AUSTRALIAN PRODUCT INFORMATION

CALCIUM GLUCONATE

(CALCIUM GLUCONATE MONOHYDRATE)

INJECTION

1 NAME OF THE MEDICINE

Calcium Gluconate monohydrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcium gluconate is a supersaturated solution. Supersaturated solutions are prone to precipitation. Examine the vial and do not use if a precipitate is present.

The 10 mL injection is a solution containing 931 mg calcium gluconate and 46 mg calcium saccharate in water for injections. The calcium saccharate is a BP approved stabiliser for the supersaturated solution.

Each 10 mL of the injection contains:

- 89 milligrams of calcium ions
- equivalent to 2.2 millimoles of calcium ions
- equivalent to 4.4 mEq of calcium ions.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

The injection is a clear and colourless, particle free solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Calcium gluconate is a calcium salt used primarily for the prevention and treatment of calcium deficiency.

Parenteral administration of calcium gluconate is needed in acute hypocalcaemia and hypocalcaemic tetany. It can be given intravenously in the treatment of severe hyperkalaemia and in overdosage of magnesium sulphate, as calcium is the antagonist of magnesium toxicity. Intravenous injections have been used in the treatment of acute renal, biliary and intestinal colic.

Calcium has been used as an inotrope in cardiac resuscitation. They may also be used for the prevention of hypocalcaemia in exchange transfusions, and in long term electrolyte replacement therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

Calcium Gluconate Injection is a supersaturated solution. Supersaturated solutions are prone to precipitation. Examine the vial and do not use if a precipitate is present.

Calcium gluconate is usually administered intravenously as a 10% solution by slow intravenous injection, or by continuous or intermittent intravenous infusion.

It is not recommended to be given by intramuscular and subcutaneous injection, due to the possibility of tissue necrosis, and it should never be given by this route in children.

Various maximum rates of administration have been recommended for direct intravenous injection, including 2 mL/min, 1.5 to 3 mL/min, and 5 mL/min. By intermittent infusion, a maximum rate of 2 mL/min (0.9 mEq of calcium ions/min) is suggested. During intravenous administration of calcium, close monitoring of serum calcium levels is essential.

Hypocalcaemia and hypocalcaemic tetany

Adults. The usual initial dose is 7 to 14 mEq, but this is dependent upon the requirements of the individual patient. In hypocalcaemic tetany doses of 4.5 to 16 mEq may be administered until response occurs. The maximum daily dose of calcium gluconate should not exceed 15 g (equivalent to 67.5 mEq of calcium ions).

Severe hyperkalaemia

Calcium salts may be given intravenously in doses of 4.5 to 9.0 mEq as an adjunct, repeated as required under ECG control.

Hypermagnesaemia

Adults. An initial dose of 7 mEq intravenously may be given with subsequent doses adjusted according to the response.

Parenteral nutrition

Calcium salts may be added to parenteral nutrition solutions to prevent hypocalcaemia.

Children. Initial dose 1 to 7 mEq, but this must always be tailored to the needs of the individual patient. This dose may be repeated every one to three days if necessary. For children with hypocalcaemic tetany, doses of 0.5 to 0.7 mEq/kg may be repeated every 8 hours until response is seen.

To assist dosing the following table shows the calcium level in different volumes of the injection.

Calcium Ion Levels	1.0 mL of Injection	10 mL of Injection	50 mL of Injection
Milligrams of Calcium ions	8.9 mg	89 mg	445 mg
Millimoles of Calcium ions	0.22 mmol	2.2 mmol	11 mmol
Milliequivalents of Calcium ions	0.44 mEq	4.4 mEq	22 mEq

Compatibilities

It is recommended that Calcium Gluconate Injection be diluted with either 0.9% sodium chloride, 5% glucose in water, Lactated Ringers injection, or 5% glucose in 0.9% sodium chloride when intended to be administered as an intravenous infusion. It has been reported that at a concentration of 1.0 to 2.0 g/L calcium gluconate is compatible in all of the infusion fluids listed above for 24 hours.

To reduce microbiological contamination hazards, it is recommended that any further dilution of the product should be done immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. Infusion should be completed within 24 hours and any residue discarded. Any solutions which are discoloured, hazy, or contain visible particulate matter, should not be used.

