SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Calrecia, 100 mmol/l, solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calrecia is provided in a bag with 1500 ml ready-to-use solution.

1000 ml solution contain:

Calcium chloride dihydrate14.7 g

Ca^{2+}	100 mmol
Cl^{-}	200 mmol

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
The solution is clear and colourless and practically free from particles.

Theoretical osmolarity: 300 mOsm/l

pH:	5.0 – 7.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Calrecia is used for calcium substitution in continuous renal replacement therapies (CRRT), sustained low efficiency (daily) dialysis (SLEDD) and therapeutic plasma exchange (TPE) using citrate for anticoagulation.

Calrecia is indicated in adults and children.

4.2 Posology and method of administration

Application of Calrecia should take place only based on the prescription of a physician familiar with citrate anticoagulation in the specific mode of CRRT, SLEDD and TPE.

Posology

Adults

Calrecia is applied in an amount adequate to keep the systemic ionised calcium concentration in the desired range. If not otherwise prescribed, the normal range for systemic ionised calcium should be targeted. The target range must not be below 0.9 mmol/l systemic ionised calcium.

The amount of Calrecia needed to keep the systemic ionised calcium concentration within the desired range depends on:

- Calcium removed during CRRT, SLEDD and TPE.
- The amount of calcium required to compensate effects of citrate reaching the systemic circulation, which can originate from the citrate solution used for regional anticoagulation or from plasma preparations used as substitution solution in TPE.
- Calcium shifts between the plasma and other compartments of the patient's body.
- Any intended change of the baseline systemic calcium concentration.
- Any impact on patient's ionised calcium concentration by other medicinal interventions.

When estimating the calcium removal during CRRT, SLEDD and TPE, the prescriber has to take into account:

- Permeability of the filter membrane for calcium and calcium-citrate complexes
- The calcium concentration in any applied fluid during CRRT, SLEDD and TPE such as dialysis fluids, haemofiltration solutions or substitution solutions used in TPE
- Prescribed blood flow and all other prescribed fluid flows during the therapy; this includes specifically the effluent flow, i.e. the fluid discarded from the extracorporeal circuit with which calcium is eliminated. In CRRT a typical calcium dose is 1.7 – 1.8 mmol/l effluent.

Dosing of Calrecia needs to be controlled by regularly measuring the systemic ionised calcium. Based on these controls, adjustments of the flow of Calrecia need to be made in order to reach the targeted range of systemic ionised calcium.

A maximum dose of 3 l/d is recommended and no chronic use is intended.

Paediatric population

The posology of Calrecia in children is the same as in adults. Due to the generally lower prescribed effluent flows in children, correspondingly lower absolute flows of Calrecia will result.

Method of administration

- Infusion only by a pump of the extracorporeal blood purification device, which is intended by its manufacturer for infusion of a 100 mmol/l calcium chloride solution and comprises an appropriate balancing of fluid volumes.
- Infusion only into the extracorporeal blood circuit or, if advised by the instruction for use of the extracorporeal blood purification device, via a separate central venous access. Calrecia is not intended for intramuscular or subcutaneous use.
- Handling instructions of the manufacturer of the used extracorporeal blood purification device and of the tubing line must be adhered to.

For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypercalcaemia (see section 4.4)
- Hyperchloremia (see section 4.4)

4.4 Special warnings and precautions for use

Calcium chloride infusion should be used with caution in patients treated with Digitalis-Glycosides. In patients considered at risk to develop cardiac arrhythmia, continuous monitoring of the electrocardiogram should be considered during citrate anticoagulation and calcium infusion (see section 4.5).

Comorbidities affecting calcium metabolism and calcium excretion such as but not limited to nephrocalcinosis, hypercalciuria and overdose of vitamin D should carefully be considered when prescribing Calrecia. Dose adaptations might be required and blood calcium levels should be closely monitored. Pre-existing hypercalcaemia should be considered by reducing initial calcium infusion rate and close monitoring of blood calcium levels. Pre-existing hypocalcaemia should be corrected prior to starting citrate anticoagulation. Pre-existing hyperchloremia might be corrected by adequate dialysis conditions; alternatively adjusted application of chloride-poor infusion solutions can be considered.

The precautions during use of the applied extracorporeal blood purification therapy must be adhered to. The electrolyte and acid-base balance must be regularly controlled during citrate-anticoagulated extracorporeal blood purification treatments. When infused into the extracorporeal circuit, the site of Calrecia infusion should regularly be inspected for signs of locally developing clotting and if observed a change of the extracorporeal circuit should be considered.

