INDICATIONS AND USAGE
Calcium Gluconate Injection is a form of elemental calcium (2.1)

Hypercalcemia (4)

DOSAGE AND ADMINISTRATION
Calcium Gluconate Injection contains 100 mg of calcium gluconate per mL which contains 9.3 mg (0.465 mEq) of elemental calcium (2.1)

Administer intravenously (bolus or continuous infusions every 4 to 6 hours and during tent infusions)

Dilute Calcium Gluconate Injection via a secure intravenous line

Continuous intravenous infusion

For continuous intravenous infusion, the diluted solution must be administered via a secure intravenous line to avoid calcinosis cutis and tissue necrosis.

Diluted solutions, which contain aluminum.

Supply in a single-dose vial or pharmacy bulk package (PBP). For PBP, dispense single doses to many patients consistent with requirements of the pharmacy admixture program; use within 4 hours of puncture

DOSAGe FORMS AND STRENGTHs
Injection: (3)

DOSAGE AND ADMINISTRATION
Contains 100 mg of calcium gluconate per mL which contains 9.3 mg (0.465 mEq) of elemental calcium (2.1)

For administration of intravenous Calcium Gluconate Injection, initial administration (2.2)

Prepare the pharmacy bulk package (PBP) for all age groups and monitor serum calcium levels every 1 to 4 hours during continuous infusions

 Dosage and Administration

Geriatric use: Dosing in elderly patients should be cautious, usually starting at the low end of the dosage range.

Dosage in Renal Impairment

Drug Incompatibilities

Dosage in Renal Impairment

5.3 Tissue Necrosis and CalcinosiS (CalcinosiS cuts): Calcinosis cutis can occur with or without extravasation of Calcium Gluconate Injection. Tissue necrosis, ulceration, and secondary infection are the most serious complications. If extravasation occurs or clinical manifestations of calcinosis cutis are noted, immediately discontinue intravenous administration at that site and treat as needed.

5.4 Aluminum Toxicity: This product contains aluminum, up to 400 mcg per liter, that may be toxic.

ADVERSE REACTIONS
The most common adverse events with Calcium Gluconate Injection are local soft tissue inflammation and necrosis, calcinosis cutis, and calcification that are related to extravasation.

Other adverse events include vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmia, syncope, and cardiac arrest.

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7776 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Cardiac Glycosides: Synynergistic arrhythmias may occur if calcium and cardiac glycosides are administered together.

Calcium Channel Blockers: Administration of calcium may reduce the response.

Drugs that may cause hypercalcemia: Vitamin D, thiazide diuretics, estrogen, calcipotriene, and teriparatide administration may cause hypercalcemia.

Monitor plasma calcium concentrations in patients taking these drugs concomitantly.

USE IN SPECIFIC POPULATIONS
Geriatric use: Dosing in elderly patients should be cautious, usually starting at the low end of the dosage range.

Renal Impairment: Initiate with the lower limit of the dosage range and monitor serum calcium levels every 4 hours.

See 17 for PATIENT COUNSELING INFORMATION

FULL PRESCRIBING INFORMATION: CONTENTS*
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*Sections or subsections omitted from the full prescribing information are not listed.
**INDICATIONS AND USAGE**

Calcium Gluconate Injection is indicated for pediatric and adult patients for the treatment of acute symptomatic hypocalcemia.

**DOSES AND ADMINISTRATION**

2.1 Important Administration Instructions

- Calcium Gluconate Injection contains 100 mg of calcium gluconate per mL which contains (approx. 0.465 mEq) of elemental calcium.
- Dilute Calcium Gluconate Injection prior to use in 5% dextrose or normal saline and assess for potential drug or IV fluid incompatibilities [see Dosage and Administration (2.5)].
- Inspect Calcium Gluconate Injection visually prior to administration. The solution should appear clear and colorless to slightly yellow. Do not administer if there is particulate matter or discoloration.
- Use the diluted solution immediately after preparation.
- Administer Calcium Gluconate Injection by bolus administration or continuous infusion.

