SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Calcium gluconate 5% w/v Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 0.0475 g calcium gluconate as monohydrate, equivalent to 0.106 mmol of calcium.

Each 10 mL ampoule contains 0.475 g calcium gluconate as monohydrate equivalent to 1.06 mmol of calcium.

Excipient with known effect: The product also contains an amount of the excipient calcium saccharate equivalent to 0.0056 mmol calcium per mL (or 0.056 mmol calcium per 10 ml).

Total calcium content: 0.1115 mmol per mL (1.115 mmol per 10 mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear, colourless to pale yellow aqueous sterile solution, with a pH between 6 and 8.2, practically free from particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral administration of calcium is indicated where the pharmacological action of a high calcium ion concentration is required, as for example, in acute hypocalcaemia, and some cases of neonatal tetany.

Intravenous injections of calcium have been used in the treatment of the acute colic of lead poisoning. Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding the treatment of symptoms of acute lead poisoning.

Calcium gluconate 5% w/v Solution for injection/infusion is used in the treatment of acute fluoride poisoning. Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding treating patients with this condition.

4.2 Posology and method of administration

The normal concentration of calcium in plasma is within the range of 2.25-2.75 mmol or 4.5-5.5 mEq per litre. Treatment should be aimed at restoring or maintaining this level.

During therapy, serum calcium levels should be monitored closely.

Posology

Acute hypocalcaemia

Adults

The usual initial dose in adults is 20 mL of Calcium gluconate 5% w/v Solution for injection/infusion, corresponding to 2.23 mmol or 4.46 mEq of calcium. If necessary, the dose may be repeated, depending on the patient's clinical condition. Subsequent doses should be adjusted according to the actual serum calcium level.

Paediatric patients (< 18 years)

The dose and the route of administration depend on the degree of hypocalcaemia and the nature and severity of the symptoms. In the case of mild neuromuscular symptoms oral calcium administration should be preferred.

Age	**mL / kg body weight (bw)**
3 months	0.8-1.8
6 months	0.6-1.4
1 year	0.4-1.0
3 years	0.8-1.4
7.5 years	0.4-0.8
12 years	0.2-0.6
> 12 years	As for adults

In cases of severe symptoms of hypocalcaemia in neonates or infants, e.g. cardiac symptoms, higher initial doses (up to 4 mL per kg bw, □ 0.45 mmol calcium per kg bw) may be necessary for a quick restoration of a normal serum calcium level.

Also, if necessary, the dose may be repeated, depending on the patient's clinical condition. Subsequent doses should be adjusted according to the actual serum calcium level.

Intravenous therapy should be followed by oral administration if indicated, e.g. in cases of calciferol deficiency.

Elderly patients

Although there is no evidence that tolerance of Calcium gluconate 5% w/v Solution for injection/infusion is directly affected by advanced age, factors that may sometimes be associated with ageing, such as impaired renal function and poor diet, may indirectly affect tolerance and may require a reduction in dosage. Renal function declines with age and prior to prescribing this product to elderly patients it should be considered that Calcium gluconate 5% w/v Solution for injection/infusion is contraindicated (See section 4.3) in severe renal failure. See also section 4.4.

Neonatal tetany

Intravenous administration of 5% calcium gluconate as a bolus of 100 – 200 mg calcium gluconate / kg bw (2-4 mL / kg bw) over approximately 10-20 minutes, followed by a continuous infusion (0.5 – 1 g calcium gluconate / kg bw / d) over 1 – 2 days.

Heart rate should be monitored during the infusion.

The IV site should also be watched closely because tissue infiltration by a calcium solution is irritating and may cause local tissue damage or necrosis.

Acute colic of lead poisoning

Adult and paediatric patients (< 18 years)

Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding the treatment of symptoms of acute lead poisoning.

Fluoride poisoning

Adult and paediatric patients (< 18 years)

Advice should be sought from specialist centres (National Poisons Information Service, tel: 111) regarding treating patients with this condition.

Calcium gluconate regime for hypocalcaemia in fluoride poisoning:

Immediate:

- give 20 mL of 5% calcium gluconate intravenously on presentation, repeat at 1 hour, or

- give 60 mL of 5% calcium gluconate intravenously if tetany present.

Maintenance:

- Maintain serum calcium with intravenous 5% calcium gluconate 20 mL every 4 hours, adjusting according to frequent serum calcium concentrations.

Mild to moderate dermal toxicity due to hydrofluoric acid/fluoride exposure:

Subcutaneous calcium gluconate (5%) for dermal exposure of hydrofluoric acid > 20%.

