PRODUCT INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Calcium gluconate / DEMO 10% w/v Solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the 10 mL ampoule contains 0.095 g calcium gluconate as monohydrate, equivalent to 0.212 mmol of calcium.
Each 10 mL ampoule contains 0.95 g calcium gluconate equivalent to 2.12 mmol of calcium.

Excipients: The product also contains an amount of the excipient calcium saccharate equivalent to 0.0112 mmol calcium per mL (or 0.112 mmol calcium per 10 mL).

Total calcium content: 0.223 mmol per mL (2.23 mmol per 10 mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless to pale yellow (not more intensely coloured than ref. sol. Y6 Ph. Eur.) aqueous sterile solution, with a pH between 6 and 8.2, practically free from visible particulate contamination.
Theoretical osmolality: 260-300 mOsm/kg

For the dilution under aseptic conditions of the calcium gluconate 10% there are used two diluents; Sodium chloride 9mg/ml (0.9%) solution for injection and Dextrose 50 mg/ml (5.0%) solution for injection in order to obtain a concentration of calcium gluconate 10 mg/ml.
The clarity, color, pH and content of calcium of the diluted solutions do note change significantly during the study along with osmolality and sterility.

The diluents are supplied separately.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of acute symptomatic hypocalcaemia.

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

Adults
The usual initial dose in adults is 10 mL of Calcium gluconate 10%, 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.

Children and adolescents (< 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	Body wt. (kg)	mL	Equiv. to mmol (mEq) calcium
3 months	5.5	2-5	0.45-1.13 (0.9-2.26)
6 months	7.5	2-5	0.45-1.13 (0.9-2.26)
1 year	10	2-5	0.45-1.13 (0.9-2.26)
3 years	14	5-10	1.13-2.26 (2.26-4.52)
7.5 years	24	5-10	1.13-2.26 (2.26-4.52)
12 years	38	5-10	1.13-2.26 (2.26-4.52)
> 12 years	>38	As for adults	As for adults

This corresponds approximately to:

- 0.4-1 ml/kg body weight (~ 0.09-0.23 mmol [0.18-0.45 mEq] of calcium per kg body weight) for children up to 3 years.
- 0.2-0.5 ml/kg body weight (~0.05-0.1 mmol [0.1-0.2 mEq] of calcium per body weight) for children from 4 to 12 years.

For patients above 12 years of age the adult dosages should be applied. In cases of severe symptoms of hypocalcaemia, e.g. cardiac symptoms, higher initial doses (up to 2 ml per body weight, ~0.45 mmol [0.9 mEq] 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.

Elderly patients
Although there is no evidence that tolerance of calcium gluconate 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 intramuscularly, preferably into the gluteal region. See also 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 the adipose tissues.
If repeated injections are necessary, the injection site should be changed every time.
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 6.5) of Calcium Gluconate 10% in children and adolescents.
Intramuscular injections should not be performed in paediatric patients.

4.3 Contraindications
Calcium Gluconate 10% w/v must not be administrated in the following conditions:

- Hypersensitivity to calcium gluconate and to the excipient,
- Elevated calcium level in blood (hypercalcaemia), e.g. in patients with hyperparathyroidism, hypervitaminosis D, decalcifying malignancies, renal insufficiency, immobilization osteoporosis, sarcoidiosis, milk-alkali syndrome,

- Increased calcium excretion in urine (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 putting the patient at immediate vital risk, if safer therapeutic alternatives are not available and calcium administration via the oral route is not possible.

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.

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.

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 paediatric patients, calcium gluconate 10% w/v 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 is insoluble in adipose tissue and may therefore cause infiltration and subsequent abscess formation, tissue indurations and necrosis if accidentally injected into the adipose tissue.

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.

Calcium is not suitable in the adipose tissue and can lead there to infiltration with subsequent abscess formation. Calcium gluconate should only be slowly injected intravenously into children and never intramuscularly. In the case of renal impairment with reduced calcium excretion, the serum calcium level must be monitored.

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 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 may lead to cardiac arrhythmia.

