SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CALCİOSEL 10% Ampoule Containing Solution for Injection

2. QUALITATIVE AND QUANTITATIVE

COMPOSITIONS Active substance:

Each ampoule contains:

Calcium gluconate monohydrate	225 mg
Calcium levulinate dihydrate	572 mg

Excipients:

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Ampoule

Clear, colorless solution for injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Hypoparathyroidism, fast growth or pregnancy-induced hypocalcemia
- Tetany due to calcium deficiency
- Auxiliary for rickets and osteomalacia treatment
- Acute colics observed in lead poisoning
- Magnesium sulfate poisoning
- Allergic conditions
- Nonthrombocytopenic purpura
- Exudative dermatoses
- Medicine-induced itching
- Prevention of hypocalcemia development in blood transfusion
- Auxiliary for acute floral poisoning
- Acute hypocalcemia
- Cardiac resuscitation
- Some forms of neonatal tetany.

4.2. Posology and method of administration

Posology/administration frequency and time:

Serum calcium levels should be closely monitored during treatment.

As antihypocalcemic and electrolyte regenerator: Intravenously, 970 mg (94.7 mg calcium ion) is slowly administered at a speed not exceeding 5 ml per minute (47.5 mg calcium ion). If necessary, this dose is repeated until the tetany is taken under control.

As antihypercalcemic: Intravenously, 1-2 g (94.7189 mg calcium ion) is slowly administered at a speed not exceeding 5 ml per minute (47.5 mg calcium ion). During administration, the change in the ECG is continually monitored and adjusted, and the amount is determined.

As antihypermagnesemic: Intravenously, 1-2 g (94.7189 mg calcium ion) is slowly administered at a speed not exceeding 5 ml per minute (47.5 mg calcium ion). Adult dose is limited to daily 15 grams (1.42 grams calcium ion).

Acute hypocalcemia: 10-20 ml (2.2-4.4 mmol)

Fluoride poisoning: 0.3 ml/kg (0.07 mmol/kg)

Lead poisoning: 0.3 ml/kg (0.07 mmol/kg)

Neonatal tetany: 0.3 ml/kg (0.07 mmol/kg)

Cardiac resuscitation: 7-15 ml (1.54-3.3 mmol). It is difficult to determine the exact calcium amount needed for this indication and it usually varies.

Method of administration

Intramuscular use:

It should be injected to the gluteus medius muscle being the most favorable area anatomically. An injector with a needle of 5cm should be used for injection. After injection, cover the injection area with a piece of cotton and help the liquid to completely distribute by deep massage. For continued injections, the injection area should be alternated as right and left. A longer needle is used for obese people. Otherwise, fatty tissues causes difficult resorption of calcium salts, and infiltration may arise. Apply heat for the infiltrations caused by subcutaneous medicine leaks.

Intravenous use:

Intravenous administration should be slow, and it should be injected within 1.5 to 3 minutes.

Patient should be in lying position.

CALCIOSEL 10% should be diluted with 5% glucose or 0.9% sodium chloride solution. The use of the diluting solutions containing bicarbonate, phosphate or sulfate should be avoided.

Additional information for specific populations:

Renal failure:

When high doses of calcium is given to the patients with chronic renal disorder, hypercalcemia may occur. As hypercalcemia is more dangerous than hypocalcemia, excessive treatment of hypocalcemia should be avoided. Plasma calcium concentration should be monitored closely in the patients with renal failure. The patient is also given vitamin D in parenteral administrations and high doses. It should not be used in those with severe renal failure.

Hepatic failure:

Dose adjustment is not necessary for patients with hepatic failure.

Pediatric population and the youth:

As antihypocalcemic:

Intravenously, 200 to 500 mg (19.5 to 48.8 mg calcium ion) is slowly administered in a single dose at a speed not exceeding 5 ml per minute (47.5 mg calcium ion). If necessary, it is repeated until the tetany is taken under control.

