SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Calcium Gluconate 10 % w/v Injection BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 94 mg calcium gluconate as active ingredient, equivalent to 0.21 mmol calcium.
10 ml contain 940 mg calcium gluconate as active ingredient, equivalent to 2.10 mmol calcium.

Excipients: The product also contains an amount of the excipient calcium D-saccharate tetrahydrate equivalent to 0.02 mmol calcium per ml (or 0.15 mmol calcium per 10 ml).

Total calcium content: 0.23 mmol per ml (2.25 mmol per 10 ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to light brown aqueous solution, practically free from particles.
Theoretical osmolarity: 660 mOsm/l
pH: 5.5 – 7.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of acute symptomatic hypocalcaemia.
- Treatment of acute severe hyperkalaemia with or without ECG changes, as an emergency treatment aiming to reduce cardiac cell excitability (cardioprotective effect) while other measures to lower potassium levels are instituted.
- Cardiac arrest only due to severe hyperkalaemia.

4.2 Posology and method of administration

The normal concentration of calcium in plasma is within the range of 2.25 – 2.62 mmol per litre. Treatment should be aimed at restoring this level. During therapy, serum calcium levels should be monitored closely.

Posology

Treatment of acute symptomatic hypocalcaemia

Adults

The usual initial dose in adults is 10 ml of Calcium Gluconate 10 % w/v Injection BP, corresponding to 2.25 mmol 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.

The following table gives usual **initial** dosage values for guidance:

Age	ml/kg
3 months	0.4 – 0.9
6 months	0.3 – 0.7
1 year	0.2 – 0.5
3 years	0.4 – 0.7
7.5 years	0.2 – 0.4
12 years	0.1 – 0.3
> 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 2 ml per kg body weight, 0.45 mmol calcium per kg body weight) 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.

Treatment of acute severe hyperkalaemia with or without ECG changes

Adults

Acute severe hyperkalaemia with or without ECG changes (serum potassium concentration above 6.5 mmol/L).
30 ml of Calcium Gluconate 10 % w/v Injection BP (corresponding to 6.69 mmol calcium) administered undiluted as a slow intravenous injection over 10 minutes.
Further doses can be considered after 5 minutes, if needed, until ECG improvement is achieved.

Paediatric population

The dose regimen for cardiac arrest should be followed.

Treatment of cardiac arrest due to hyperkalaemia

Treatment should be tailored to the individual patient. The onset of action of intravenous calcium gluconate is within three minutes. With a relatively short duration of action (30 – 60 minutes) further doses may be necessary if hyperkalaemia remains uncontrolled.

Adults
30 ml of Calcium Gluconate 10 % w/v Injection BP (corresponding to 6.69 mmol calcium) administered undiluted as a rapid intravenous injection.
Further doses can be repeated if return of spontaneous circulation is not achieved within 5-10 minutes, or if the resuscitation attempt is prolonged.

Paediatric population
Neonates (0 to 27 days)
0.5 ml/kg body weight of Calcium Gluconate 10 % w/v Injection BP (corresponding to 0.11 mmol calcium/kg body weight) administered undiluted (in the case of emergency) as a slow intravenous injection over 5-10 minutes.
The dose should be given centrally whenever possible. If no central access is available, the dose should be diluted with sodium chloride 0.9% to five times the volume.
The dose can be repeated if ECG changes persist after 5-10 minutes following administration of the first dose.

Children (28 days to < 18 years)
0.5 ml/kg of body weight of Calcium Gluconate 10 % w/v Injection BP (corresponding to 0.11 mmol calcium/kg body weight) by slow intravenous injection over 5-10 minutes.
In the case of emergency, Calcium gluconate 10 % w/v Injection BP can be administered undiluted via central IV access.
The dose can be diluted to 50 ml with sodium chloride 0.9% over 10 minutes.
The dose can be repeated if ECG changes persist after 5-10 minutes following administration of the first dose.
In children with a body weight ≥ 20 kg a maximum recommended dose of 20 ml of Calcium Gluconate 10 % w/v Injection BP (corresponding to 4.46 mmol calcium) can be given.

Elderly patients
Although there is no evidence that tolerance of calcium gluconate injection 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.

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.

Adults
Intravenous use or intramuscular use. Because of the risk of local irritation, deep intramuscular injections should only be performed if slow intravenous injection is not possible.
Care should be taken to administer the intramuscular injections sufficiently deep intramuscular, preferably into the gluteal region (see sections 4.4 and 4.8).
In the case of adipose patients a longer needle will have to be chosen for safe positioning of the injection into the muscle and not into adipose tissues.
If repeated injections are necessary, the injection site should be changed every time.
According to the NHS guideline for the treatment of hypocalcaemia in adults the intravenous administration rate should not exceed 2 ml (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 1:10 dilution per minute (see section 6.6) of Calcium Gluconate 10% B. Braun in children and adolescents.
Intramuscular injections should not be performed in paediatric patients.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypercalcaemia (e.g. in patients with hyperparathyroidism, hypervitaminosis D, decalcifying malignancies, renal insufficiency, immobilisation osteoporosis, sarcoidosis, milk-alkali syndrome)
- Hypercalciuria
- Intoxication with cardiac glycosides
- Therapy with cardiac glycosides.
  The only exception may be that intravenous calcium administration is imperative for treatment of severe hypocalcaemia symptoms or acute severe hyperkalaemia putting the patient at immediate vital risk, if safer therapeutic alternatives are not available and calcium administration via the oral route is not possible (see sections 4.4 and 4.5).
- Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in premature neonates and neonates (≤ 28 days of age). Ceftriaxone should not be used in premature neonates and neonates (≤ 28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products.