- Infiltrate each square centimeter of the exposed area with 0.5 mL of 5% calcium gluconate.

In the case of significant burn due to hydrofluoric acid/fluoride exposure, calcium salts may be administered intravenously (for systemic toxicity) or intra-arterially (for hand burns predominantly).

- 20 mL of 5% calcium gluconate plus heparin 5000 units in a total volume of 40 mL is administered intravenously.

- 20 mL of 5% calcium gluconate in 50 mL of 0.9% sodium chloride solution is intra-arterially infused over 4 h.

Hypocalcaemia during transfusion

Adults

Calcium should be administered during massive transfusion if Ca^{2+} concentration is low, in order to preserve normocalcaemia.

20 mL of Calcium gluconate 5% w/v Solution for injection/infusion IV diluted in 100 mL D5W (5% Glucose in water), given over 10 min or 20-40 mL Calcium gluconate 5% w/v Solution for injection/infusion for each 500 mL of blood infused.

Pediatric patients (< 18 years)

During transfusion / exchange transfusion the patient's clinical condition and the calcium serum concentration have to be monitored, and a clinically significant hypocalcaemia should be treated according to dosing recommendations for acute hypocalcaemia.

Method of administration

The patient should be in the lying position and should be closely observed during injection. Monitoring should include heart rate or ECG.

Extravasation must be avoided; the injection site should be monitored carefully.

Adults

Slow intravenous injection.

For the intramuscular route, if intravenous injection is not possible, only the 10% w/v solution should be used.

The intravenous administration rate should not exceed 4 mL (0.0.45 mmol of calcium) per minute.

Paediatric patients (<18 years)

Only slow intravenous injection or intravenous infusion (both after dilution), in order to achieve sufficiently low administration rates and to avoid irritation/necrosis in case of accidental extravasation. The intravenous administration rate should not exceed 5 mL of a 1:5 dilution per minute (see section 6.6) of Calcium gluconate 5% w/v Solution for injection/infusion in children and adolescents.

Acute fluoride poisoning

In case of finger injuries in acute fluoride poisoning, a volume of 0.5 ml Calcium gluconate 5% w/v Solution for injection/infusion per phalanx should not be exceeded.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

This product is contraindicated in severe renal failure, hypercalcaemia (e.g. in hyperparathyroidism, hypervitaminosis D, neoplastic disease with decalcification of bone), severe hypercalciuria, and in patients receiving cardiac glycosides (see also sections 4.4 and 4.5).

Simultaneous administration of Calcium gluconate 5% w/v Solution for injection/infusion and ceftriaxone in patients of any age (see section 4.4) is contraindicated.

Calcium gluconate 5% w/v Solution for injection/infusion must not be co-administered with ceftriaxone in:

- premature newborns up to a corrected age of 41 weeks (weeks of gestation + weeks of life),
- full-term newborns (up to 28 days of age)

because of the risk of precipitation of ceftriaxone-calcium (see section 4.4, 4.8 and 6.2)

4.4 Special warnings and precautions for use

Plasma calcium levels and calcium excretion should be monitored when calcium is administered parenterally, especially in children, in chronic renal failure or where there is evidence of calculi formation within the urinary tract. If plasma calcium exceeds 2.75 mmol per litre or if 24 hour urinary calcium excretion exceeds 5 mg / kg, treatment should be discontinued immediately as cardiac arrhythmias may occur at these levels. Also see section 4.3.

In the exceptional case of intravenous administration of calcium gluconate to patients receiving cardiac glycosides, adequate cardiac monitoring is mandatory and emergency treatment of cardiac complications such as serious arrhythmias must be available.

Intravenous injections should be accompanied by heart rate or ECG control because bradycardia with vasodilatation or arrhythmia can occur when calcium is administered too quickly.

Renal impairment may be associated with hypercalcaemia and secondary hyperparathyroidism. Therefore, in patients with renal impairment, parenteral calcium should be administered only after careful assessment of the indication and the calcium-phosphate balance should be monitored.

Calcium salts should be used with caution in patients with nephrocalcinosis. Care is also required in patients with cardiac disease.

Calcium salts should only be used with caution and after careful establishment of the indication in patients with sarcoidosis (Boeck's disease), in patients receiving epinephrine (see section 4.5).

Calcium salts are irritant. The infusion site must be monitored regularly to ensure extravasation injury has not occurred.

