SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CALCİOSEL 225 mg + 572 mg / 10 mL Solution for Injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each ampoule contains;

Calcium gluconate monohydrate	225 mg
Calcium levulinate dihydrate	572 mg

Excipient(s):

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Ampoule

Clear, colorless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Hypoparathyrodism, rapid growth or pregnancy-induced hypocalcemia
- Tetany due to calcium deficiency
- Helps treat rickets and osteomalacia
- Acute colic seen in lead poisoning
- Magnesium sulfate poisoning
- Allergic conditions
- Non-thrombocytopenic purpura
- Exudative dermatoses
- Itching caused by drugs
- Prevention of development of hypocalcemia in blood transfusion
- As an aid in acute floral poisoning
- Acute hypocalcemia
- Cardiac resuscitation
- Used in some forms of neonatal tetania.

4.2. Posology and method of administration

Posology/administrationfrequency and duration

Serum calcium levels should be closely monitored during treatment.

Antihippocalcemic and electrolyte replenisher: 970 mg (94.7 mg calcium ions) administered slowly intravenously at a rate not exceeding 5 mL per minute (47.5 mg calcium ions). This dose is repeated if necessary, until tetany is under control.

Antihyperkalaemically: 1 to 2 grams (94.7 to 189 mg of calcium ions) are administered slowly intravenously at a rate not exceeding 5 mL per minute (47.5 mg calcium ions). During the administration, the change of ECG is constantly monitored and adjusted and its amount is determined.

Antihypermagnesemic: 1 to 2 grams (94.7 to 189 mg of calcium ions) is administered slowly intravenously at a rate not exceeding 5 mL per minute (47.5 mg calcium ions). Adult dose limit is 15 grams (1.42 grams of calcium ions) per day.

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). Determining the exact amount of calcium required for this indication is difficult and often varies.

Method of administration:

Intramuscular administration:

Anatomically, the most convenient place is to inject into the gluteus medius muscle. An injector with a 5cm long needle should be used for injection. After the injection, the needle site is covered with a piece of cotton and the liquid is spread thoroughly with deep massage. In continuous injections, the injection site should be changed to the right and left. Longer needles are used in obese people. Otherwise, calcium salts are difficult to absorb by adipose tissues and may cause infiltration. It should be applied hot in infiltrations caused by the ingress of the drug under the skin.

Intravenous administration:

Intravenous administration should be done slowly and should be injected in 1.5 to 3 minutes. The patient should be in a lying position.

CALCİOSEL should be diluted with 5% glucose or 0.9% sodium chloride solution. The use of dilution solutions containing bicarbonate, phosphate or sulfate should be avoided.

Additional information for special populations:

Renal impairment:

Hypercalcemia may occur when high doses of calcium are given in patients with chronic kidney disease. Since hypercalcemia is a more dangerous condition than hypocalcemia, excessive treatment of hypocalcemia should be avoided. Plasma calcium concentration should be closely monitored in patients with renal insufficiency. Vitamin D is also given to the patient in parenteral administration and in high doses. It should not be used in patients with severe kidney failure.

Hepatic impairment:

No dose adjustment is required in patients with hepatic impairment.

Pediatric population and adolerescents:

As an antihypocalcemic:

Intravenously, 200 to 500 mg (19.5 to 48.8 mg of calcium ions) are administered slowly in a single dose and at a rate not exceeding 5 ml per minute (47.5 mg calcium ions). It is repeated if necessary, until the tetany is under control.

Geriatric population:

Although there is no evidence that calcium tolerance is affected by eld, a dose reduction may be required as some factors associated with aging, such as renal dysfunction and poor diet may indirectly affect tolerance. It should be kept in mind that recurrent and prolonged doses of calcium injection are contraindicated in patients with impaired renal function, while renal function is impaired at advanced ages and elderly patients are prescribed this product (See Section 4.3).

4.3. Contraindications

CALCİOSEL is contraindicated in the following situations:

- Hypersensitivity to calcium gluconate monohydrate, calcium levulinate dihydrate substances.
- Those with severe kidney disease,
- In patients treated with cardiac glycosides,
- Those with ventricular fibrillation or hypercalcemia,
- Those with sarcoidosis, kidney and heart disease,
- Those with severe hypercalciuria.

4.4. Special warnings and special precautions for use

When CALCİOSEL is required to be administered to patients who have received high doses of digitalis treatment, it can be used after a 3-day pause to digitalis treatment in order not to cause digitalis accumulation.

Plasma calcium level and excretion should be closely monitored.

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

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

Concomitant use with tetracycline class antibiotics, these render antibiotics ineffective.

Increased risk of hypercalcemia when used with thiazides.

It also affects some laboratory techniques. For example, with the "Titan Yellow" method, it gives a false negative value for magnesium in serum and urine. Transient increases also occur in the determination of 11-Hydroxycorticosteroid concentration in plasma by "Glenn-Nelson" technique.

