B BRAUN

Calcium Gluconate B. Braun 10% Solution for injection

1. NAME OF THE MEDICINAL PRODUCT

Calcium Gluconate B. Braun 10% solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Other constituent material with known effect: The product also includes the component calcium-D-saccharat-Tetrahydrate in a quantity that corresponds 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).

Complete list of other constituent material, see section **6.1**.

3. DOSAGE FORM

Solution for injection
Clear, colourless to light brown watery solution, practically particle-free.

Osmolarity (theoretical):	660 mosm/l
pH:	5.5 - 7.5

4. CLINICAL PARTICULARS

4.1 Areas of application

Treatment of acute symptomatic hypocalcaemia.

4.2 Dosage and method of use

The normal concentration of calcium in the plasma is in the range of 2.25 - 2.62 mmol per litre. The treatment should aim at restoring these plasma calcium levels. During treatment, serum calcium levels should be monitored closely.

Dosage

Adults:
The usual starting dose for adults is 10 ml Calcium Gluconate B. Braun 10% solution for injection, corresponding to 2.25 mmol calcium. If necessary, the dose can be repeated depending on the clinical condition of the patient. The level of subsequent doses varies in accordance with the current serum calcium concentration.

Adolescents and children (< 18 years):
Dose and type of application varies according to the degree of hypocalcaemia, as well as the type and severity of symptoms. Oral administration of calcium is preferable in cases of mild neuromuscular symptoms.

See table

This is roughly equivalent to:

Infants, toddlers, and children

<4 years
- 0.4-1 ml/kg body weight
  (≙ 0.09 – 0.23 mmol calcium per kg body weight) for infants, toddlers and children up to 3 years.

The following table shows common values for the **initial dose**:

Age	Body weight (kg)	ml	Corresponds to mmol calcium
3 months	5.5	2 - 5	0.45 – 1.13
6 months	7.5	2 - 5	0.45 – 1.13
1 year	10	2 - 5	0.45 – 1.13
3 years	14	5 - 10	1.13 – 2.25
7.5 years	24	5 - 10	1.13 – 2.25
12 years	38	5 - 10	1.13 – 2.25
> 12 years	> 38	as for adults	

In cases of severe hypocalcaemic symptoms in new-borns and infants, as for example with cardiac symptoms, higher initial doses may be required to achieve a quick normalization of serum calcium levels (up to 2 ml per kg body weight, ≙0.45 mmol calcium per kg of body weight).

Children from > 4 to 12 years old
- 0.2 - 0.5 ml/kg body weight
  (≙ 0.05 – 0.11 mmol calcium per kg body weight) for children aged 4-12.

Young people > 12 years
In patients over 12 years of age, use the same dosage as adults.

If necessary, the dose can be repeated depending on the clinical condition of the patient. The level of subsequent doses varies in accordance with the current serum calcium concentration.

Where appropriate, a subsequent treatment with oral calcium can be indicated after intravenous therapy, such as in cases of Calciferol deficiency.

Elderly patients:
Although there is no indication that advanced age has a direct impact on the compatibility of Calcium Gluconate, factors that sometimes accompany ageing can indirectly affect the compatibility, such as impairment of kidney function and malnutrition, making a reduction in dose necessary.

Type of application
The patient should lie down and be carefully monitored during the injection. Monitoring should include monitoring the heart rate or ECG monitoring.

Adults
Intravenous or intramuscular application
Because of the risk of local tissue irritation, deep intramuscular injections should only be performed if a slow intravenous administration is not possible. It is important to ensure that intramuscular injections are given at a sufficient depth in the muscle, preferably in the gluteal region (see sections 4.4 and 4.8).
In obese patients, a longer cannula should be selected in order to safely position the injection in muscle and not in fat.
The injection site should be changed each time for further injections.

According to the NHS guidelines on treatment of hypocalcaemia in adults, the intravenous injection rate should not exceed 2 ml (0.45 mmol calcium) per minute.

Adolescents and children (< 18 years)
Only slow intravenous injections or infusions should be given (both after dilution), to achieve sufficiently low feed rates and to avoid tissue irritation or necrosis as a result of accidental extravasation. In children and adolescents, the intravenous feed rate should not exceed 5 ml per minute (see section 6.6) of a 1:10 diluted Calcium Gluconate B. Braun 10% solution.
Intramuscular injections should be avoided in paediatric patients.