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.
The medicinal product should not be mixed with any other drugs, unless compatibility has been satisfactorily demonstrated.
Calcium salts can form complexes with many drugs and this may result in a precipitate.
Calcium salts are incompatible with oxidizing agents, citrates, soluble carbonates, bicarbonates, oxalates, phosphates, tartrates and sulphates.
Physical incompatibility has also been reported with amphotericin, cephalothin sodium, cephazolin sodium, cephamandole nafate, novobiocin sodium, dobutamine hydrochloride, prochlorperazine and tetracyclines.
Calcium salts reduce the absorption of a number of other drugs such as biophosphonates, fluoride, some fluoroquinolones, and tetracyclines; doses should be separated by at least 3 hours.

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 should not be used during pregnancy unless clearly necessary. The administered dose should be carefully calculated, and serum calcium level regularly evaluated in order to avoid hypercalcaemia, which may be deleterious to the foetus.

Lactation
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 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

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

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. Under the conditions of proper administration, they are rare (<1:1000).

Cardiac and vascular disorders
Hypotension, bradycardia, cardiac arrhythmia, vasodilatation, vasomotor collapse (possibly fatal), flushing, mainly after too rapid injection.

Gastro-intestinal disorders
Nausea, vomiting.

General disorders
Heat sensations, sweating.

Administration site conditions
Common (<1:10, ≥1:100).
Intramuscular injection may be accompanied by pain sensations or erythema.

Adverse reactions only occurring with improper administration technique:
If intramuscular injection is not made at adequate depth, infiltration into the adipose tissue may occur with subsequent abscess formation, tissue induration, and necrosis.
Soft tissue calcification, possibly followed by skin ablation and necrosis, due to extravasation of calcium solutions, has been reported.
Reddening of skin, burning sensation or pain during intravenous injection may indicate accidental perivascular injection, which may lead to tissue necrosis.
Note:
Patients should inform their doctor or pharmacist if they notice any side effects not mentioned in this leaflet.

4.9 Overdose

Symptoms
Symptoms of hypercalcaemia may include anorexia, nausea, vomiting, constipation, abdominal pain, polyuria, polydipsia, dehydration, muscle weakness, 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 isotonic sodium chloride solution 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: mineral supplements, calcium gluconate.
ATC code: A12AA03
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 – 2.75 mmol/l. As about 50% of the plasma calcium is bound to albumin, total plasma calcium is coupled to the plasma protein

concentration. The concentration of ionized calcium is between 1.23 and 1.43 mmol/l, regulated by calcitonin and parathormone.
Hypocalcaemia (total calcium below 2.5 mmol/l or ionized calcium below 1.23 mmol/l, respectively) may be caused by renal failure, vitamin D deficiency, magnesium deficiency, massive blood transfusion, osteoblastic malignant tumors, hypoparathyroidism, or intoxication with phosphates, oxalates, fluorides, strontium or radium.
Hypocalcaemia may be accompanied by the following symptoms: increased neuromuscular excitability up to tetany, paraesthesiae, 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 normalization of pathologically low serum calcium levels and thus relief of the symptoms of hypocalcaemia.

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 50% is bound to proteins, mainly albumin, and 5% 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
Excertion of calcium occurs in the urine although a large proportion undergoes renal tubular reabsorption.

5.3 Preclinical safety data

No further information other than what is included in the Product Information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Saccharate, $4H_2O$
Water for injections

6.2 Shelf life

Shelf life as packaged for sale
3 years

Shelf life after first opening the container
For single dose use only. Any unused solution should be discarded immediately after initial use.

Shelf life after dilution according to directions

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 when stored at room temperature and at 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 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.3 Special precautions for storage

Store below 30˚C.

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 when stored at room temperature and at 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 24 hours at 2 °C – 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 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.

6.5 Special precautions for disposal and other handling

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 intefrity of the container prior to use. The solution should only be used if it is clear, colourless to pale yellow aqueous solution, practically free from particles and the container is undamaged.

Dilution
For intravenous infusion, Calcium gluconate may be diluted 1:10 to a concentration of 10 mg/ 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.

Before using this product together with other solutions via a Y connector or bypass set, the compatibility of these fluids should be checked.

7. PRODUCT REGISTRATION HOLDER

Pahang Pharmacy Sdn. Bhd.
Lot 5979, Jalan Teratai,
5 ½ Mile Off Jalan Meru, 41050 Klang, Selangor, Malaysia

8. MANUFACTURER

DEMO S.A. Pharmaceutical Industry
21st km National Road Athens – Lamia, 145 68 Krioneri, Attiki, Greece
Tel: +30 210 81 61 802, Fax: +30 210 81 61 587

9. DATE OF REVISION OF THE TEXT

May 2024