1. Name of the veterinary medicinal product:

CALCIMIP VETERINARY

2. Qualitative and quantitative composition :

100 ml solution for infusion contain:

Pharmacological active substances:

Calcium gluconate (Ph. Eur.) (equivalent to Ca^{2+}: 2.15 g or 54 mmol)	24.0 g
Magnesium chloride, 6 H_2O (equivalent to Mg^{2+}: 0.72 g or 30 mmol)	6.0 g
Boric acid	6.0 g

For the full list of excipients, see section 6.1.

The solution does not contain any endotoxins.

Highly hypertonic solution.

3. Pharmaceutical form:

Solution for slow intravenous infusion.
Clear, colourless to slightly yellowish solution for infusion.

4. Clinical particulars

4.1 Target animal species:

Cattle, Sheep.

4.2 Areas of application:

Cattle, Sheep:

For the treatment of hypocalcamia complicated by a deficiency of magnesium in cattle and sheep.

4.3 Contraindications:

- hypercalcaemia and hypermagnesaemia,
- idiopathic hypocalcaemia in foals,
- calcinosis in cattle and small ruminants,
- septicaemic processes in the course of acute mastitis in cattle,
- application in the wake of high doses of vitamin D_3 preparations,
- chronic renal insufficiency,
- intravenous administration of inorganic phosphorous solutions at the same time or shortly thereafter.

4.4 Special warnings for each target animal species:

None known.

4.5 Special precautions for use

Special precautions for use in animals:

Intravenous administration must be performed slowly.

During infusion, cardiac rate and rythm and circulation must be controlled. If any signs of overdose (disturbances of the cardiac rhythm decrease in blood pressure, restlessness) appears, the infusion has to be stopped immediately.

Special safety precautions to be taken by the person administering the medicinal product to animals

None known.

4.6 Adverse reactions (frequency and seriousness)

Even if the therapeutic dosage is correct, transient hypercalcaemia can occur due to the calcium concentration. It presents as follows:

- initial bradycardia,
- restlessness, muscle tremor, salivation,
- increased respiratory frequency.

An increase of heart rate following an initial bradycardia is to be judged as start of an overdose. If this is the case, stop the infusion immediately. Delayed undesirable effects may appear in form of disturbances of the general state of health and symptoms of hypercalcaemia up to 6 – 10 hours after administration and must not be diagnosed as a relapse of hypocalcaemia.

Please also refer to “Overdosing”.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.7 Use during pregnancy, lactation or lay

Not specified.

4.8 Interactions with other medications and other interactions:

Calcium increases the effectiveness of cardiac glycosides.

Calcium strengthens the cardiac effects of β-adrenergic drugs and methylxanthines.

Glucocorticoids increase the renal excretion of calcium due to vitamin D antagonism.

4.9 **Amount(s) to be administered and administration route**

For slow intravenous administration.

Cattle:

Acute hypocalcaemic conditions:
40-50 ml CALCIMIP Veterinary per 50 kg body weight
(equivalent to 0.43 – 0.54 mmol Ca^{2+} and 0.24 – 0.30 mmol Mg^{2+} per kg body weight).

Sheep:

30 ml CALCIMIP Veterinary per 50 kg body weight
(equivalent to 0.32 mmol Ca^{2+} and 0.18 mmol Mg^{2+} per kg body weight).

Intravenous infusion must be administered slowly over a period of 20-30 minutes.

The dosage instructions are guide values and should be adjusted to any existing deficits and particular conditions of the circulatory system.
Observe a reaction time of at least 6 hours after initial treatment before administering the first after treatment. Wait 24 hours before administering addition treatments after ensuring that the persisting symptoms are caused by an on-going hypocalcaemic condition.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

It the intravenous infusion is administered too quickly or if overdosing occurs, hypercalcaemia and/or hypermagnesaemia with cardiotoxic symptoms like initial bradycardia and subsequent tachycardia, cardiac arrhythmia and in severe cases ventricular fibrillation with cardiac arrest can occur due to the calcium content. Further hypercalcaemic symptoms to be considered: motoric weakness, muscle tremor, increased excitability, restlessness, sweat, polyuria, decrease in blood pressure, depression and coma.

If the maximal infusion rate is exceeded, allergic symptoms can occur due to a release of histamine.

In these cases, the infusion must be stopped immediately.

Symptoms of hypercalcaemia may occur even 6 – 10 hours after the infusion and may not be misdiagnosed as recurrence of the hypocalcaemia due to the similarity of the symptoms.