During the application of Calrecia, the serum ionised calcium concentration must be regularly checked. The calcium status of the patient and its trend during blood purification therapy must be considered. If hypocalcaemia is present or tends to develop, starting or increasing the supplementation of calcium may be required. If hypercalcaemia is present or tends to develop (e.g. caused by accumulation of calcium due to inefficient blood purification resulting from a clogged membrane or due to overdose) decreasing the supplementation of calcium may be required. Hypocalcaemia and an unexpectedly high need of Calrecia infusion to stabilise the systemic ionised calcium in the desired range might be caused by citrate accumulation: Citrate anticoagulation mostly will result in a moderate increase of the systemic citrate concentration and of systemically present calcium-citrate chelate complexes. In case of impaired citrate metabolism, citrate accumulation can result. A ratio of systemic total calcium to systemic ionised calcium above 2.25 can be a sign of clinically relevant citrate accumulation and strategies to reduce the systemic citrate exposure should be evaluated or a complete stop of the citrate anticoagulated extracorporeal blood purification treatment should be considered. In addition to monitoring systemic ionised calcium, monitoring of parathyroid hormone levels and other parameters of bone metabolism should be considered, specifically if treatment duration is prolonged (i.e. longer than 2 weeks) or citrate-anticoagulated treatments are repetitively applied.

After the stop of the citrate anticoagulated extracorporeal blood purification treatment, citrate metabolism will continue and calcium released from calcium-citrate chelate complexes might lead to ionised hypercalcaemia.

Calcium chloride injection is irritating to the veins and must not be injected into tissues, since severe necrosis and sloughing may occur. Great care should be taken to avoid extravasation or accidental infusion into perivascular tissues. In case of perivascular infiltration, intravenous administration at that site should be discontinued at once. Uncontrolled infusion must be avoided (i.e. use a pump dedicated for calcium infusion) to minimise risks related to dosing inaccuracy.

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.

No other substance or solution must be added to Calrecia. In case Calrecia is applied not via the extracorporeal circuit but via a separate central venous catheter, the respective catheter lumen must not be used for any other infusion in parallel. Of note, calcium chloride solution has been demonstrated to be incompatible with various other solutions containing, e.g. inorganic phosphate, carbonates, tetracycline antibiotics, ceftriaxone and others.

Patients treated with Digitalis glycosides may show signs of Digitalis overdose after application of calcium containing solutions (see section 4.4).

Thiazide diuretics decrease urinary calcium excretion. Caution is therefore required if such drugs are administered with both calcium chloride and other calcium-containing preparations.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of calcium chloride in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Calrecia is not recommended during pregnancy unless the clinical condition of the woman requires CRRT, SLEDD or TPE.

Breastfeeding
Calcium is excreted in human milk, but at therapeutic doses of calcium chloride no effects on the breastfed newborns/infants are anticipated. Calrecia can be used during breast-feeding unless no other concern arises from the clinical condition of the mother.

Fertility
No human data on the effect of calcium chloride on fertility are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following adverse reactions can be anticipated for the treatment mode:
General disorders and administration site conditions
- Hypothermia

Metabolism and nutrition disorders
- Hyper- or hypohydration
- Hypercalcaemia at a dose of Calrecia considered appropriate. In this case, accumulation of calcium due to inefficient blood purification resulting from a clogged membrane should be considered (see section 4.4)

- Hypocalcaemia due to underdosing of Calrecia. In this case, citrate accumulation related to the use of citrate anticoagulation for CRRT, SLEDD and TPE should be considered (see section 4.4)
- Metabolic acidosis or alkalosis
- Other electrolyte disturbances (e.g. hypokalaemia, hypophosphataemia)

Vascular disorders
- Hypotension.

The following undesirable effects have to be considered specifically related to the application of Calrecia:
Injury, poisoning and procedural complications
- Application of Calrecia via other than the intended routes (i.e. infusion into the extracorporeal circuit or central venous infusion). In this context irritation at the site of infusion can occur. Extravasation can cause burning, necrosis and sloughing of tissue, cellulitis and soft tissue calcification

Metabolism and nutrition disorders
- Hypercalcaemia due to overdose of Calrecia (see section 4.9).

The exact frequency of such events is not known (cannot be estimated from the available data).

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 Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Rapid or excessive administration of calcium salts may lead to hypercalcaemia (total plasma concentration >3 mmol/l, ionised calcium > 1.2 mmol/l, respectively). Too rapid injection of calcium salts may also lead to the signs and symptoms of hypercalcaemia as well as chalky taste, tingling, hot flushes, nausea, vomiting and peripheral vasodilation with hypotension, bradycardia, syncope and arrhythmia with a possibility of cardiac arrest.

Signs and symptoms of hypercalcaemia
- 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.

Hypercalcaemic crisis (plasma total calcium concentration > 4 mmol/l) results in vomiting, colic, intestinal atony, intestinal obstruction, generalised asthenia, disturbance of consciousness, initially increased diuresis, subsequently often diminished or completely absent.