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

It should be used according to the doctor's recommendation since there are not enough studies in women during pregnancy and lactation.

Women with child-bearing potential/Contraception

There is no study showing that CALCİOSEL has an effect on women with childbearing potential or birth control (contraception).

Pregnancy

Animal studies are insufficient in terms of effects on pregnancy/and/or/embryonal/fetal development/and/or/birth/and-or/postnatal development (see section 5.3). The potential risk for humans is unknown.
CALCİOSEL should not be used during pregnancy unless necessary.

Lactation
Calcium passes into breast milk, so caution should be exercised when administering it to nursing mothers.

Fertility
There is no data available.

4.7. Effects on ability to drive and use machines
It has no effect on driving and machine use.

4.8. Undesirable effects
All side effects with a higher incidence than placebo are listed below in terms of organ system and frequency.
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 (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: Hypercalcemia.

Cardiac diseases
Very rare: Vasodilation, drop in blood pressure, bradycardia, cardiac arrhythmia, syncope and cardiac arrest, rupture, cardiac tamponade or pneumothorax, ventricular fibrillation.

General disorders and administration site conditions
Common: Distress, heat fluctuation, feeling of chalk taste
Very rare: Local necrosis, abscess.

<u>Reporting of suspected adverse reactions</u>
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

Symptoms:

Excessive increase in the amount of calcium in the blood, signs of hypercalcemia; Lack of appetite, vomiting, constipation, abdominal pain, muscle weakness, thirst, polyuria, numbness, confusion, bone pain due to demineralization, nephrocalcinosis, loss of kidney concentration capacity, cardiac arrhythmia, coma and cardiac arrest in some serious cases.

In moderate hypercalcemia, oral phosphate compounds can be given in the form of a neutral solution (pH = 7.4), up to 3 grams of phosphorus equivalent per day.

Treatment:

Disodium edetate substance is used for salvage treatment of hypercalcemia or ventricular arrhythmia with digitalis poisoning. It is a substance that forms a chelate compound with calcium ion.

For the treatment of hypercalcemia, the usual adult dosage is 50 mg/kg of disodium edetate, up to a total of up to 3 grams in 24 hours, administered slowly by intravenous infusion. Commercially available disodium edetate concentrate solution should be diluted at this rate. Undiluted solution is very irritating to the tissue. Extravasation should be avoided. A rapid intravenous infusion or a high concentration of disodium edetate causes the serum calcium concentration to drop abruptly.

The calculated amount of disodium edetate solution is added to 500 mL of 5% dextrose or 0.9% sodium chloride and given intravenously over 3 hours or more. The duration of disodium edetate treatment and the frequency of administration vary widely. Conditions should be determined based on the patient's serum calcium concentration. The daily dose for hypercalcemia in children is 40-70 mg / kg.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium (combination of different salts)

ATC code: A12AA20

Calcium is an essential body electrolyte. It is necessary for the functional integrity of nerves and

muscles and is essential for muscle contraction, heart function and blood coagulation.
Normally, thanks to the extracellular extraction of calcium and its secretion by intracellular organelles (especially the endoplasmic reticulum), the cytoplasmic concentration of calcium are kept constant at very low levels of about 0.1-1.0 µmol per liter. Many electrical or chemical stimuli trigger the intake of calcium ions through the plasma membrane or its release from cell stocks. These calcium ions interact with the high affinity binding sites of specific intracellular proteins such as troponin and thus regulate many functional and metabolic processes.
Calcium ions are essential for the normal functions of the neuromuscular apparatus. Hypocalcemia causes the arousal threshold to drop, resulting in tetany. Hypercalcemia raises the stimulation threshold of nerves and muscles, which can lead to muscle weakness and lethargy. Calcium ions are essential for muscle contraction. Calcium binds to troponin, removing the inhibitory effect of troponin on actin and myosin.
Calcium ions also play an important role in providing the stimulation-secretion link in many endocrine and exocrine glands.
Calcium ions are essential for the normal excitation-contraction link in the heart muscle and for the transmission of electrical impulses (especially from the AV node) in certain areas of the heart. The initiation of contraction in vascular and other smooth muscles also depends on calcium ions.
These cardiac and vascular smooth muscle effects can be prevented by various calcium channel blocker drugs used in the treatment of angina, hypertension, and cardiac arrhythmias.
Calcium ions also take part in intrinsic and extrinsic pathways of blood coagulation.

5.2 Pharmacokinetic properties

Absorption:

When administered intramuscularly or intravenously, calcium salts are absorbed directly. Absorption is increased by parathormone and vitamin D.

Distribution:

After absorption, calcium first enters the intercellular fluid and then into skeletal tissue.