4.3 Contra-indications

- Hypersensitivity to the active substance or any of the other components referred to in section 6.1,
- Hypercalcaemia (for example in patients with over functioning of the parathyroid glands, vitamin D hypervitaminosis, decalcifying malignant diseases, renal failure, osteoporosis by immobilization, sarcoidosis, milk-alkali syndrome)
- Hypercalciuria,
- Poisoning with cardiac glycosides,
- Treatment with cardiac glycosides, with the sole exception of a compelling indication for an intravenous calcium application 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 also sections 4.4 and 4.5).
- The concomitant administration of ceftriaxone and IV calcium-containing products is contraindicated in immature neonates and new-borns (< 28 days old). Ceftriaxone should not be administered to immature neonates and new-borns (< 28 days old) if they receive calcium-containing intravenous products (or are expected to).

4.4 Special warnings and precautions for use

Special warnings
If Calcium Gluconate must be injected intravenously for patients undergoing treatment with cardiac glycosides, sufficient monitoring of cardiac function is essential, and all options for an emergency treatment of cardiac complications such as severe cardiac arrhythmias must be available.
In patients with nephrocalcinosis, heart disease, sarcoidosis (Boeck's disease) calcium salts should only be administered with caution and after a thorough indication, similarly in patients concurrently taking medication with epinephrine (see section 4.5) and in older patients.

Impairment of kidney function may be associated with hypercalcaemia and a secondary hyperfunction of the parathyroid glands. Therefore, patients with impaired kidney function should only be administered parenteral calcium doses after careful diag-

nosis and monitoring of calcium and phosphate levels.

Patients who are prescribed Ceftriaxone In patients of any age, ceftriaxone should not be mixed with calcium-containing intravenous solutions or administered together via different infusion tubes or gateways (see section 6.2).

Cases have been reported of severe reactions as a result of calcium ceftriaxone precipitates in the lungs and the kidneys of pre-term and mature new-borns aged less than one month.

To prevent precipitation in patients who are older than 28 days, ceftriaxone and calcium-containing solutions can be administered successively when the infusion systems are given in different places, or the infusion system is replaced, or when a physiological saline solution is used to thoroughly rinse between infusions.

With hypovolaemia, the sequential infusion of ceftriaxone and calcium-containing pharmaceutical products are to be avoided.

Usage precautions
Calcium-containing solutions should be administered slowly in order to best minimize the risk of peripheral vasodilation or a reduction of cardiac output.

Intravenous injections should be carried out under monitoring of the heart rate or ECG control, since taking in calcium too quickly can cause bradycardia with vasodilation, or cardiac arrhythmias.

In children and adolescents, Calcium Gluconate B. Braun 10% solution for injection should not be administered intramuscularly, but only intravenously and slowly.

For any treatment with calcium salts, the patient should be carefully monitored to ensure normal calcium levels and to avoid sediment build-up in the tissues.

During high-dose parenteral calcium intake, plasma levels and calcium excretion should be monitored in the urine.

Calcium Gluconate B. Braun 10% solution for injection should not be injected into fatty tissue, since the calcium in fat tissue is not soluble and can lead to infiltration with subsequent abscess formation, tissue hardening and necrosis.

After perivascular or superficial intramuscular injection, local tissue irritation can occur, also referred to as skin ablations or tissue necrosis (see section 4.8). Extravasations must be avoided; the injection site is to be carefully observed.

A high-dose vitamin D intake is to be avoided

4.5 Interactions with other medicinal products and other forms of interaction

Cardiac glycosides
The effect of Digoxin and other cardiac glycosides can be enhanced by calcium, with the possible consequence of severe toxic effects. Therefore, intravenous administration of calcium supplements in patients undergoing treatment with cardiac glycosides is contraindicated, with the sole exception of a compelling indication for intravenous calcium application 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 also sections 4.3 and 4.4).

Epinephrine
The simultaneous administration of calcium and epinephrine weakens the ß-adrenergic effect of epinephrine in patients following cardiac surgery (see section 4.4).

Magnesium
Calcium and magnesium inhibit each other in their effects.

Calcium antagonists
Calcium can mitigate the effects of calcium antagonists (calcium channel blockers).

Thiazide diuretics
The concomitant administration of Thiazide diuretics can lead to hypercalcaemia, because these drugs reduce renal calcium excretion.
Interactions with ceftriaxone, see sections 4.4 and 6.2.

4.6 Fertility, pregnancy and lactation

Pregnancy
Calcium crosses the placental barrier and achieved higher concentrations in foetal blood than in maternal blood. Calcium Gluconate B. Braun 10% solution for injection must not be administered during pregnancy, unless the administration of Calcium Gluconate B. Brown 10% solution for injection is indispensable due to the clinical findings of pregnant women. The dose is carefully determined and the serum calcium levels regularly monitored in order to avoid hypercalcaemia, which can be harmful to the foetus.

