4.

The following undesirable effects have been described in published literature: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

The following side effects may be triggered by treatment with this medicine (the exact frequency of such side effects is not known):

Metabolism and nutrition disorders	- Hypervolaemia or hypovolaemia - Hypercalcaemia due to Icalziss overdose or at adequate dose. If this occurs, calcium build-up as a result of inefficient blood purification due to membrane occlusion should be considered (see section 4.4) - Hypocalcaemia due to Icalziss underdose or at adequate dose. If this occurs, citrate accumulation should be considered (see section 4.4) - Metabolic acidosis or alkalosis <u>Other electrolyte imbalance (i.e. hypokalaemia, hypophosphatemia and hyperchloremia)</u>
Vascular disorders	Hypotension

The following side effects can be expected for the treatment method:

Injuries, poisonings and treatment complications

- Infusion site irritation and extravasation may occur when administration of Icalziss via routes other than intended (i.e., infusion into the extracorporeal circulation or central venous infusion). Symptoms may be burning, necrosis, tissue death, cellulitis and soft tissue calcification.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Rapid or excessive administration of Icalziss may lead to hypercalcaemia (total plasma concentration >3 mmol/L, ionized calcium >1.3 mmol/L, respectively), which must be corrected as medically appropriate.

Emergency measures, countermeasures

Immediately stop or reduce the administration of this medicine if signs or symptoms of hypercalcaemia are noticed. In cases of severely elevated calcium levels, an urgent reduction of calcium levels must be undertaken. If adequate renal function is maintained, a forced diuresis with concomitant infusion of isotonic sodium chloride solution (9 mg/mL NaCl) should be considered with strict monitoring of fluid balance and plasma electrolyte concentrations. In patients with renal impairment, dialysis with calcium-free dialysate may be considered.

Signs and symptoms of hypercalcaemia include:

- Nervous system disorders, e.g., lethargy, disorientation, hyporeflexia
- Cardiac disorders, e.g., tachycardia and tendency to develop cardiac arrhythmia, hypertension, changes in the electrocardiogram (shortening of QT-interval)
- Gastrointestinal disorders, e.g., nausea, vomiting, constipation, tendency to develop ulcers
- Renal and urinary disorders, e.g., increased diuresis, thirst, aquaresis, renal deposition of calcium salts
- General disorders, e.g., fatigue

Rapid administration of calcium salts may also lead to chalky taste, tingling, hot flushes, peripheral vasodilation with hypotension, bradycardia, syncope and arrhythmia with a possibility of cardiac arrest.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Electrolyte solutions, calcium chloride

ATC code: B05XA07

Icalziss is a solution administered intravenously. It is intended to be used as a calcium replacement during regional citrate anticoagulation (RCA) in continuous renal replacement therapies (CRRT) and therapeutic plasma exchange (TPE), either as single treatment or in combination.

As the fifth most abundant element in the body, calcium is essential for the functional integrity of the nervous and muscular systems and for normal cardiac contractility. It also functions as an enzyme cofactor and affects the secretory activity of endocrine and exocrine glands. Serum total calcium levels range from 8.8 – 10.4 mg/dL (2.2 – 2.6 mmol/L) in healthy subjects. It comprises free ions (approximately 51%), protein-bound complexes (approximately 40%), and ionic complexes (approximately 9%).

When the serum concentration of calcium falls below of the normal range, hypocalcaemia ensues which initially manifests as neuromuscular irritability that can escalate to renal and cardiac complications. Calcium also plays a prominent role in the chemical reactions involved with blood coagulation.

5.2 Pharmacokinetic properties

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

Renal excretion of calcium is affected by normal or abnormal physiologic changes (e.g., changes in parathyroid hormone level, renal failure) and other drugs classes (e.g., vitamin D, thiazide diuretics) (see section 4.4 and section 4.5).

During RCA-CRRT, calcium excretion depends mainly on losses of citrate-calcium complexes through the filter. When CRRT is discontinued, due to renal recovery, calcium excretion occurs primarily in the urine.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. See section 6.6 for further instructions on the use of the product with additives.

6.3 Shelf life

Shelf life as packaged: 18 months.

In-use shelf life: 72 hours after the overwrap is removed.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

The product bag is a flexible plastic container fabricated from a multilayer sheeting composed of Polypropylene (PP), Polyamide (PA) and Polyethylene (PE).

The port system for the product bag is composed of an administration port made of high-density polyethylene, which allows access to the bag content, and a non-accessible medication port, which prevents the addition of medication. The administration port will only drip once the spike is introduced through the administration port.

Each filled bag contains 500 ml of Icalziss and is enclosed in a clear overpouch made of a co-extruded Polypropylene (PP) and Polyamide (PA) film.

Pack size: 20 x 500 ml in a box

6.6 Special precautions for disposal and other handling

The following instructions for use shall be followed:

Aseptic technique should be used throughout the handling and administration to the patient.

This medicine should be inspected visually for particulate matter and discoloration prior to administration. Do not administer unless the solution is clear and colorless, and the seal is intact. In case of damage, the container should be discarded.

Remove the overwrap from the bag immediately before use. As soon as the overwrap is removed, Icalziss must be used within 72 hours. Press bag firmly to test for any leakage. If leakage is discovered, discard the solution immediately since sterility can no longer be assured. The solution should be used immediately after bag opening to avoid microbiological contamination.

Calcium chloride solution has shown to be incompatible with solutions containing inorganic phosphate, carbonates, tetracycline antibiotics, ceftriaxone and others.

In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions through the same infusion line (e.g., via Y-connector). If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid.

Remove plastic protector from outlet port at bottom of container. Grip the small wing on the neck of the port with one hand. Grip the large wing on the cap with the other hand and twist. The cap will pop off.

Introduce the spike through the rubber septum. Refer to the directions of the set for connection. Verify that the fluid is flowing freely.

Do not reconnect partially used containers. The solution is for single use only. Discard any unused portion. If not used according to Instructions for Use, the in-use storage times and conditions are the responsibility of the user.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The solution can be disposed of via wastewater without harming the environment.

7 MARKETING AUTHORISATION HOLDER

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Boulevard D'Angleterre 2
Braine-L'Alleud
1420
Belgium

8 MARKETING AUTHORISATION NUMBER

PA25288/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2026