4.4 Special warnings and precautions for use

Special warnings

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 (see also sections 4.2, 4.3 and 4.5). Calcium Gluconate 10% solution for injection/infusion should be administered slowly (in 100 ml glucose 5% over 20 minutes). Rapid calcium administration may precipitate myocardial digoxin toxicity therefore other methods e.g. haemodialysis should also be considered after consultation with specialists.

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

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 gluconate and calcium chloride are presented in 10 ml ampoules at 10% (w/v) for injection but are **not equivalent** in calcium content:
- 10 ml of Calcium Gluconate 10 % w/v Injection BP contains 2.23 mmol calcium
- 10 ml of calcium chloride 10% solution contains 6.8 mmol of calcium

The difference in calcium content should be accounted for to achieve the correct calcium dose when using either salt to avoid medication errors.

Patients receiving ceftriaxone

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.

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.

Calcium Gluconate 10% solution for injection/infusion must not be mixed with or administered through the same intravenous line as sodium bicarbonate (sometimes used for treatment of severe hyperkalaemia) due to the risk of precipitation.

Precautions for use

Solutions containing calcium should be administered slowly to minimise peripheral vasodilation and cardiac depression.

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.

In paediatic patients, Calcium Gluconate 10 % w/v Injection BP should not be injected intramuscularly but only slowly intravenously.

Patients receiving calcium salts should be monitored carefully to ensure maintenance of correct calcium balance without tissue deposition.

Plasma levels and urinary excretion of calcium should be monitored when high-dose parenteral calcium is administered.

Calcium Gluconate 10 % w/v Injection BP should not be injected in adipose tissue as calcium is insoluble in adipose tissue and may cause infiltration and subsequent abscess formation, tissue indurations and necrosis.

After perivascular or superficial intramuscular injection local irritation, possibly followed by skin ablation or tissue necrosis, may occur (see section 4.8). Extravasation must be avoided; the injection site should be monitored carefully.

High Vitamin D intake should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Cardiac glycosides
The effects of digoxin and other cardiac glycosides may be potentiated by calcium, which may result in serious toxicity. Therefore, intravenous administration of calcium preparations to patients under therapy with cardiac glycosides is contraindicated. The only exception may be that intravenous calcium administration is imperative for treatment of severe hypocalcaemia symptoms or acute severe hyperkalaemia putting the patient at immediate vital risk, if safer therapeutic alternatives are not available and calcium administration via the oral route is not possible (see sections 4.3 and 4.4).

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).

Thiazide diuretics
Combination with thiazide diuretics may induce hypercalcaemia as these medicinal products reduce renal calcium excretion.

Physical incompatibilities including interaction with ceftriaxone and sodium bicarbonate
See sections 4.4 and 6.2.

4.6 Fertility, pregnancy and lactation

Pregnancy

Calcium passes across the placental barrier and its concentration in foetal blood is higher than in maternal blood.

Calcium Gluconate 10%w/v Injection BP should not be used during pregnancy unless the clinical condition of the woman requires treatment with Calcium Gluconate 10%w/v Injection BP. The administered dose should be carefully calculated, and the serum calcium level regularly evaluated in order to avoid hypercalcaemia, which may be deleterious for the foetus.

Breast-feeding

Calcium is excreted in breast milk. 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/abstain from Calcium Gluconate 10%w/v Injection BP therapy

taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

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.

Cardiovascular 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.

Cardiac disorders

Not known: Bradycardia, cardiac arrhythmia

Vascular disorders

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

Gastrointestinal disorders

Not known: Nausea, vomiting

General disorders and administration site conditions

Not known: Heat sensations, sweating

Not known: Intramuscular injection may be accompanied by pain sensations or erythema.

Ceftriaxone-calcium salt precipitation

Rarely, severe, and in some cases, fatal, adverse reactions have been reported in pre-term and full-term neonates (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 neonates is a result of their low blood volume and the longer half-life of ceftriaxone compared with adults (see sections 4.3, 4.4, and 6.2).

***Adverse reactions only occurring with improper administration technique*:**

If intramuscular injection is not performed sufficiently deep intramuscularly, infiltration into the adipose tissue may occur with subsequent abscess formation, tissue induration, and necrosis.

Calcinosis cutis, possibly followed by skin ablation and necrosis, due to extravasation, has been reported.