For bolus intravenous administration:

- Dilute Calcium Gluconate Injection in 5% dextrose or normal saline to a concentration of 10-50 mg/mL prior to administration. Administer the dose slowly and DO NOT exceed an infusion rate of 200 mg/minute in adults or 100 mg/minute in pediatric patients, including neonates, preterm neonates, and term neonates with central nervous system and bone damage, in order to avoid extracellular hypercalcemia. If extravasation occurs or clinical manifestations of extracutaneous hypercalcemia are noted, immediately discontinue intravenous administration at that site and treat as follows:
  - Aluminum toxicity: Tissue loading may occur at even lower end of the dosage range. Calcium Gluconate Injection is required, the rate of intravenous administration should not exceed 200 mg/minute in adults and 100 mg/minute in pediatric patients and ECG monitoring during administration is recommended [see Dosage and Administration (2.1)].

2.2 Recommended Dosage

Initiate dosage of Calcium Gluconate Injection within the recommeded range depending on the severity of symptoms of hypocalcemia, the serum calcium level, and the acuity of onset of hypocalcemia.

**WARNINGS AND PRECAUTIONS**

5.1 Arrhythmias with Concomitant Cardiac Glycoside Use

Cardiac arrhythmias may occur if cardiac and cardiac glycosides are administered together. Hypercalcemia increases the risk of digitalis toxicity. Administration of Calcium Gluconate Injection should be avoided in patients receiving cardiac glycosides. If concomitant therapy is necessary, Calcium Gluconate Injection should be administered in small amounts, and with close ECG monitoring [see Drug Interactions (7.1)].

5.2 End-Organ Damage due to Intravenous Ceftriaxone-Calcium Precipitates

Concomitant administration of ceftriaxone and calcium gluconate may lead to the formation of ceftriaxone-calcium precipitates that may act as emboli, resulting in vascular spasm or infarction [see Contraindications (4)]. In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid. Do not administer Ceftriaxone simultaneously with Calcium Gluconate Injection via a Y-site in any age group.

5.3 Tissue Necrosis and Calcinosis

Intravenous administration of Calcium Gluconate Injection and local trauma may result in calcinosis cutis due to transient increase in local calcium concentration. Calcinosis cutis can occur with or without extravasation of Calcium Gluconate Injection, is characterized by abnormal dermal deposits of calcium salts, and clinically manifests as papules, plaques, or nodules that may be associated with erythema, swelling, or induration. Tissue necrosis, ulceration, and secondary infection are the most serious complications.

5.4 Hypotension, Bradycardia, and Cardiac Arrhythmias with Rapid Administration

This product is a 10% solution of Calcium Gluconate Injection in 100 mL (100 mg per mL) which contains 9.3 mg (0.465 mEq) of elemental calcium.

**ADVERSE REACTIONS**

The following serious adverse reactions are also described elsewhere in the labeling:

- **Warnings and Precautions**: Arthralgias and Concomitant Cardiac Glycoside Use [see Warnings and Precautions (5.1)]
- **End-Organ Damage due to Intravenous Ceftriaxone-Calcium Precipitates**: [see Warnings and Precautions (5.2)]
- **Tissue Necrosis and Calcinosis**: [see Warnings and Precautions (5.3)]
- **Hypotension, Bradycardia, and Cardiac Arrhythmias**: [see Warnings and Precautions (5.4)]
- **Aluminum Toxicity**: [see Warnings and Precautions (5.5)]

**ADVERSE REACTIONS**

The following adverse reactions are described elsewhere in the labeling:

- **Warnings and Precautions**: Arthralgias and Concomitant Cardiac Glycoside Use [see Warnings and Precautions (5.1)]
- **End-Organ Damage due to Intravenous Ceftriaxone-Calcium Precipitates**: [see Warnings and Precautions (5.2)]
- **Tissue Necrosis and Calcinosis**: [see Warnings and Precautions (5.3)]
- **Hypotension, Bradycardia, and Cardiac Arrhythmias**: [see Warnings and Precautions (5.4)]
- **Aluminum Toxicity**: [see Warnings and Precautions (5.5)]

The following adverse reactions associated with the use of calcium gluconate were identified in the literature. Because these reactions are reported voluntarily, and the incidence cannot be estimated with certainty, it is not possible to reliably estimate the frequency of occurrence or to establish a causal relationship to this medication.
from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

**Cardiovascular:** Vasodilation, decreased blood pressure, bradycardia, cardiac arrhythmia, syncope, cardiac arrest

**Administration site reactions:** Local soft tissue inflammation, local necrosis, calcinosis cutis and calcification due to extravasation.

