AMERICAN REGENT

February 12, 2018

Re: 10% Calcium Chloride Injection, USP

Dear Healthcare Professional,

In an effort to reduce medication errors and ensure patient safety, American Regent, Inc. is informing you of recent changes to the presentation of our Calcium Chloride Injection, USP vials. Please note there is a marketed unapproved Calcium Chloride Injection, USP 10% as a drug shortage product. In addition, the FDA has approved 10% Calcium Chloride Injection, USP. The presentations have different indications, NDCs, cap colors and vial label colors. The formulations and the vial sizes are the same.

The FDA-approved 10% Calcium Chloride Injection, USP is indicated for the treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels.

Please see the full prescribing information which includes important safety information for 10% Calcium Chloride Injection, USP by clicking the link below.

10% Calcium Chloride Injection, USP Prescribing Information

The marketed unapproved Calcium Chloride Injection, USP 10% is indicated for the immediate treatment of hypocalcemic tetany. Other therapy, such as parathyroid hormone or vitamin D, may be indicated according to the etiology of the tetany. It is also important to institute oral calcium therapy as soon as practicable. Calcium salts have been used as adjunctive therapy in a number of conditions, including the following:

Insect bites or stings, such as Black Widow Spider bites.
Sensitivity reactions, particularly when characterized by urticaria.
As an aid in the treatment of depression due to overdosage of magnesium sulfate.
As an aid in the management of the acute symptoms in lead colic.
In cardiac resuscitation, particularly after open heart surgery, calcium chloride has been used when epinephrine has failed to improve weak or ineffective myocardial contractions.

Please click the link below to review the unapproved Calcium Chloride Injection, USP 10% prescribing information. This product will no longer be available but may remain in the market for some time.

Calcium Chloride Injection, USP 10% Prescribing Information

The Calcium Chloride Injection USP, 10% vials, NDC 0517-2710-25, have *blue* and *mauve* colored caps. The blue colored vials were discontinued and the mauve colored vials are currently in the market as a drug shortage product. This product is not FDA approved.

A DIVISION OF LUITPOLD PHARMACEUTICALS, INC

One Luitpold Drive | P.O. Box 9001 | Shirley, NY 11967
1-800-645-1706 | Fax: 631-924-1731 | www.americanregent.com

American Regent, Inc. has recently obtained FDA approval to market the 10% Calcium Chloride Injection, USP, NDC 0517-6710-01. This product will have a *grey* cap color and a white and yellow label.

The FDA-approved presentation is expected to launch in February and may be on your shelves at the same time as the marketed unapproved vial with the mauve colored cap. The vial presentations with their respective NDCs are provided below for your reference.

We appreciate your review of this information and please feel free to utilize this information, as you deem applicable. This information will appear on our website, www.americanregent.com, under "Products", then "Safety Updates".

American Regent, Inc. is dedicated to reducing medication errors and providing timely information to healthcare providers.

Marketed Unapproved

Marketed Unapproved

FDA Approved

Please see links above or attached for accompanying full Prescribing Information included herewith for both products.

You are encouraged to report Adverse Drug Events (ADEs) to American Regent:
Email: pv@luitpold.com; Fax: 1-610-650-0170;
Phone: 1-800-734-9236

ADEs may also be reported to the FDA
at 1-800-FDA-1088 or to
www.fda.gov/Medwatch

Drug Information:
1-888-354-4855
(9:00 am - 5:00 pm Eastern Time, Monday - Friday)
Email: inquiry@americanregent.com

Please contact American Regent, Inc. at 1-888-354-4855 if you have any questions about Calcium Chloride Injection, USP or the information above.

Sincerely,

Shivani Kapadia

Shivani Kapadia, R.Ph., Pharm.D.
Clinical Pharmacist, Medical Affairs

CALCIUM CHLORIDE INJECTION, USP 10% (Unapproved)
Rx Only

100 mg/mL (13.6 mEq Calcium/10 mL)
FOR INTRAVENOUS USE ONLY
Osmolarity 2.04 mOsmol/mL

DESCRIPTION: Each mL contains: Calcium Chloride Dihydrate 100 mg in Water for Injection q.s. pH (range 5.5-7.5) adjusted with Hydrochloric Acid and/or Sodium Hydroxide. Each 10 mL contains 13.6 mEq Calcium and 13.6 mEq Chloride. The molecular weight is 147.02 and the molecular formula is $CaCl_2 \bullet 2H_2O$. Sterile, nonpyrogenic.

CLINICAL PHARMACOLOGY
Calcium is the fifth most abundant element in the body; the major fraction is in bone. It is essential for the functional integrity of the nervous and muscular systems, for normal cardiac contractility and the coagulation of blood. It also functions as an enzyme cofactor and affects the secretory activity of endocrine and exocrine glands.

INDICATIONS AND USAGE
Calcium Chloride is indicated in the immediate treatment of hypocalcemic tetany. Other therapy, such as parathyroid hormone or vitamin D, may be indicated according to the etiology of the tetany. It is also important to institute oral calcium therapy as soon as practicable. Calcium salts have been used as adjunctive therapy in a number of conditions, including the following:

Insect bites or stings, such as Black Widow Spider bites.