The phenomenon of compatibility/incompatibility of calcium salts with phosphates in solution is a very complex one and may be affected by solubility and concentration phenomena, pH, as well as temperature and time of storage of the admixture and the presence of other substances. Consequently, Calcium Gluconate Injection should not be further diluted with phosphate-containing infusion fluids.

Incompatible solutions

See Section 6.2 Incompatibilities.

DO NOT USE IF SOLUTION IS DISCOLOURED, CLOUDY, TURBID, OR IF A PRECIPITATE IS PRESENT.

Compatible solutions

Calcium Gluconate Injection should be diluted with either 0.9% sodium chloride, 5% glucose in water, lactated Ringers injection, or 5% glucose in 0.9% sodium chloride, as an intravenous infusion. To reduce contamination hazards, any further dilution of the product should be done immediately prior to use, and infusion commenced as soon as possible after preparation of the mixture. Infusion should be completed in 24 hours and any residue must be discarded. Any solution which is discoloured, hazy or contains visible particulate matter should not be used.

Calcium Gluconate Injection should not be diluted with infusion fluids containing phosphates. (See Section 6.2 Incompatibilities.)

Calcium Gluconate Injection is a supersaturated solution stabilised with Calcium saccharate.

4.3 CONTRAINDICATIONS

Calcium Gluconate Injection should not be given concurrently with digitalis or cardiac glycoside therapy.

Also it is not to be used in hypercalcaemia, hypercalciuria (e.g. hyperparathyroidism, vitamin D overdosage, decalcifying tumours such as plasmocytoma, bone metastases), and severe renal disease, severe cardiac disease and calcium loss due to immobilisation.

It is NOT advisable to administer calcium gluconate to galactosaemic patients.

It is contraindicated when serum calcium concentrations are above normal levels (i.e., 4.5 to 5.2 mEq/L).

Calcium Gluconate Injection should not be given via the intramuscular or subcutaneous routes, as necrosis or sloughing may occur.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Calcium gluconate and calcium chloride are presented in 10 mL vials at 10% (w/v) for injection but are **not equivalent** in calcium content:

- 10 mL of Calcium Gluconate 10 % solution for injection/infusion BP contains 2.2 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.

Calcium Gluconate Injection is a supersaturated solution. Supersaturated solutions are prone to precipitation. Examine the vial and do not use if a precipitate is present.

Intramuscular injection in infants has been reported to cause abscess formation. The oral or intravenous route is to be used.

Solutions of calcium salts, particularly calcium chloride, are irritants, and care should be taken to prevent extravasation during intravenous injection.

Calcium Gluconate Injection should be administered slowly through a small needle into a large vein to avoid too rapid an increase in serum calcium and extravasation into the surrounding

tissue (see Section 4.8 Adverse Effects (Undesirable Effects)). Slow intravenous injection also helps prevent high concentrations of calcium from reaching the heart and causing cardiac syncope. Administration should be temporarily discontinued if abnormal ECG readings or patient discomfort occur; it may be resumed following resolution of the abnormal ECG reading or discomfort.

The injection should be warmed to body temperature prior to administration unless emergency administration is required. Following injection, the patient should lie down for a short period of time, to prevent dizziness.

Calcium salts should be given cautiously to patients with impaired renal function, cardiac disease, or diseases associated with elevated vitamin D concentrations such as sarcoidosis. Calcium salts should generally be avoided in patients with calcium renal calculi, or with a history of renal calculi. When used in large doses, serum calcium concentrations and kidney function should be determined weekly or at the first sign of hypercalcaemia, which is characterised by symptoms such as anorexia, lassitude, muscle and joint pains, nausea and vomiting, thirst, and polyuria.

Dehydration or other electrolyte imbalances may increase the risk of hypercalcaemia.

Ventricular fibrillation present during cardiac resuscitation increases the risk of arrhythmias after calcium administration. Frequent determinations of serum calcium concentrations should be performed, particularly in children. Hypercalcaemia is rarely produced by administration of calcium alone, but may occur when large doses are given to patients with chronic renal failure. Since hypercalcaemia may be more dangerous than hypocalcaemia, over treatment of hypocalcaemia should be avoided.