7 DRUG INTERACTIONS

7.1 Cardiac Glycosides

Hypercalcemia increases the risk of digoxin toxicity, while digoxin may be therapeutically ineffective in the presence of hypocalcemia. Synergistic arrhythmias may occur if calcium and cardiac glycosides are administered together. Avoid administration of Calcium Gluconate Injection in patients receiving cardiac glycosides; if considered necessary, administer Calcium Gluconate Injection slowly in small amounts and monitor ECG closely during administration.

7.2 Calcium Channel Blockers

Administration of calcium may reduce the response to calcium channel blockers.

7.3 Drugs that may cause Hypercalcemia

Vitamin D, vitamin A, thiazide diuretics, estrogen, calcipotriene and teriparatide administration may cause hypercalcemia. Monitor plasma calcium concentrations in patients taking these drugs concurrently.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Limited available data with Calcium Gluconate Injection use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. There are risks to the mother and the fetus associated with hypocalcemia in pregnancy [see Clinical Considerations].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal risk

Maternal hypocalcemia can result in an increased rate of spontaneous abortion, premature and dysfunctional labor, and possibly preeclampsia.

Fetal/Neonatal adverse reactions

Infants born to mothers with hypocalcemia can have associated fetal and neonatal hyperparathyroidism, which in turn can cause fetal and neonatal skeletal demineralization, subperiosteal bone resorption, osteitis fibrosa cystica and neonatal seizures. Infants born to mothers with hypocalcemia should be carefully monitored for signs of hypocalcemia or hypercalcemia, including neuromuscular irritability, apnea, cyanosis and cardiac rhythm disorders.

8.2 Lactation

Risk summary

Calcium is present in human milk as a natural component of human milk. It is not known whether intravenous administration of Calcium Gluconate Injection can alter calcium concentration in human milk. There are no data on the effects of Calcium Gluconate Injection on the breastfed infant, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Calcium Gluconate Injection and any potential adverse effects on the breastfed infant, or on milk production.

Pediatric approval for Calcium Gluconate Injection, including doses, is not based on adequate and well-controlled clinical studies. Safety and dosing recommendations in pediatric patients are based on published literature and clinical experience [see Dosage and Administration (2.9)].

Concomitant use of ceftriaxone and Calcium Gluconate Injection is contraindicated in neonates (28 days of age or younger) due to reports of fatal outcomes associated with the presence of lung and kidney ceftriaxone-calcium precipitates. In patients older than 28 days of age, ceftriaxone and Calcium Gluconate Injection may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid [see Contraindications (4) and Warnings and Precautions (5.2)]. This product contains up to 400 mcg/L aluminum which may be toxic, particularly for premature neonates due to immature renal function. Parenteral administration of aluminum greater than 4 to 5 mcg/kg/day is associated with central nervous system and bone toxicity [see Warnings and Precautions (5.6)].

8.5 Geriatric Use

In general dose selection for an elderly patient should start at the lowest dose of the recommended dose range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Renal Impairment

For patients with renal impairment, initiate Calcium Gluconate Injection at the lowest dose of the recommended dose range across all age groups. Monitor serum calcium levels every 4 hours [see Dosage and Administration (2.4)].

8.7 Hepatic Impairment

Hepatic function does not impact the availability of ionized calcium after calcium gluconate intravenous administration. Dose adjustment in hepatically impaired patients may not be necessary.

10 OVERDOSAGE

Overdosage of Calcium Gluconate Injection may result in hypercalcemia. Symptoms of hypercalcemia typically develop when the total serum calcium concentration is ≥12 mg/dL. Neurologic symptoms include depression, weakness, fatigue, and confusion at lower levels, with patients experiencing hallucinations, disorientation, hypotonicity, seizures, and coma. Effects on the kidney include diminished ability to concentrate urine and diuresis.

If overdosage of Calcium Gluconate Injection occurs immediately discontinue administration and provide supportive treatments to restore intravascular volume as well as promote calcium excretion in the urine if necessary.

