Miacalcic® Ampoules

Regulator of calcium homeostasis

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Miacalcic® is available as a solution for injection or infusion in:

- ampoules (1 mL) containing 50 IU/mL or 100 IU/mL.

Active substance

The active substance is synthetic salmon calcitonin (INN name Calcitonin).

One millilitre contains 50 IU or 100 IU of synthetic salmon calcitonin.

One International Unit (= IU) corresponds to about 0.2 micrograms of synthetic salmon calcitonin.

Certain dosage strengths may not be available in all countries.

Active moiety

Salmon calcitonin.

Excipients

Acetic acid, sodium acetate trihydrate, sodium chloride, water for injections.

INDICATIONS

Miacalcic solution for injection or infusion is indicated for:

Prevention of acute bone loss due to sudden immobilization such as in patients with recent osteoporotic fractures. The duration of treatment should not be more than 4 weeks.

For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment. The duration of treatment is limited to 3 months.

Treatment of hypercalcaemia of malignancy.

DOSAGE AND ADMINISTRATION

Due to the association between long-term calcitonin use and the onset of malignancies (see "Warnings and Precautions"), treatment with calcitonin in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

Prevention of Osteoporosis

The lowest effective dose is not yet precisely known. The following dosage is currently recommended:

The standard maintenance dose is 50 IU daily or 100 IU every second day by s.c. or i.m. injection.

Initially, 50 IU should be administered every second day. If treatment is well tolerated, the dosage can be increased to the standard maintenance dose of 50 IU daily or 100 IU every second day. In the further course of treatment, a dose of 50 IU every second day is often adequate.

The duration of treatment should not be more than 4 weeks.

Paget's disease

100 IU daily by s.c. or i.m. injection. Subcutaneous injection is well tolerated and may be self-administered by the patient (after appropriate instruction from the physician or nurse). Injections may also be limited to every second day in certain cases. Daily administration of 50 IU may be considered, particularly following an improvement in objective and subjective symptoms.

If necessary, the daily dosage may be increased to 200 IU.

The duration of treatment depends on the therapeutic indication and the patient's response. In exceptional circumstances (contraindication of bisphosphonates, severe renal impairment or pathological fractures), treatment may be given for up to 6 months. Thereafter, further treatment is only permissible following careful assessment of the benefits and risks (tumour risk).

Hypercalcaemia

Emergency treatment of hypercalcaemic crisis

Intravenous drip infusion is the most effective method of administration and should therefore always be used in the treatment of emergencies or severe cases.

Intravenous infusion of 5 to 10 IU per kg body weight in 500 ml physiological saline solution over at least six hours per day, or by slow i.v. injection in 2 to 4 divided doses spread over the day.

The patient must be rehydrated. Where necessary, emergency treatment should be followed by targeted treatment of the underlying condition.

Treatment of chronic hypercalcaemic states

The dosage depends on the patient’s clinical and biochemical response. The usual daily dose is 5 to 10 IU per kg body weight by s.c. or i.m. injection, given in a single dose or in two divided doses. If the volume of Miacalcic to be injected exceeds 2 mL, i.m. administration at varying sites of injection is preferable. The duration of treatment depends on the general condition and serum calcium levels of the patient. The benefits of Miacalcic must be periodically evaluated.

Special remarks

Treatment considerably reduces serum alkaline phosphatase and urinary hydroxyproline excretion, often even to normal levels. Pain is fully or partially alleviated.

In rare cases, alkaline phosphatase and hydroxyproline excretion levels rise after an initial fall. If this happens, the physician must decide on the basis of the clinical picture whether treatment should continue.

Disorders of bone metabolism may recur one to several months after treatment with Miacalcic has been discontinued, necessitating a new course of Miacalcic therapy.

Antibodies to calcitonin may develop in some patients during long-term calcitonin therapy; clinical efficacy is usually not affected, however. Signs of loss of efficacy ("escape phenomenon"), sometimes observed in pagetic patients receiving long-term therapy, are probably due to saturation of the receptors and are apparently not related to the development of antibodies. Following interruption of treatment, the therapeutic response to Miacalcic is restored.

Use in children

Miacalcic should not be administered to children for more than a few weeks unless the physician sees compelling reasons for a longer period of treatment. Experience relating to long-term treatment in children is insufficient.

Use in elderly patients / special patient populations

Extensive experience with the use of Miacalcic in elderly patients has shown no evidence of reduced tolerability or of the need for dose adjustment. The same applies to patients with renal or hepatic impairment, although no specific studies have been carried out in this patient population.

CONTRAINDICATIONS

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients.

WARNINGS AND PRECAUTIONS

Allergic reactions

Since salmon calcitonin is a polypeptide, allergic reactions are possible. Allergic-type reactions, including isolated cases of anaphylactic shock, have been reported in patients receiving Miacalcic. In patients with suspected hypersensitivity to calcitonin, skin testing using diluted, sterile solution from Miacalcic ampoules (synthetic salmon calcitonin) should be considered prior to initiating treatment.