In mild hypercalciuria (exceeding 300 milligrams/24 hours) as well as in chronic renal failure, or when there is evidence of stone formation in the urinary tract, adequate checks must be kept on urinary calcium excretion. If necessary the dosage should be reduced or calcium therapy discontinued. In patients prone to formation of calculi in the urinary tract an increased fluid intake is recommended.

ECG monitoring is required when calcium is administered by intravenous injection for treating severe hyperkalaemia.

In patients with severe hypocalcaemia and hyperphosphataemia, the hyperphosphataemia should be treated prior to administration of intravenous calcium. Treatment should aim to achieve a proper calcium / phosphate ratio to prevent extra-skeletal deposition of calcium.

Use in the elderly

See Section 4.8 Adverse Effects (Undesirable Effects).

Paediatric use

Intramuscular injection in infants has been reported to cause abscess formation. The oral or intravenous route is to be used.

See Section 4.2 Dose and Method of Administration, Parenteral nutrition.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Cardiac glycosides. The inotropic and toxic effects of cardiac glycosides and calcium are synergistic and arrhythmias may occur if these drugs are given together (particularly when calcium is given intravenously). Intravenous administration of calcium should be avoided in patients receiving cardiac glycosides (see Section 4.3 Contraindications). If considered necessary, calcium should be given slowly in small amounts. Close electrocardiograph (ECG) monitoring is recommended.

Tetracyclines. Calcium is known to complex with tetracycline antibiotics, thus rendering them inactive. The two drugs should therefore not be mixed prior to parenteral administration.

Vitamin D increases the gastrointestinal absorption of calcium (e.g., from dietary sources). High vitamin D intake should be avoided during calcium therapy unless especially indicated. Plasma calcium concentrations should be monitored in patients taking these drugs concurrently.

Administration of calcium may reduce the response to *verapamil* and possibly other *calcium channel blockers*.

Calcium salts may antagonise the effect of *calcitonin* in the treatment of hypercalcaemia. However, when calcitonin is used to treat Paget's disease, sufficient calcium should be administered to prevent hypocalcaemia and secondary hypoparathyroidism.

Concurrent use of *thiazide diuretics* with calcium may result in hypercalcaemia, as thiazide diuretics reduce urinary calcium excretion. Serum calcium levels should be monitored in patients receiving these drugs concurrently.

The effects of non-depolarising neuromuscular blocking agents are usually reversed by concurrent administration of parenteral calcium salts. Calcium salts may enhance or prolong the neuromuscular blocking action of *tubocurarine*.

Concurrent administration of calcium salts with other *calcium-containing preparations* or with oral *magnesium- containing* preparations may increase serum calcium or magnesium concentrations in susceptible patients, particularly those with impaired renal function, leading to hypercalcaemia or hypermagnesaemia, respectively.

Concurrent use of calcium salts with *potassium and/or sodium phosphates* may increase the potential for calcium to be deposited in soft tissues in the presence of high serum calcium levels.

Excessive *vitamin A* intake may stimulate bone loss, counteracting the effects of calcium administration on bone, and may cause hypercalcaemia.

Administration of calcium in patients who have received transfusions of *citrated blood* may result in higher than normal total serum calcium concentrations. In overdose hypercalcaemia may occur, especially when given to patients with chronic renal failure. Symptoms include anorexia, lassitude, muscle and joint pains, nausea, vomiting, thirst and polyurea. Deposition of calcium in the kidneys leads to renal damage. Elevated serum calcium concentrations can produce bradycardia and cardiac arrhythmias. Treatment consists of withdrawing all calcium supplements, administering large volumes of fluid, and in mild cases, sodium phosphate, sulphate chloride or citrate may be given intravenously. *Frusemide* and *ethacrynic acid* may be useful adjuncts. In these patients, however, most of the excess calcium is bound to citrate and is inactive; therefore serious toxicity usually does not result.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

There is no information available on the use of Calcium Gluconate Injection during pregnancy. Calcium crosses the placenta and reaches higher concentrations in fetal blood than in maternal blood. The decision to treat pregnant women with Calcium Gluconate Injection should therefore consider the potential benefits to the mother against the potential harm to the fetus.