Biotransformation:

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

Elimination:

Calcium is excreted mainly in the urine. A smaller amount is lost through sweat, skin, hair and nails.
Calcium crosses the placenta and is found in breast milk.

Linearity / nonlinearity situation:
It did not show linearity in animal studies.

5.3 Preclinical safety data
There is no additional pre-clinical safety information.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Water for injection

6.2 Incompatibilities
Concominant use with the tetracycline class of antibiotics, it makes these antibiotics ineffective.

6.3 Shelf life
24 months

6.4 Special precautions for storage
It should be stored at room temperature below 25 °C, protected from light. It must be protected from freezing.
The product is stable for 24 hours at 25 °C when mixed with 5% dextrose and 0.9% Sodium Chloride.
Only clear, transparent ampoule solutions can be used. If any crystallization has occurred in the ampoule, it can be used after complete removal of crystallization by heating the ampoule up to 30-40 °C before use. Ampoules that cannot be removed or have sediment cannot be used.

6.5 Nature and contents of container
10 mL amber colored, 5 pieces glass ampoules in a carton box

6.6 Instructions for use and handling and disposal
Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

HAVER FARMA İlaç A.Ş.
Akbaba Mah. Maraş Cad. No:52/2/1 34820 Beykoz / İstanbul
Tel: 0216 324 38 38
Faks: 0216 317 04 98
E-posta: info@haver.com.tr

8. MARKETING AUTHORISATION NUMBER

2016/372

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20.04.2016

Date of latest renewal: ----

10. DATE OF REVISION OF THE TEXT

PATIENT INFORMATION LEAFLET

CALCİOSEL 225 mg + 572 mg / 10 mL Solution for Injection

Sterile

Administered intravenously and intramuscularly.

- ***Active substance:*** Each ampoule contains 225 mg calcium gluconate monohydrate and 572 mg calcium levulinate dihydrate.
- ***Excipients:*** Water for injection

Before using this medicine, read all of this PATIENT INFORMATION LEAFLET carefully. Because, this leaflet includes important information for you.

- *Keep this PATIENT INFORMATION LEAFLET. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you. Do not pass it on to others.*
- *During the use of this medicine, tell that you are using this medicine when you go to a doctor or hospital.*
- *Follow these instructions exactly as written. Do not use **higher or lower** dose other than your recommended dose.*

What is in this leaflet:

Headings are included.

1. What CALCİOSEL is and what it is used for?

CALCİOSEL is the ampoule included in the class of calcium drug substance from the mineral support group.

CALCİOSEL is a clear, colorless solution in 10 mL amber glass ampoules.

Each box contains 5 ampoules.

CALCİOSEL helps the treatment due to the slow functioning of the parathyroid gland, the amount of calcium in the blood below normal due to rapid growth or pregnancy, the muscle

twitching due to the calcium amount being below normal, in children (rachitis) and adults, to help the treatment due to defects in bone formation, to prevent intestinal contractions in case of lead poisoning, magnesium, in sulphate poisoning, allergic conditions, in case of purple spots due to bleeding under the skin, itching due to drugs used in non-inflammatory skin disease with water accumulation, preventing the decrease in calcium level in the blood when blood transfusion, fluoride poisoning, sudden decreases in the amount of calcium in the blood, sudden heart, in the treatment of arrest, neonatal tetany (a condition that affects the muscles in newborn babies).

2. What you need to know before you use CALCİOSEL

If you are taking medication for heart disease, tell your doctor.

DO NOT USE CALCİOSEL;

If;

- You are sensitive to calcium gluconate monohydrate, calcium levulinate dihydrate,
- You have severe kidney failure,
- You are being treated with medications that cause stronger heart contraction,
- You have a palpitations,
- You have sarcoidosis,
- You have kidney and heart disease

Do not use.

USE CALCİOSEL CAREFULLY in the following situations;

If you are pregnant

If these warnings are valid for you, even at any time in the past, please consult your doctor.

Use of CALCİOSEL with food and drink

No interaction with food and drink with CALCİOSEL.

Pregnancy

Consult your doctor or your pharmacist before using the drug.

Should not be used during pregnancy unless necessary.

If you notice you are pregnant during treatment, consult your doctor or pharmacist immediately.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

Calcium passes into breast milk, so caution should be exercised when administering it to nursing mothers.

Driving and using machines

It has no effect on the ability to drive and use machines.

Important information about some excipients found in the composition of CALCİOSEL

There are no excipients that require warning.

Use with other medicines

CALCİOSEL should not be used with drugs such as digoxin, which cause stronger contraction of the heart.

Thiazide diuretic (increasing urine excretion) drugs may increase the blood calcium level by reducing urinary calcium excretion.

CALCİOSEL can inactivate tetracycline class antibiotics.

If you are using or have recently used any type of prescription or non-prescription drugs, please inform your physician or your pharmacist.