11 DESCRIPTION

Calcium Gluconate Injection, USP is a sterile, preservative-free, nonpyrogenic, supersaturated solution of calcium gluconate, a form of calcium, for intravenous use. Calcium Gluconate is calcium D-gluconate (1:2) monohydrate. The structural formula is:

\[
\text{Ca}^{2+} \left[ \begin{array}{c}
\text{HO} \\
\text{OH} \\
\text{OH} \\
\text{O} \\
\text{H}_2\text{O}
\end{array} \right] \text{H}_2\text{O}
\]

Molecular formula: C_{6}H_{12}CaO_{6}•H_{2}O

Molecular weight: 448.39

Solubility in water: 3.5 g/100 mL at 25°C

Calcium Gluconate Injection, USP is available as 1,000 mg per 10 mL (100 mg per mL) or 5,000 mg per 50 mL (100 mg per mL) in a single-dose vial, or 10,000 mg per 100 mL (100 mg per mL) in a pharmacy bulk package. Each mL of Calcium Gluconate Injection, USP contains 100 mg of calcium gluconate (equivalent to 94 mg of calcium gluconate and 4.5 mg of calcium saccharate tetrahydrate), hydrochloric acid and/or sodium hydroxide for pH adjustment.
(6.0 to 8.2) and sterile water for injection, q.s. It contains no antimicrobial agent.

Each mL of Calcium Gluconate Injection, USP contains 9.3 mg (0.465 mEq) of elemental calcium.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Intravenous administration of calcium gluconate increases serum ionized calcium level. Calcium gluconate dissociates into ionized calcium in plasma. Ionized calcium and gluconate are normal constituents of body fluids.

12.3 Pharmacokinetics
Absorption
Calcium Gluconate Injection is 100% bioavailable following intravenous injection.

Metabolism
Calcium itself does not undergo direct metabolism. The release of ionized calcium from intravenous administration of calcium gluconate is direct and does not seem to be affected by the first pass through the liver.

Distribution
Calcium in the body is distributed mainly in skeleton (99%). Only 1% of the total body calcium is distributed within the extracellular fluids and soft tissues. About 50% of total serum calcium is in the ionized form and represents the biologically active part. 8% to 10% serum calcium is bound to organic and inorganic acid and approximately 40% is protein-bound (primarily to albumin).

Elimination
Studies have shown a relationship between urinary calcium excretion and the intravenous administration of calcium gluconate, with a significant increase in urinary calcium excretion observed after the intravenous administration of calcium gluconate.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Calcium Gluconate Injection. Calcium gluconate was not mutagenic with or without metabolic activation in the Ames test with Salmonella typhimurium (strains TA-1535, TA-1537, and TA-1538) or Saccharomyces cerevisiae (Strain D4). Fertility studies in animals have not been conducted with calcium gluconate administered by the intravenous route.

16 HOW SUPPLIED/STORAGE AND HANDLING
Calcium Gluconate Injection, USP is a clear, colorless to slightly yellow solution supplied as follows:

<table>
<thead>
<tr>
<th>NDC</th>
<th>Strength/Vial Size (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63323-360-19</td>
<td>1,000 mg calcium gluconate per 10 mL, (100 mg per mL), in a</td>
</tr>
<tr>
<td></td>
<td>10 mL plastic, single-dose vial, packaged in a tray of 25.</td>
</tr>
<tr>
<td>63323-360-59</td>
<td>5,000 mg calcium gluconate per 50 mL, (100 mg per mL), in</td>
</tr>
<tr>
<td></td>
<td>a 50 mL plastic, single-dose vial, packaged in a tray of 25.</td>
</tr>
<tr>
<td>63323-360-61</td>
<td>10,000 mg calcium gluconate per 100 mL, (100 mg per mL),</td>
</tr>
<tr>
<td></td>
<td>in a 100 mL plastic, Pharmacy Bulk Package vial,</td>
</tr>
<tr>
<td></td>
<td>packaged in a tray of 20.</td>
</tr>
</tbody>
</table>

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze.

Preservative Free. Discard any unused portion in the single-dose vial immediately or the Pharmacy Bulk Package vial within 4 hours after initial closure puncture.

Each dose dispensed from the Pharmacy Bulk Package vial must be used immediately.

The diluted solution must be used immediately.

NOTE: Supersaturated solutions are prone to precipitation. The precipitate, if present, may be dissolved by warming the vial to 60° to 80°C, with occasional agitation, until the solution becomes clear. Shake vigorously. Allow to cool to room temperature before dispensing. Use injection only if clear immediately prior to use.

17 PATIENT COUNSELING INFORMATION

• Advise the patient that the risks associated with infusion including local tissue inflammation, local necrosis and calcinosis, [see Warnings and Precautions (5.3)].