Sensitivity reactions, particularly when characterized by urticaria.

As an aid in the treatment of depression due to overdosage of magnesium sulfate.

As an aid in the management of the acute symptoms in lead colic.

In cardiac resuscitation, particularly after open heart surgery, calcium chloride has been used when epinephrine has failed to improve weak or ineffective myocardial contractions.

CONTRAINDICATIONS
In cardiac resuscitation, the use of calcium chloride is contraindicated in the presence of ventricular fibrillation.

If neonates are required, or expected to require, treatment with calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition, ceftriaxone sodium injection is contraindicated because of the risk of precipitation of ceftriaxone-calcium.

A small number of cases of fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving calcium-containing fluids and ceftriaxone. In some of these cases, the same intravenous infusion line was used for both calcium-containing fluids and ceftriaxone and in some a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom calcium-containing fluids and ceftriaxone were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates.

WARNINGS
This solution is suitable only for intravenous use. Calcium chloride solution injection into muscle or into subcutaneous or perivascular tissue may cause severe necrosis and sloughing. Intravenous injections of this drug must be made with great care to avoid leakage into the perivascular tissue.

This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS
To avoid undesirable reactions that may follow intravenous administration of calcium chloride, the rate of injection should not exceed 0.5 mL to 1 mL per minute.

Because of the danger involved in the simultaneous use of calcium salts and drugs of the digitalis group, a digitalized patient should not receive an intravenous injection of a calcium compound unless the indications are clearly defined.

Interaction with Ceftriaxone Sodium Injection: **Do not use diluents containing calcium to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form. Precipitation of ceftriaxone-calcium can also occur when calcium-containing solutions are mixed with ceftriaxone in the same IV administration line. Calcium-containing IV solutions, including continuous calcium-containing infusions such as parenteral nutrition must not be administered simultaneously with ceftriaxone via a Y-site. However, in patients other than neonates, calcium-containing solutions and**

ceftriaxone may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. *In vitro* studies using adult and neonatal plasma from umbilical cord blood demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium.

There have been no reports of an interaction between oral calcium-containing products and ceftriaxone or interaction between calcium-containing products (IV or oral) and intramuscular ceftriaxone.

USE IN PREGNANCY
Safety for use in pregnancy has not been established. Use of calcium chloride in women of childbearing potential requires that anticipated benefits be weighed against possible hazards.

ADMINISTRATION AND DOSAGE
The usual adult dose of this preparation varies from 5 to 10 mL at intervals of 1 to 3 days.

In cardiac resuscitation, the usual dose is 2 to 4 mL injected into the ventricular cavity. Care should be taken to avoid injection into the cardiac muscle.

Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permit.

TREATMENT OF OVERDOSE
Inadvertent systemic overloading with calcium ion can produce an acute hypercalcemic syndrome. The syndrome is characterized by weakness, lethargy, intractable nausea and vomiting, coma, and sudden death, and a markedly elevated plasma calcium level. It is suggested that details of treatment of this problem be obtained by reference to Harrison's Principles of Internal Medicine Sixth Edition, pg. 475, column 2, "Acute Hypercalcemic Syndrome".

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) (See USP Controlled Room Temperature).

HOW SUPPLIED: Calcium Chloride Injection, USP 10%. (No preservative added).

NDC 0517-2710-25 10 mL single dose vial packed in a box of 25

IN2710
Rev. 7/11
MG #14274

AMERICAN
REGENT, INC.
SHIRLEY, NY 11967

10% Calcium Chloride Injection, USP

1 Gram (100 mg/mL)

Represents 27 mg (1.4 mEq) Ca++/mL

A HYPERTONIC SOLUTION IN A 10 ML SINGLE-DOSE VIAL FOR PROMPT INTRAVENOUS INJECTION.

CAUTION: This solution must not be injected intramuscularly or subcutaneously.

Administer only by slow injection (not to exceed 1 mL/minute)

Rx only

DESCRIPTION

10% calcium chloride injection is a sterile, nonpyrogenic, hypertonic solution. Each mL contains 100 mg (1.4 mEq/mL) of calcium chloride, dihydrate (1.4 mEq each of Ca++ and Cl−) in water for injection. It is provided in a 10 mL single-dose vial to facilitate prompt intravenous injection. The solution contains no bacteriostat, antimicrobial agent or added buffer and is intended for use only as a single-dose injection. The pH of 10% calcium chloride injection is 6.3 (5.5 to 7.5) when diluted with water for injection to make a 5% solution. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment. The osmolar concentration is 2.04 mOsmol/mL (calc.). 10% calcium chloride injection is oxygen sensitive.

Calcium chloride dihydrate is chemically designated $CaCl_2 \bullet 2H_2O$ (dihydrate) and is described as white, odorless fragments or granules freely soluble in water.

CLINICAL PHARMACOLOGY

Calcium is the fifth most abundant element in the body and the major fraction is in the bony structure. Calcium plays important physiological roles, many of which are poorly understood. It is essential for the functional integrity of the nervous and muscular systems. It is necessary for normal cardiac function and is one of the factors that operates in the mechanisms involved in the coagulation of blood.