Reddening of skin, burning sensation or pain during intravenous injection may indicate accidental perivascular injection, which may lead to tissue necrosis.

Reporting of suspected adverse reactions
Reporting of 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.

4.9 Overdose

Symptoms
Symptoms of hypercalcaemia may include: anorexia, nausea, vomiting, constipation, abdominal pain, polyuria, polydipsia, dehydration, muscle weakness, bone pain, renal calcification, drowsiness, confusion, hypertension and, in severe cases, cardiac arrhythmia up to cardiac arrest, and coma.

If intravenous injection is too rapid, symptoms of hypercalcaemia may occur as well as a chalky taste, hot flushes and hypotension.

Emergency treatment, antidotes
Treatment should be aimed at lowering the elevated plasma calcium concentration.

Initial management should include rehydration and, in severe hypercalcaemia, it may be necessary to administer sodium chloride by intravenous infusion to expand the extracellular fluid. Calcitonin may be given to lower the elevated serum calcium concentration. Furosemide may be administered to increase calcium excretion but thiazide diuretics should be avoided as they may increase renal absorption of calcium.

Haemodialysis or peritoneal dialysis may be considered where other measures have failed and where the patient remains acutely symptomatic. Serum electrolytes should be carefully monitored throughout treatment of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions affecting the electrolyte balance, electrolytes.
ATC code: B05BB01.

Calcium is the most abundant mineral in the human organism (approx. 1.5 % of the entire body weight). More than 99% of the body's total calcium are located in bones and teeth, approx. 1% are dissolved in intra- and extracellular fluid.

Calcium is necessary for the functional integrity of nerves and muscles. It is essential for the muscle contraction, cardiac function and blood coagulation.

The physiological level of the plasma calcium concentration is maintained at 2.25 – 2.62 mmol/l. As about 40-50% of the plasma calcium is bound to albumin, total plasma calcium is coupled to the plasma protein concentration. The concentration of ionised calcium lies between 1.23 and 1.43 mmol/l, regulated by calcitonin and parathormone.

Hypocalcaemia (total calcium below 2.25 mmol/l or ionised calcium below 1.23 mmol/l, respectively) may be caused by renal failure, vitamin D deficiency, magnesium deficiency, massive blood transfusion, osteoblastic malignant tumours, hypoparathyroidism, or intoxication with phosphates, oxalates, fluorides, strontium or radium.

Hypocalcaemia may be accompanied by the following symptoms: increased neuromuscular excitability up to tetany, paraesthesia, carpopedal spasms, spasms of smooth muscles e.g. in the form of intestinal colic, muscle weakness, confusion, cerebral convulsive seizures and cardiac symptoms like prolonged QT interval, arrhythmia and even acute myocardial failure.

The therapeutic effect of parenteral calcium substitution is normalisation of pathologically low serum calcium levels and thus relief of the symptoms of hypocalcaemia.

Hyperkalaemia

In acute severe hyperkalaemia (with or without ECG changes) which is defined as a serum potassium concentration above 6.5 mmol/L in adults, calcium is given to reduce the threshold potential of cardiac cells by restoring the normal gradient with the resting potential that has been increased with the elevated potassium levels. Calcium does not affect potassium levels.

5.2 Pharmacokinetic properties

Distribution

After injection the administered calcium shows the same distribution behaviour as the endogenous calcium. About 45-50% of the total plasma calcium is in the physiologically active ionised form, about 40-50% is bound to proteins, mainly albumin, and 8-10% 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

Excretion of calcium occurs in the urine although a large proportion undergoes renal tubular reabsorption.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium-D-saccharate tetrahydrate
Water for injections

6.2 Incompatibilities

Calcium salts can form complexes with many drugs and this may result in a precipitate.

Calcium salts are incompatible with oxidising agents, citrates, soluble carbonates, bicarbonates, oxalates, phosphates, tartrates and sulphates.

Physical incompatibility has also been reported with amphotericin, cephalothin sodium, ceftriaxone (see section 4.4), cephazolin sodium, cephamandole nafate, 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 or unless compatibility has been satisfactorily demonstrated.

6.3 Shelf life

Unopened
3 years

After dilution
When diluted to 10mg/ml, according to directions, with the recommended infusion fluids (i.e. sodium chloride 9mg/ml (0.9%) solution for injection or 50mg/ml (5%) glucose solution for injection) physical in-use stability has been demonstrated for 48 hours at room temperature.

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 24 hours at 2 to 8ºC, 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

10ml LDPE ampoules packed in cardboard box.

Pack size: 20 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Disposal

No special requirements 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, discoloration and the integrity of the container prior to use.

The solution should only be used if it is clear, colourless to light brown aqueous solution, practically free from particles and the container is undamaged.

Dilution

For intravenous infusion, Calcium Gluconate 10% w/v Injection BP may be diluted 1:10 to a concentration of 10mg/ml with the following two infusion fluids: sodium chloride 9mg/ml (0.9%) solution for injection or 50mg/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.

7 MARKETING AUTHORISATION HOLDER

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