Lactation period
Calcium is excreted into breast milk. This is taken into account when administering calcium to nursing mothers. A decision has to be made about whether breastfeeding is to be interrupted or whether treatment with Calcium Gluconate B. Braun 10% solution for injection should be abandoned / treatment with calcium gluconate B. Braun 10% solution for injection is to be interrupted. In this, the benefits of breastfeeding for the child as well as the benefits of treatment for the woman are taken into account.

Fertility
There is no data available

4.7 Impact on the ability to drive and the ability to operate machinery
Not applicable.

4.8 Side effects
The below specified frequency of side effects are defined as follows:

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 rarely	< 1/10,000)
Unknown	Frequency is not known on the basis that the available data cannot be assessed

Cardiovascular and other systemic side effects can occur as symptoms of acute hypercalcaemia as a result of intravenous overdose, or rapid intravenous injection. Occurrence and frequency are directly influenced by the injection speed and the administered dose.

Heart disease
Unknown: Bradycardia, cardiac arrhythmia

Vascular disease
Unknown: Drops in blood pressure, vasodilation, heart circulatory collapse (with possibly fatality), hot flushes, mainly after a too rapid injection

Diseases of the gastrointestinal tract
Unknown: Nausea, vomiting

General disorders and complaints in the application area
Unknown: Sensation of heat, sweating
Unknown: Intramuscular injections can be accompanied by pain or formation of erythema.

Ceftriaxone calcium salt precipitates
In rare cases, severe or even fatal adverse reactions in preterm and mature new-borns (age < 28 days) were observed and were treated with intravenous ceftriaxone and calcium. Ceftriaxone calcium salt precipitates were found *post mortem* in the lungs and kidneys. Due to their low

blood volume and the longer half-life of ceftriaxone as compared to adults, newborns are at a high risk of such precipitation (see sections 4.3, 4.4 and 6.2).

Side effects, which occur only after improper application:

If an intramuscular injection is not administered deeply enough, it can infiltrate the fatty tissue, leading to the formation of abscesses, tissue hardening and necrosis.

It was reported through calcinosis cutis, which can certainly result in extravasation, and possible ablations of the skin and necrosis can follow.

Skin redness, burning sensation or pain during the intravenous injection may suggest an accidental perivascular injection, which can lead to tissue necrosis.

Reporting suspicions of side effects
The reporting of suspicions of side-effects after approval is very important. It allows a continuous monitoring of the risk-benefit balance of the medicinal product. Healthcare professionals are asked to report every suspected case of a side effect to Bundesinstitut für Arzneimittel und Medizinprodukte, Abt. Pharmakovigilanz, Kurt-Georg-Kiesinger Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

Symptoms
Symptoms of hypercalcaemia can be: Loss of appetite, nausea, vomiting, constipation, abdominal pain, polyuria, severe thirst, dehydration, muscle weakness, bone pain, renal calcification, drowsiness, confusion, high blood pressure and in severe cases, cardiac arrhythmia, cardiac arrest, and coma.
After a rapid intravenous injection, symptoms of hypercalcaemia may be experienced, such as calcareous taste, hot flushes and a drop in blood pressure.

Emergency measures, countermeasures
The treatment aims to reduce excessive plasma calcium concentration.
At the beginning of the treatment is rehydration; in the event of severe hypercalcaemia, intravenous infusion of sodium chloride solution may be required for expansion of the extracellular fluid volume. Calcitonin can be administered for the reduction of excessive plasma calcium concentration. To increase calcium excretion, furosemide can be given, but not thiazide diuretics, because they increase renal calcium re-absorption.

Haemodialysis or peritoneal dialysis can be considered if other measures are ineffective and the acute symptoms have continued. The serum electrolytes are to be monitored carefully during the entire treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Activity

Pharmacotherapeutic groups: Solutions with impact on the electrolyte balance, electrolytes.
ATC code: B05B B01.
Calcium is the most common mineral substance in the human body (approximately 1.5% of body weight). Over 99% of the calcium is located in the bones and teeth, approximately 1% is dissolved in the intra - and extracellular fluid.

Calcium is required for the proper functioning of nerves and muscles. It is important for muscle contraction, heart function and blood clotting.

Physiologically, the calcium concentration in the plasma is maintained at 2.25 - 2.62 mmol/l. As about 40-50% of plasma calcium is bound to albumin, the total plasma calcium concentration is linked to the plasma protein concentrate. The concentration of ionized calcium is between 1.23 and 1.43 mmol/l and is regulated by calcitonin and parathyroid hormone.