Use in lactation

Calcium crosses into breast milk. No problems have been documented with women who are breast feeding when having the Calcium Gluconate Injection administered, but the potential benefits to the mother against the potential harm to the infant must be weighed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Calcium salts are irritating to tissue when administered by intramuscular or subcutaneous injection and cause mild to severe local reactions including burning, necrosis and sloughing of tissue, cellulitis, and soft tissue calcification. Calcium Gluconate Injection should, therefore, not be administered by intramuscular or subcutaneous injection (see Section 4.3 Contraindications).

Venous irritation may occur with intravenous administration. When injected intravenously, calcium salts should be administered slowly through a small needle into a large vein to avoid too rapid an increase in serum calcium and extravasation of calcium solution into the surrounding tissue with resultant necrosis.

Patients may complain of tingling sensations, a sense of oppression or heat waves, and a calcium or chalky taste following intravenous administration of calcium salts. Other adverse effects commonly associated with parenteral calcium administration include hypotension or dizziness, irregular heartbeat, nausea or vomiting, or sweating. Skin redness, rash, pain or burning at the injection site are also common; these reactions may indicate extravasation, and can precede sloughing or skin necrosis. Severe necrosis requiring skin grafting, and calcification can occur at the injection site, especially after rapid intravenous injection. Rapid intravenous injection of calcium salts may cause vasodilation, hot flushes, decreased blood pressure, bradycardia, cardiac arrhythmias, syncope, and cardiac arrest.

Transient increases in blood pressure, particularly in elderly or hypertensive patients, may occur during intravenous administration of calcium salts.

Hypercalcaemia is rarely produced by administration of calcium alone, but may occur when large doses are given to patients with chronic renal failure (see Section 4.9 Overdose). Since hypercalcaemia may be more dangerous than hypocalcaemia, overtreatment of hypocalcaemia should be avoided.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms of overdosage

Hypercalcaemia may occur when large doses of calcium gluconate are given, especially when such doses are given to patients with chronic renal failure. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi, and in severe cases, cardiac arrhythmias, coma and cardiac arrest.

Treatment of overdosage

A serum calcium concentration exceeding 10.5 milligrams per 100 mL (2.6 mmol/L) is considered a hypercalcaemic condition. Withholding additional administration of calcium and any other medications that may cause hypercalcaemia usually resolves mild hypercalcaemia in asymptomatic patients, when renal function is adequate.

When serum calcium concentrations are greater than 12 milligrams per 100 mL, immediate measures may be required with possible use of the following:

- Hydration with intravenous 0.9% Sodium Chloride Injection and forced diuresis with frusemide to rapidly increase calcium excretion.
- Monitoring of potassium and magnesium serum concentrations and early replacement to prevent complications of therapy.
- ECG monitoring and the possible use of beta-adrenergic blocking agents to protect the heart against serious arrhythmias.
- Possible treatment with calcitonin, diphosphonate dmp and other measures.
- Determining serum calcium concentrations at frequent intervals to guide therapy adjustments.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Calcium is essential for the maintenance of the functional integrity of the nervous, muscular, and skeletal systems, and cell-membrane and capillary permeability. This cation is an important activator in many enzymatic reactions and is essential to a number of physiologic processes including the transmission of nerve impulses; contraction of cardiac, smooth, and skeletal muscles; renal function; respiration; and blood coagulation. Calcium also plays a regulatory role in the release and storage of neurotransmitters and hormones, in the uptake

and binding of amino acids, in cyanocobalamin (vitamin B12) absorption and in gastrin secretion.

The calcium of bone is in a constant exchange with the calcium of plasma. Since the metabolic functions of calcium are essential for life, when there is a disturbance in the calcium balance because of dietary deficiency or other causes, the stores of calcium in bone may be depleted to fill the body's more acute needs. Therefore, on a chronic basis, normal mineralisation of bone depends on adequate amounts of total body calcium.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Dietary calcium is absorbed from the small intestine. About one third of ingested calcium is absorbed, although this can vary depending upon dietary factors and the state of the small intestine.