Geriatric population:

Although there is no evidence proving that the calcium tolerance is affected at advances ages, a dose reduction might be necessary as some aging-related factors such as renal function disorder and weak diet may affect the tolerance indirectly. Renal functions become weaker at advanced ages; when prescribing this product for old patients, remember that the use of calcium injection with repeated and long-term doses in the patients with impaired renal functions contraindicates (See Section 4.3).

4.3. Contraindications

CALCIOSEL 10% is contraindicated in the following cases:

- The patients hypersensitive to any of calcium gluconate monohydrate or calcium levulinate dihydrate,
- Those with severe renal disorders,
- Patients treated with cardiac glycosides,

- Those with ventricular fibrillation or hypercalcemia,
- Those with sarcoidosis, renal and cardiac disorders,
- Those with severe hypercalciuria.

4.4. Special warnings and precautions for use

When it is required to administer CALCIOSEL 10% to the patients receiving high doses of digitalis treatment, it can be used after the digitalis treatment is discontinued for 3 days in order not to cause digitaline accumulation.

Plasma calcium level and excretion should be closely monitored.

4.5. Interactions with other medicinal products and other forms of interaction

Especially when the calcium is administered intravenously, the toxic effects of cardiac glycosides and calcium are synergistic, and arrhythmias may occur.

When received concomitantly with tetracycline class antibiotics, it deactivates these antibiotics. Hypercalcemia risk may increase when it is used with thiazides.

It also affects some laboratory techniques. For example, it produces erroneous negative value for magnesium in serum and urine in the "Titan Yellow" method. "Glenn-Nelson" technique causes temporary increases in the determination of plasma 11-Hydroxycorticosteroid concentration.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Due to the lack of adequate studies conducted on females in pregnancy and lactation period, it should be used according to doctor’s recommendation.

Fertile women / Birth control (Contraception) There is no study showing the effect of CALCIOSEL 10% on the fertile women and the birth control (contraception).

Pregnancy

The animal studies are insufficient to provide data for the effects on pregnancy and/or embryonal/fetal development and/or delivery and/or postnatal development (see Section 5.3). The potential risk for human is unknown.

CALCIOSEL 10% should not be taken during pregnancy unless necessary.

Lactation

Calcium passes to the breast milk; therefore, care should be exercised when administering to lactating mothers.

Fertility

No data is available.

4.7. Effects on ability to drive and use machines

It has no adverse effect on driving and using machines.

4.8. Undesirable effects

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), unknown (cannot be estimated with available data).

Blood and lymphatic system disorders

Uncommon: Hypercalcemia.

Cardiac disorders

Very rare: Vasodilation, reduced blood pressure, bradycardia, cardiac arrhythmia, syncope and cardiac arrest, tear, cardiac tamponade or pneumothorax, ventricular fibrillation.

General disorders and diseases related with administration site

Common: Distress, heat wave, chalk taste

Very rare: Local necrosis, apse

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

The the symptoms of excessively increased blood calcium include loss of appetite, vomiting, constipation, stomach ache, muscle weakness, thirst, polyurea, numbness, confusion, demineralization-induced bone pain, nephrocalcinosis, loss of renal concentration capacity, sometimes cardiac arrhythmia, comatose and cardiac arrest.

For moderate hypercalcemia, oral phosphate compounds can be administered as phosphorus

equivalent in the form of neutral solution (pH= 7.4) up to 3 grams per day.

Antidote

Disodium edetate is used for the rescue treatment of the hypercalcemia or the ventricular arrhythmia accompanied by digitalis poisoning. This substance forms a chelate compound with the calcium ion.

For hypercalcemia treatment, the disodium edetate dose of 50 mg/kg is slowly administered through intravenous infusion provided that the general total adult dose is up to 3 grams per 24 hours at most. Commercially available concentrated disodium edetate solution should be diluted to this ratio. The undiluted solution is very irritating on the tissue. Extravasation should be avoided. A fast intravenous infusion or a high concentration of disodium edetate causes a sudden drop in the serum calcium concentration.