Calcium gluconate is physically incompatible with many other compounds (see section 6.2). Care should be taken to avoid admixture of calcium gluconate and incompatible medicinal products in giving sets, or in the circulation after separate administration. Serious complications, including fatalities, have occurred following microcrystallisation of insoluble calcium salts in the body following separate administration of physically incompatible solutions or total parenteral nutrition solutions containing calcium and phosphate.

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. At least one of them had received ceftriaxone and calcium at different times and through different intravenous lines. In the available scientific data, there are no reports of confirmed intravascular precipitations in patients, other than newborns, treated with ceftriaxone and calcium-containing solutions or any other calcium-containing products. *In vitro* studies demonstrated that newborns have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups.

In patients of any age ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites.

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. (see sections 4.3, 4.8, and 6.2).

Calcium is insoluble in adipose tissue and may therefore cause infiltration and subsequent abscess formation, tissue induration and necrosis.

Extravasation must be avoided; the injection site should be monitored carefully.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac glycosides

The effects of digoxin and other cardiac glycosides may be accentuated by calcium and digitalis intoxication may be precipitated. Therefore, this product is contraindicated in patients receiving cardiac glycosides (see also sections 4.3 and 4.4).

Thiazide diuretics

There is increased risk of hypercalcaemia with thiazides.

Epinephrine

Co-administration of calcium and epinephrine attenuate epinephrine's β-adrenergic effects in postoperative heart surgery patients (see section 4.4).

Magnesium

Calcium and magnesium mutually antagonise their effects.

Calcium antagonists

Calcium may antagonise the effect of calcium antagonists (calcium channel blockers).

Interaction with ceftriaxone

See sections 4.4 and 6.2.

Physical incompatibilities

See section 4.4 (Special warnings and precautions for use) and section 6.2 (Incompatibilities).

4.6 Fertility, Pregnancy and lactation

Pregnancy

Calcium passes the placental barrier and its concentration in fetal blood is higher than in maternal blood. Calcium gluconate should be used during pregnancy only if considered to be essential by the physician. The administered dose should be carefully calculated, and serum calcium levels regularly evaluated in order to avoid hypercalcaemia, which may be deleterious to the fetus.

Lactation

Calcium is excreted in breast milk and this should be borne in mind when administering calcium to women who are breast-feeding their infants. A decision must be made whether to discontinue breast-feeding or to discontinue <*Calcium gluconate*> therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable effects

The frequency of undesirable effects listed below is defined using the following convention:

Very common ≥1/10

Common ≥1/100 to <1/10

Uncommon ≥1/1,000 to <1/100

Rare ≥1/10,000 to <1/1,000

Very rare < 1/10,000

Not known: Frequency cannot be estimated from the available data

Vascular and other systemic undesirable effects are likely to occur as symptoms of acute hypercalcaemia resulting from intravenous overdose or too rapid intravenous injection. Their occurrence and frequency is directly related to the administration rate and the administered dose.

Vascular disorders

Not known: Hypotension, circulatory collapse (possibly fatal), flushing, mainly after too rapid injection.

Cardiac disorders

Not known: bradycardia, cardiac arrhythmia.

Gastrointestinal disorders

Not known: Nausea, vomiting.

General disorders and administration site conditions

Not known: Heat sensations, sweating

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases fatal, adverse reactions have been reported in preterm and full-term newborns (aged < 28 days) who had been treated with intravenous ceftriaxone and calcium.

Precipitations of ceftriaxone-calcium salt have been observed in lung and kidneys *post-mortem*. The high risk of precipitation in newborns is due to their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3 and 4.4).

Adverse reactions only occurring with improper administration technique:

Not known: Soft tissue calcification due to extravasation of calcium solutions has been reported.

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

4.9 Overdose

Excessive administration of calcium salts leads to hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, polydipsia, polyuria, mental disturbances, bone pain, nephrocalcinosis, renal calculi and if severe, cardiac arrhythmias and coma.

Severe hypercalcaemia should be treated with infusion of sodium chloride, intravenously, to expand the extracellular fluid volume. This may be given with or followed by furosemide to increase calcium excretion. If this treatment is unsuccessful, other medicinal products which may be used include calcitonin, bisphosphonates, disodium edetate and phosphates. Haemodialysis may be considered as a last resort. During treatment of overdose, serum electrolytes should be monitored carefully.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: mineral supplements, calcium gluconate.

ATC code: A12AA03

Calcium is an essential body electrolyte. It is necessary for the functional integrity of nerve and muscle and is essential for muscle contraction, cardiac function and coagulation of the blood.