3. How to use CALCİOSEL

Instructions for appropriate use and dose/administration frequency:

Your doctor will determine the dose of the drug depending on your illness and which will be administered to you.

Method of administration:

CALCİOSEL is administered intravenously and intramuscularly by your doctor.

Different age groups:

Pediatric Use:

Your doctor will determine and administer the dose of the medicine depending on your child's condition.

Geriatric Use:

Your doctor will determine and administer the dose of the medicine depending on your condition.

Special use cases:

If you have severe kidney disorder, tell your doctor. Follow-up by the doctor is required for use in kidney patients.

Unless your doctor recommends otherwise follow these instructions.

Your doctor will inform you about how long your treatment will take with CALCİOSEL.

Talk to your doctor or pharmacist if you have the impression that the effect of CALCİOSEL is too strong or weak.

If you have used more CALCİOSEL than you should

If you have used more CALCİOSEL than you should use, talk to a doctor or pharmacist.

If you use CALCİOSEL more than you should, because the calcium levels in your blood will increase excessively, loss of appetite, vomiting, constipation, abdominal pain, muscle weakness, feeling as thirsty, frequent urination, lethargy, confusion, bone pain due to mineral deficiency, calcification in kidney tissue will cause pain in the kidney due to its arrival, excessive increase in the amount of urine due to loss of kidney concentration capacity, heart rhythm disturbances, coma and cardiac arrest may occur in some serious cases.

If you forget to use CALCİOSEL

Your doctor will decide when to administer the missed dose. It is important to follow your doctor's instructions for the new administration time of the following dose.

Effects which may occur when treatment with CALCİOSEL is concluded

Your doctor will inform you about how long your treatment will take with CALCİOSEL.

Do not conclude the treatment without consulting to your doctor.

4. What are the possible side effects?

Like all medicines, CALCİOSEL may have side effects in people who are sensitive to the substances in its content.

If any of the following occur, stop using CALCİOSEL and IMMEDIATELY tell your doctor or go to the nearest emergency department:

- Low blood pressure (blood pressure), (symptoms: fatigue, weakness, tinnitus, forgetfulness, difficulty concentrating, cold hands and feet, dizziness, blackout)
- Decrease or increase in the number of heartbeats, rhythm disturbances
- Feeling faint.

These are all very serious side effects.

If you have one of these, you have a serious allergy to CALCİOSEL. You may need urgent medical attention or hospitalization.

Side effects are classified as follows:

Very common: It can be seen in at least 1 of 10 patients.

Common: less than one in 10 patients but more than one in 100 patients.

Uncommon: less than one in 100 patients but more than one in 1,000 patients.

Rare: less than one in 1,000 patients but more than one in 10,000 patients.

Very rare: less than one in 10,000 patients.

Unknown: It cannot be estimated from the available data.

Common:

- Hot and distressed flashes
- Chalky taste in the mouth

Uncommon:

- Excessive increase in the amount of calcium in the blood (loss of appetite, vomiting, constipation, abdominal pain, weakness in the muscles, feeling of thirst, frequent urination, lethargy, mental confusion, bone pain due to mineral deficiency, kidney pain, heart rhythm disorders indicating an increased level of calcium in the blood. symptoms).

Very rare:

- Low blood pressure (blood pressure), (symptoms: tiredness, weakness, tinnitus, forgetfulness, difficulty concentrating, cold hands and feet, dizziness, blackout)
- Decrease or increase in the number of heartbeats, rhythm disturbances
- Feeling faint
- Pain, swelling and bruising at the injection site

If you encounter any side effects not mentioned in this patient information leaflet, inform your doctor or pharmacist.

Reporting of the side effects:

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.

5. How to store CALCİOSEL

Keep CALCİOSEL out of the sight and reach of children, and in its packaging.

Store CALCİOSEL at room temperature below 25 °C, protect from light. Protect CALCİOSEL from freezing. The product is stable for 24 hours at 25 °C when mixed with 5% dextrose and 0.9% sodium chloride. If there is any crystallization in the ampoule, it can be used after the crystallization is completely removed by heating the ampoule up to 30-40 °C before use. Ampoules have sediment that cannot be removed, are not used.
Use only clear, transparent ampoule solutions.

Use in compliance with the expiry date.

Do not use CALCİOSEL after the expiration date stated on the packaging/use before the expiration date.

Do not use CALCİOSEL if you notice any damage in the product and/or its package.
Do not throw away expired or unused medicines! Give to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Authorization Holder:

HAVER FARMA İlaç A.Ş.
Akbaba Mah. Maraş Cad. No:52/2/1 34820 Beykoz/İstanbul

Manufacturing Site:

OSEL İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Cad. No.:52 Beykoz/İstanbul

This patient information leaflet was approved on ../../....