The calculated amount of disodium edetate is added into 500 ml of 5% dextrose or 0.9% sodium chloride, and it is administered intravenously for 3 hours or longer. The duration and administration frequency of disodium edetate treatment are quite variable. The conditions should be determined according to the serum calcium concentration of the patient. The daily dose for hypercalcemia is 40-70 mg/kg for children.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Calcium (combination of different salts)
ATC code: A12AA20

Calcium is a basic body electrolyte. It is necessary for the functional integrity of the nerves and muscles, and essential for muscle contraction, cardiac functions and blood coagulation.

Normally, the cytoplasmic concentration of calcium is kept stable at very low levels such as 0.1-1.0 μmol per liter due to extracellular calcium extraction and the secretion by intracellular organelles (particularly endoplasmic reticulum). Many electrical or chemical stimulants affect the calcium ion intake from plasma membranes or its release from cell stocks. These calcium ions interact with the high-affinity binding areas of specific intracellular proteins such as troponin so that they regulate many functional and metabolic processes.

Calcium ions are essential for the normal functions of neuromuscular appaartus. Hypocalcemia causes reduction in the stimulation threshold, thereby results in tetany. Hypercalcemia increases the stimulation threshold of the nerves and muscles, thereby results in

weakness and lethargy. Calcium ions are necessary for muscle contraction. Calcium is bound to troponin and removes the inhibiting effect of troponin on actin and myosin.

Calcium ions also play an important role in ensuring the stimulation-secretion link in many endocrine and exocrine glands

Calcium ions are essential for ensuring the normal stimulation-secretion link in the myocardium and conveying electrical stimulations at certain cardiac areas (particularly from AV node). The start of contraction in vascular or other smooth muscles also depends on the calcium ions.

These cardiac and vascular smooth muscle effects can be prevented by several calcium channel blocking medicines used in the treatment of angina, hypertension and cardiac arrhythmias.

Calcium ions also serves in the intrinsic and extrinsic pathways of blood coagulation.

5.2. Pharmacokinetic properties

Absorption:

When administered by intramuscular or intravenous routes, calcium salts are directly absorbed. Absorption is increased with parathormone and vitamin D.

Distribution:

After absorption, calcium firstly passes to the intercellular fluid, then to the skeletal tissue.

Biotransformation:

The calcium concentration in the blood serum immediately rises following the intravenous injection of calcium salts, and it returns to the baseline values after 30 minutes to 2 hours.

Elimination:

Calcium is excreted mainly through urine. A smaller amount of it is lost through sweat, skin, hair and nails. Calcium pass through the placenta and exists in the breast milk.

Linearity/non-linearity:

Linearity was not shown in the animal studies.

5.3. Pre-clinical safety data

No additional pre-clinical safety data is available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injection

6.2. Incompatibilities

When received concomitantly with tetracycline class antibiotics it deactivates these antibiotics.

6.3. Shelf life

24 months

6.4. Specific precautions for storage

Keep at room temperatures below 25°C by protecting from light. Protect from freezing. When the product is mixed with 5% dextrose and 0.9% sodium chloride, it remains stable for 24 hours at 25 ºC.

Only use the clear, transparent ampoule solutions. If there is any crystallization inside the ampoule, it can be used after eliminating the crystallization by heating the ampoule up to 30-40 °C before use. If crystallization is not eliminated or there are residues, do not use the ampoules.

6.5. Nature and content of the package

5 amber glass ampoules of 10 ml, within carton box

6.6 Disposal of the residues of the medicinal products for human use and other special precautions Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulations" and "Packaging and Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

2016/372

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 20.04.2016

Renewal date of the authorization: ---

10. DATE OF REVISION OF THE TEXT

20/04/2016