Calcium homeostasis is mainly regulated by three endocrine factors: parathyroid hormone is secreted in response to a fall in plasma calcium concentration and acts by accelerating calcium transfer from bone and by increasing its intestinal absorption and its renal reabsorption; calcitonin lowers plasma calcium by decreasing bone resorption and by increasing renal excretion of the ion; vitamin D stimulates intestinal absorption of calcium and decreases its renal excretion.

The cytoplasmic concentration of calcium is normally maintained at very low levels of about 0.1-1.0 μmol per litre by the extrusion of calcium from the cell and by its sequestration within cellular organelles, particularly the endoplasmic reticulum (called the sarcoplasmic reticulum, in muscle fibres). Various electrical or chemical stimuli trigger the influx of calcium ions across the plasma membrane or release of the ion from cellular stores. These calcium ions interact with high-affinity binding sites on specific intracellular proteins, such as troponin, and thus regulate a number of functional and metabolic processes.

Calcium ions are essential for normal function of the neuromuscular apparatus. Hypocalcaemia causes a decrease in the threshold for excitation, resulting in tetany. Hypercalcaemia increases the threshold for excitation of nerve and muscle, leading to muscle weakness and lethargy. Calcium ions are necessary for muscle contraction. By binding to troponin, calcium removes the inhibitory effect of troponin on the interaction of actin and myosin.

Calcium ions also play an important role in stimulus-secretion coupling in most exocrine and endocrine glands.

Calcium ions are essential for normal excitation-contraction coupling in cardiac muscle, and for the conduction of electrical impulses in certain regions of the heart, especially through the Av node. The initiation of contraction in vascular and other smooth muscle is also dependent on calcium ions.

These cardiac and vascular smooth muscle effects can be opposed by various calcium-channel blocking drugs in the treatment of angina, hypertension and cardiac arrhythmias.

Calcium ions are also involved in both the intrinsic and extrinsic pathways of blood coagulation.

5.2 Pharmacokinetic properties

Distribution

After injection the administered calcium shows the same distribution behaviour as the endogenous calcium. About 50% of the total plasma calcium is in the physiologically active ionised form, about 40% is bound to proteins, mainly albumin, and 10% is complexed with anions.

Biotransformation

After injection the administered calcium adds to the intravascular calcium pool and is handled by the organism in the same manner as the endogenous calcium.

Elimination

Calcium is excreted mainly in the urine with some faecal loss. Urinary excretion is the net result of the quantity filtered and the amount reabsorbed. The tubular reabsorption of calcium is enhanced by Vitamin D and by parathyroid hormone, whereas calcitonin increases the urinary excretion of calcium ions. Calcium is also excreted in saliva, bile, pancreatic juice, sweat and breast milk.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium saccharate (0.18 % w/v)

Water for Injections

6.2 Incompatibilities

Calcium salts can form complexes with many ingredients of medicinal products, and this may result in a precipitate (See section 4.4). Calcium salts are incompatible with oxidising agents, citrates, soluble carbonates, bicarbonates, phosphates, tartrates and sulphates. Physical incompatibility has also been reported with amphotericin, cephalothin sodium, cephazolin sodium, cephamandole nafate, ceftriaxone, novobiocin sodium, dobutamine hydrochloride, prochlorperazine, and tetracyclines.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After dilution

When diluted to 10 mg per mL, according to directions, with the recommended infusion fluids, sodium chloride 9 mg / mL (0.9%) solution for injection or 50 mg / mL (5%) glucose solution for injection, physical in-use stability has been demonstrated for 48 hours at 23 °C – 27 °C and 2 °C – 8 °C.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 48 hours at 23 °C – 27 °C or 2 °C – 8 ° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene ampoules of 10 mL. Packed in cartons to contain 10, 20 or 50 ampoules x 10 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Handling

The product is intended for single use only. Discard any unused solution.

The medicinal product should be visually inspected for particulate matter or discoloration. The solution should only be used if it is clear, colourless to pale yellow aqueous solution, practically free from particles.

Dilution

For intravenous infusion, Calcium gluconate 5% w/v Solution for injection/infusion may be diluted 1:5 to a concentration of 10 mg calcium gluconate / mL with the following two infusion fluids: sodium chloride 9 mg / mL (0.9%) solution for injection or 50 mg / mL (5%) glucose solution for injection. When diluted with these recommended infusion fluids, the resulting solutions are intended for immediate single use. Dilution should be performed under controlled and validated aseptic conditions. After mixing, the container should be gently agitated to ensure homogeneity.

Use as directed by a physician.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 55035/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/01/2024

10 DATE OF REVISION OF THE TEXT