Following absorption, calcium first enters the extracellular fluid and is then rapidly incorporated into skeletal tissue. Bone formation, however, is not stimulated by administration of calcium. Bone contains 99% of the body's calcium; the remaining 1% is distributed equally between the intracellular and extracellular fluids.

Normal total serum calcium concentration ranges from 9 to 10.4 mg/dL (4.5-5.2 mEq/L), but only ionised calcium is physiologically active. Serum calcium concentrations are not necessarily accurate indications of total body calcium; total body calcium may be decreased in the presence of hypercalcaemia, and hypocalcaemia can occur even though total body calcium is increased. Of the total serum calcium concentration, 50% is in the ionic form and 5% is complexed by phosphates, citrates, and other anions. Approximately 45% of the serum calcium is bound to plasma proteins; for a change in serum albumin of 1 gram/dL, the serum calcium concentration may change about 0.8 mg/dL (0.04 mEq/dL). Hyperproteinaemia is associated with increased total serum calcium concentrations; in hypoproteinaemia, total serum calcium concentrations decrease. Acidosis results in increased concentrations of ionic calcium, while alkalosis promotes a decrease in the ionic serum calcium concentration.

Distribution

Cerebrospinal fluid (CSF) concentrations of calcium are about 50% of serum calcium concentrations and tend to reflect ionised serum calcium concentrations. Calcium crosses the placenta and reaches higher concentrations in foetal blood than in maternal blood. Calcium is distributed into milk.

Metabolism

No data available.

Excretion

Calcium is excreted mainly in the faeces and consists of unabsorbed calcium and that which is secreted via bile and pancreatic juice into the lumen of the GI tract. Most of the calcium filtered by renal glomeruli is reabsorbed in the ascending limb of the loop of Henle and proximal and distal convoluted tubules. Only small amounts of the cation are excreted in urine. Parathyroid hormone, vitamin D, and thiazide diuretics decrease urinary excretion of calcium, whereas other diuretics, calcitonin, and growth hormone promote renal excretion of the cation. Urinary excretion of calcium decreases with reduction of ionic serum calcium concentrations but is proportionately increased as serum ionised calcium concentrations increase. In healthy adults on a regular diet, urinary excretion of calcium may be as high as 250 to 300 milligrams daily. With low calcium diets, urinary excretion usually does not exceed 150 milligrams daily. Urinary excretion of calcium decreases during pregnancy and in the early stages of renal failure. Calcium is also excreted by the sweat glands.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The injection contains 46 mg calcium saccharate in water for injections. Calcium saccharate is an approved stabiliser for supersaturated solution.

6.2 INCOMPATIBILITIES

Calcium Gluconate Injection has been reported as being **incompatible with the following solutions:**

- Fat Emulsion 10% Intravenous
- Cefamandole nafate
- Cephalothin sodium
- Dobutamine HCl

- Floxacillin sodium
- Methylprednisolone sodium succinate
- Prochlorperazine edisylate
- Metoclopramide HCl
- Aldesleukin
- Indomethacin sodium trihydrate
- Phosphates
- Soluble carbonates, phosphates and sulphates

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Do not refrigerate.

6.5 NATURE AND CONTENTS OF CONTAINER

The injection is supplied in a 10 mL Type 1 glass vial with a chlorobutyl stopper (not made with natural rubber latex) and an aluminium seal capped with a white flip off seal. Each carton contains 10 vials.

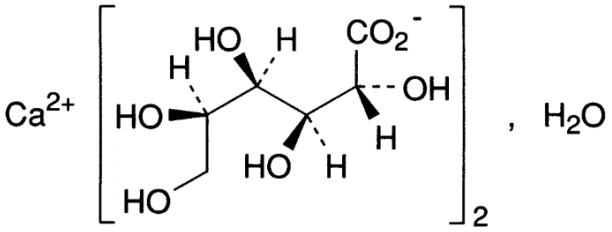
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The molecular weight of the compound is 448.4. The molecular formula is $C_{12}H_{22}CaO_{14}.H_2O$.

Chemical structure



[1]AUST R 355191

CAS number

18016-24-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

UNSCHEDULED

8 SPONSOR

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9 DATE OF FIRST APPROVAL

13 May 2021

10 DATE OF REVISION

05 Dec 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	More safety added
All	Minor editorial changes throughout the PI

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