4.11 Withdrawal period(s)

Cattle, sheep, goats, horses:	Edible tissues:	0 days
	Milk:	0 days
Pig:	Edible tissues:	0 days

5. Pharmacological properties:

Substance or indication group:	calcium and magnesium containing infusion
ATCvet code:	QA12AX, calcium, combination with other pharmaceuticals

5.1 Pharmacological properties:

Calcium

Calcium is one of the most important cations in the organism. Only the free ionised calcium in the blood is biologically active and acts as regulative in the calcium metabolism. The free calcium is required for many functions within the body, a.o. at the release of hormones and neutrotransmitters, acts as a mediator in the activity of second messangers, in the blood coagulation and at the building of action potentials on susceptible membranes and the electromechanical coupling of the muscles. The physiological blood calcium concentration in animals is between 2.3 and 3.4 mmol/l. Especially in times of increased requirement of calcium, e.g. post partum, hypocalcaemic conditions may develop. The symptoms of an acute hypocalcaemia are characterized by tetany or paresis. Besides the compensation of a calcium deficit in the case of an acute peripartal hypocalcaemia, the sealing effect of calcium on the blood vessels is used for diseases with an increased permeability of the vessels, e.g. in allergy and inflammation.

Magnesium

Magnesium is an important cation in the organism as well. It is taking part as a cofactor in numerable enzyme systems and transport processes and is of importance in polarization and conduction in nerves and muscle cells. In the neuromotoric excitation at the motoric end-plate magnesium decreases the liberation of acetylcholin. Magnesium ions may influence the release of transmitters at synapses of the CNS and vegetative ganglions. In the heart magnesium leads to a delayed conduction. Magnesium stimulates the secretion of parathormone and acts therefore regulating on the serum calcium level. The physiological serum levels of magnesium are different in the animal species and vary between 0.75 and 1.1 mmol/l. At magnesium serum concentrations below 0.5 mmol/l symptoms of an acute hypomagnesaemia occur. Especially in ruminants disturbances in magnesium metabolism appear, as in these animal species the absorption is less than in monogastric animals, especially after intake of young, protein-rich grass. As a consequence of hypomagnesaemia an increase of neuromuscular excitation in form of hyperaesthesia, incoordinated movements, muscle tremor, tetany, downers, increasing loss in consciousness, and arrhythmia up to cardiac arrest may be observed.

C-B-Gluconat 24% plus 6% contains calcium in an organic compound, and magnesium in form of magnesium chloride as active ingredients. By the addition of boric acid, calciumborogluconate is formed, which increases its solubility and tissue tolerability. The main indication for its use are hypocalcaemic conditions. In this context, magnesium is acting in a regulatory way on one hand, by antagonizing possible cardiac effects of calcium, especially at overdose or rapid infusion, on the other hand therapeutic in hypomagnesaemia, which frequently occurs in combination with hypocalcaemia

5.2 Pharmacokinetic particulars

Calcium

Calcium is bound to more than 90% in bone tissue. Only about 1% are free to be exchanged with the calcium in serum and interstitial fluid. In the serum calcium is bound to 35 – 40% to proteins, 5 – 10% are complex bound and 40 – 60% are present in ionized form. The blood level is subjected within small limits to hormonal regulation by the parathormone, calcitonin, and dihydrocholecalciferol.

The elimination of calcium not absorbed from the nutrition is performed with the faeces, additionally a hormonal regulated renal excretion occurs.

Magnesium

In adult animals, magnesium is found by 50% in the bones, 45% in the intracellular space and only by 1% in the extracellular space, where it is bound by 30% to proteins. In ruminants about 80% are absorbed from the rumen. The amount of magnesium utilized from the nutrition varies between 15 and 26 % in adult cattle. When grazing on young protein-rich grass pasture, the absorption may decrease to 8%.

Magnesium is mainly eliminated in the kidneys. Low levels of magnesium in the blood will decrease, high levels will increase the amount excreted.

6. Pharmaceutical particulars

6.1 List of excipients

Water for injection

6.2 Incompatibilities:

Mixing should be avoided due to possible incompatibilities with other medications.

6.3 Shelf life:

Shelf life after first opening the container:
Use immediately upon opening the container. Any residue remaining in the container must be disposed of.

Shelf life after dilution or reconstitution according to directions: not applicable

6.4 Special precautions for storage

Store below 25°C, keep away from light and moisture

Do not store at temperatures below 8 °C.

Only use clear solutions in intact containers.

6.5 Type and condition of the primary packing:

Infusion bottle made from polypropylene with veral stopper made from bromine butyl rubber and aluminium cap.

OP (1 x 500 ml),
OP (6 x 500 ml),
OP (12 x 500 ml),
BP 1 x (6 x 500 ml),
BP 1 x (12 x 500 ml).

It is possible that not all packaging sizes will be introduced.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Veterinary medicinal products which have not been used up should preferably be handed in at a pollutant collecting point. It they are disposed of with the household waste, it must be ensured that improper access to such waste is impossible. Veterinary pharmaceuticals may not be disposed of with the wastewater or in the sewers.

7. **License Holder and Importer**
MIP VETERINARIA LTD
POB 10437, HAIFA BAY, 2611302, ISRAEL

8. Manufacturer:

Bela-Pharm GmbH & Co.KG
Lohner Str. 19
49377 Vechta, Germany

9. Product license number:

083-86-92389-00

10. Date of issue of initial prduct license / extension of product license:

06/07/2006

11. Date of revision of the text

revised December 2020

12. Prohibition of sale, distribution and/or use:

Not applicable.

13. Only available by prescription / in pharmacies:

Only available by prescription.