Therapy
Immediate stop or dose reduction of Calrecia.
Particularly in cases of excessively increased calcium levels an acute reduction of calcium levels is mandatory, therefore in case of still sufficient renal function forced diuresis with concomitant infusion of normal saline solution (0.9% NaCl) should be considered under stringent supervision of fluid balance and plasma electrolyte concentrations. In patients with impaired renal function, dialysis against calcium-free dialysate can be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Electrolyte solutions, calcium chloride
ATC code: B05XA07
Solution for calcium substitution in CRRT, SLEDD and TPE using regional citrate-anticoagulation.

Basic principles of extracorporeal blood purification and regional citrate anticoagulation e.g. CRRT, SLEDD and TPE
Extracorporeal blood purification therapies are applied for various indications, for instance CRRT, SLEDD and TPE. These therapies have in common that blood is taken from the patient's blood circulation and is guided through an extracorporeal circuit. There the blood is purified from toxins, the type of which varies between the different extracorporeal blood purification therapies. After the blood has been purified, it is re-transfused into the patient's blood circulation.
Extracorporeal blood purification techniques usually require anticoagulation to prevent clotting in the extracorporeal circuit. Depending on the patient´s status and the intended extracorporeal blood purification therapy, the prescribing physician might have decided to apply regional citrate anticoagulation. In this case, citrate is infused into the blood taken from the patient where it forms soluble chelate complexes with ionized calcium and thereby reduces the ionized calcium concentration in the blood flowing through the extracorporeal circuit.

Depending on the individual citrate-anticoagulated extracorporeal blood purification therapy, calcium is extracted from the patient's blood in variable quantity which makes calcium substitution necessary. Further, a part of the citrate infused for regional citrate anticoagulation unavoidably enters the patient's systemic circulation with the re-transfused blood. This induces an increase of the systemic citrate concentration, which generally stabilises at a new level depending on the actual citrate infusion rate and the citrate metabolism in the liver and other tissues. In the extracorporeal circuit citrate binds ionised calcium and reduces the systemic ionised calcium concentration, which can be counteracted by calcium substitution.

Calcium-citrate chelate complexes present in the patient's blood dissociate when more citrate is metabolised than systemically infused. As a net effect, free ionised calcium remains in the patient's blood and thereafter redistributes in the patient's body where it is essential both for bone remodelling and as an electrolyte with crucial cellular functions throughout the body (e.g. in muscle cells and neurons).

5.2 Pharmacokinetic properties

Calrecia has to be administered by a pump of the extracorporeal blood purification device, which is intended to be used for calcium infusion.

Distribution/ Biotransformation/ Elimination
As the therapeutic purpose of Calrecia of calcium substitution in CRRT, SLEDD and TPE employing regional citrate anticoagulation is limited to stabilise the calcium in the patient's blood at physiological levels, the pharmacokinetic properties of calcium provided via infusion of Calrecia are considered to be identical to those of calcium found endogenously in the systemic circulation and resulting from the physiological regulation of blood calcium.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber.

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. For substances known to be incompatible with calcium refer also to section 4.5.

6.3 Shelf life

2 years

Shelf life after opening: The content must be used immediately.

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Solution bag with 1500 ml ready-to-use solution.

The medicinal product is provided pairwise, as two identical solution bags which can be separated by a tear seam. The solution bag is made of a polyolefine based foil. Each bag is equipped with connective tubing made of polyolefines and a connector made of polycarbonate and is covered by a protective multilayer foil.

Pack sizes
8 bags of 1500 ml

6.6 Special precautions for disposal

Disposal
The solution is for single use only. Any unused solution and damaged container should be discarded.

Handling

The following points prior to the use of the solution bag have to be considered:

1. Separate the two bags at the tear seam.
2. Remove the overwrap only immediately before using the solution. Check the solution bag (label, expiry date, clearness of the solution, bag and overwrap not damaged).
   Plastic containers may occasionally be damaged during transport from the manufacturer to the dialysis clinic or hospital clinic or within the clinic itself. This can lead to contamination and the growth of bacteria or a fungus in the solution. Therefore careful inspection of the bag and the solution before use is essential. Particular attention should be paid to even the slightest damage to the closure of the bag, the welding seams and the corners of the bag. The solution should only be used if colorless and clear and if the bag and connector are undamaged and intact.
3. Put the bag on the dedicated attachment by its hanger hole.
4. For connection remove the protection cap from the connector. The connector only fits to its counterpart to prevent misconnection. Do not touch the unprotected part especially do not touch on top of the connector. The inner part of the connector is sterile and is not intended to be further treated with chemical disinfectants. Put together the connector with the appropriate counterpart and press together until you can turn it clockwise against the resistance to the stop point. You may hear a “click” sound when the connection is fixed.
5. Proceed with the further steps as indicated in the treatment description.

The solution is not intended to be used for the addition of any drugs and not intended to be used for peripheral intravenous infusion. See also section 4.2.

7 MARKETING AUTHORISATION HOLDER

Fresenius Medical Care Deutschland GmbH,
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.H.,
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL13689/0026

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