Hypocalcaemia (total calcium < 2.25 mmol/l or ionized calcium < 1.23 mmol/l) can cause kidney failure, vitamin D deficiency, magnesium deficiency, mass transfusion, osteoblastic malignancy, hypoparathyroidism or intoxication with phosphates, oxalic acid, fluoride, strontium and radium.

The following can occur as symptoms of hypocalcaemia: increased neuromuscular excitability leading to tetany, paraesthesia, carpopedal spasm, spasms of the smooth muscles (such as intestinal colic), muscle weakness, confusion, seizures and cardiac symptoms from the extension of the QT interval and arrhythmia up to acute myocardial failure.

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

5.2 Pharmacodynamic Activity

Distribution
After injection, the injected calcium shows the same dispersion behaviour as the body's calcium. There are about 45-50% of the total calcium in the plasma in the ionized physiologically active form, about 40-50% are bound to proteins, mainly albumin, and 8-10% form complexes with anions.

Biotransformation
Injected calcium is added to the intravascular calcium pool and is metabolized by the body as if it is the body's calcium.

Elimination
Calcium is excreted in the urine, where a large proportion is absorbed in the tubules of the kidney.

5.3 Preclinical safety data

The preclinical data from conventional studies of safety pharmacology, toxicity in event of repeated administration, reproductive and developmental toxicity, indicate no particular hazards for humans.

6. PHARMACEUTICAL INFORMATION

6.1 List of constituent material

Calcium-D-saccharat-Tetrahydrate water for water for injection

6.2 Incompatibilities

Calcium salts can form complexes with many drugs, which can lead to precipitation.

Calcium salts are incompatible with oxidizing substances, citrates, soluble carbonates, bi-carbonates, oxalates, phosphates, tartrate and sulphates.

Physical incompatibility has been reported for amphotericin, cephalothine sodium, ceftriaxone (see section 4.4), cephazolin sodium, cephamandole nafate, novobiocin sodium, dobutamine hydrochloride, prochlorperazine, and tetracycline.

The medicinal product shall not be mixed with other medicines, except those listed in section 6.6, unless compatibility has been demonstrated to be sufficiently safe.

6.3 Storage life

Unopened:
3 years

After dilution
The physical stability of use was demonstrated at room temperature for a period of 48 hours for the dilution according to the instructions on 10 mg / ml with the recommended infusion solutions (i.e. 9 mg / ml (0.9%) Sodium chloride solution for injection 50 mg / ml (5%) Glucose solution for injection).
From a microbiological perspective, solutions should be used immediately. If they are not immediately used, the user is responsible for the duration and conditions of storage. If the production of solutions do not take place under controlled and validated aseptic conditions, they are usually kept no longer than 24 hours at 2 to 8°C.

6.4 Special precautions for storage

No special storage conditions are required for these medicines.

6.5 Nature and content of container

10 ml LDPE (low density polyethylene) ampoules, in a cardboard box.

Package sizes:
20 ampoules.

Not all pack sizes are brought to market.

6.6 Special precautions for disposal and other handling instructions

Disposal
No special requirements for disposal.

Handling
The medicinal product is intended for single use. Unused solution is to be discarded.
The medicinal product is to be visually checked before application for particles, colour and integrity of the container.
Only use the solution if it is clear, colourless to light brown, and watery, virtually free of particles and the container is intact.

Dilution
Calcium Gluconate B. Braun 10% solution for injection 1:10 can be diluted to a concentration of 10 mg/ml for intravenous infusion with the following infusion solutions: 9 mg/ml (0.9%) Sodium chloride solution for injection or 50 mg/ml (5%) Glucose solution for injection. Ready for use solutions are designed according to dilution with the recommended infusion solutions for immediate one-time use. The dilution should be carried out under controlled and validated aseptic conditions. After the addition, the container should be shaken gently to ensure homogeneity.

7. AUTHORISATION HOLDER

B. Braun Melsungen AG
Carl-Braun-Str. 1,
34212 Melsungen, Deutschland

Postal address:
34209 Melsungen
Germany
Tel.: + 49/5661/71-0
Fax: +49/5661/71-4567

8. LICENCE NUMBER(s)

6697892.00.00

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION LICENCE

December 28, 2005 / June 6, 2010

10. DATE OF REVISION OF TEXT

July 2014

11. PRESCRIPTION / PHARMACY DUTY

Available over the counter

Central requests to:
Rote Liste Service GmbH
Fachinfo-Service [Information Service]
Mainzer Landstraße 55
60329 Frankfurt