Calcium chloride in water dissociates to provide calcium (Ca++) and chloride (Cl−) ions. They are normal constituents of the body fluids and are dependent on various physiological mechanisms for maintenance of balance between intake and output. Approximately 80% of body calcium is excreted in the feces as insoluble salts; urinary excretion accounts for the remaining 20%.

INDICATIONS AND USAGE

10% calcium chloride injection is indicated for the treatment of hypocalcemia in those conditions requiring a prompt increase in plasma calcium levels.

CONTRAINDICATIONS

Calcium chloride is contraindicated for cardiac resuscitation in the presence of ventricular fibrillation or in patients with the risk of existing digitalis toxicity.

Calcium chloride is not recommended in the treatment of asystole and electromechanical dissociation.

WARNINGS

10% Calcium chloride injection is irritating to veins and must not be injected into tissues, since severe necrosis and sloughing may occur. Great care should be taken to avoid extravasation or accidental injection into perivascular tissues.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

Do not administer unless solution is clear and seal is intact. Discard unused portion.

Because of its additive effect, calcium should be administered very cautiously to a patient who is digitalized or who is taking effective doses of digitalis or digitalis-like preparations.

Injections should be made slowly through a small needle into a large vein to minimize venous irritation and avoid undesirable reactions. It is particularly important to prevent a high concentration of calcium from reaching the heart because of the danger of cardiac syncope.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies with solutions in polypropylene syringes have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pediatric Use:
Safety and effectiveness are based on similar clinical conditions in children and adults.

Pregnancy:
Animal reproduction studies have not been conducted with calcium chloride. It also is not known whether calcium chloride can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Calcium chloride should be given to a pregnant woman only if clearly needed.

Geriatric Use:
An evaluation of current literature revealed no clinical experience identifying differences in response between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Rapid injection may cause the patient to complain of tingling sensations, a calcium taste, a sense of oppression or “heat wave”.

Injections of calcium chloride are accompanied by peripheral vasodilatation as well as a local “burning” sensation and there may be a moderate fall in blood pressure.

Should perivascular infiltration occur, intravenous administration at that site should be discontinued at once. Local infiltration of the affected area with 1% procaine hydrochloride, to which hyaluronidase may be added, will often reduce venospasm and dilute the calcium remaining in the tissues locally. Local application of heat may also be helpful.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

Too rapid injection may produce lowering of blood pressure and cardiac syncope. Persistent hypercalcemia from overdosage of calcium is unlikely because of rapid excretion. In the event of untoward effects from excessive calcium administration, the drug should be discontinued promptly, the patient re-evaluated and appropriate countermeasures instituted, if necessary. See **PRECAUTIONS** and **ADVERSE REACTIONS**.

DOSAGE AND ADMINISTRATION

10% calcium chloride injection is administered only by slow intravenous injection (not to exceed 1 mL/min), *preferably in a central or deep vein*.

The usual precautions for intravenous therapy should be observed. If time permits, the solution should be warmed to body temperature. The injection should be halted if the patient complains of any discomfort; it may be resumed when symptoms disappear. Following injection, the patient should remain recumbent for a short time.

The usual adult dosage in hypocalcemic disorders ranges from 200 mg to 1 g (2 to 10 mL) at intervals of 1 to 3 days depending on the response of the patient and/or results of serum ionized calcium determinations. Repeated injections may be required because of rapid excretion of calcium.

The pediatric dosage in hypocalcemic disorders ranges from 2.7 to 5 mg/kg hydrated calcium chloride (or 0.136 to 0.252 mEq elemental calcium per kg, or 0.027 to 0.05 mL of 10% calcium chloride injection per kg). No data from clinical trials is available about repeated dosages, though textbook references recommend repeat dosages q 4 to 6 hours.

Caution: 10% calcium chloride injection consists of 1 gram of calcium chloride in a 10 mL vial, or 100 mg/mL. This concentration represents 27 mg or 1.4 mEq of elemental calcium per mL. Thus, one 10 mL vial provides 270 mg of elemental calcium. The dosage recommendation in various references is given either as amount of calcium chloride or amount of elemental calcium, and often it is not specified. Ionized calcium concentrations should be measured, to assist in dosage adjustment.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. See **PRECAUTIONS**.

HOW SUPPLIED

10% calcium chloride injection, USP is supplied in single-dose containers as follows:

NDC No.	**Container**	**Size**	**Carton**
0517-6710-10	Glass Vial	10 mL	10 Vials

Store at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

CLINICAL STUDIES

Medical literature also refers to the administration of calcium chloride in the treatment of magnesium intoxication due to overdosage of magnesium sulfate, and to combat the deleterious effects of hyperkalemia as measured by electrocardiogram (ECG), pending correction of the increased potassium level in the extracellular fluid. However, adequate well-controlled, randomized clinical studies have not been done to support these indications.

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

AMERICAN REGENT
SHIRLEY, NY 11967

Revised: July 2017

IN6710