Risk of malignancies

Meta-analyses of randomized, controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that long-term calcitonin use is associated with a small but statistically significant increase in the incidence of malignancies compared to placebo (see "Adverse effects"). Patients in these trials were treated with oral or intranasal formulations. The meta-analyses demonstrated an increase in the absolute rate of occurrence of tumours in patients treated with calcitonin compared to placebo, which varied between 0.7% (oral formulation) and 2.36% (nasal spray). Numerical imbalances between calcitonin and placebo were observed after 6 to 12 months of therapy. A mechanism for this observation could not be identified. The benefits for the individual patient should be carefully evaluated against possible risks (see "Adverse effects").

Miacalcic ampoules contain less than 23 mg sodium per 1 ml, and can therefore be considered “sodium-free”.

INTERACTIONS

Concomitant use of calcitonin and lithium may lead to a reduction of up to 30% in plasma lithium concentrations. The dose of lithium may need to be adjusted.

PREGNANCY/BREAST-FEEDING

Women of child-bearing potential

There are no data suggesting that there should be any special recommendations for women of child-bearing potential.

Pregnancy

Reproductive toxicity studies in animals have shown that Miacalcic is devoid of embryotoxic and teratogenic potential. However, there have been no controlled studies and there are insufficient data documented for Miacalcic injections in pregnant women. For this reason, Miacalcic should be used with caution during pregnancy.

Breast-feeding

Since there are insufficient data documented for Miacalcic injections in breast-feeding women, breast-feeding is not recommended during treatment. It is not known whether Miacalcic is excreted in breast milk.

Fertility

There are no human fertility data for Miacalcic.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies exist on the effects of Miacalcic on the ability to drive and to use machines. Miacalcic may cause transient fatigue, dizziness and visual disturbances, which may impair the patient’s reactions. Patients must therefore be warned that these effects may occur, in which case they must not drive or use machines.

ADVERSE EFFECTS

Nausea, vomiting, flushing and dizziness are dose-dependent, and are more frequent after i.v. than after i.m. or s.c. administration. Polyuria and chills usually subside spontaneously, and a temporary dose reduction is only necessary in exceptional cases.

Frequencies:

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), including isolated reports; in post-marketing use: Frequency not known.

Immune system disorders

Rare: Hypersensitivity.

Very rare: Anaphylactic and anaphylactoid reactions, anaphylactic shock.

Metabolism and nutrition disorders

Frequency not known: Hypocalcaemia.

Nervous system disorders

Common: Headache, dizziness, dysgeusia.

Frequency not known: Tremor.

Eye disorders

Uncommon: Visual impairment.

Vascular disorders

Common: Flushing.

Uncommon: Hypertension.

Gastrointestinal disorders

Common: Nausea, diarrhoea, abdominal pain.

Uncommon: Vomiting.

Skin and subcutaneous tissue disorders

Rare: Generalized rash.

Frequency not known: Urticaria.

Musculoskeletal disorders

Common: Arthralgia.

Uncommon: Musculoskeletal pain.

Renal and urinary disorders

Rare: Polyuria.

General disorders and administration site reactions

Common: Fatigue.

Uncommon: Influenza-like symptoms, oedema (facial, peripheral or generalized).

Rare: Injection site reactions, pruritus.

Meta-analyses of randomized, controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that long-term calcitonin use is associated with a small but statistically significant increase in the incidence of malignancies compared to placebo. A mechanism for this observation could not be identified (see "Warnings and precautions").

OVERDOSE

Depending on the dose, parenteral administration may give rise to nausea, vomiting, flushing and dizziness.

Nausea and vomiting have been reported following parenteral overdose of Miacalcic, but no severe reactions have been observed.

Management of overdose should be symptomatic.

PHARMACODYNAMICS

All calcitonins consist of 32 amino acids in a single chain, with a ring of 7 amino acids at the N-terminus that differs in sequence from species to species. Salmon calcitonin is more potent and longer-acting than calcitonins from mammalian species due to its greater affinity for receptor binding sites.

Salmon calcitonin inhibits the activity of osteoclasts via their specific receptors. It markedly reduces, and may even normalize, bone turnover in conditions with an increased rate of bone resorption, such as osteoporosis. Salmon calcitonin has been shown both in animal models and in humans to have analgesic activity, presumably via a direct effect on the central nervous system.

Clinical efficacy

Miacalcic produces a clinically relevant biological response in humans after only a single dose, as shown by an increase in the urinary excretion of calcium, phosphorus and sodium (by reducing their tubular re-uptake) and a decrease in the urinary excretion of hydroxyproline.

Long-term parenteral administration of Miacalcic leads to a significant reduction in markers of bone turnover such as pyridinoline crosslinks and skeletal isoenzymes of alkaline phosphatase.

Calcitonin inhibits gastric and exocrine pancreatic secretion.

PHARMACOKINETICS

Absorption / Distribution

Bioavailability after subcutaneous and intramuscular injection in humans is high, and is similar for the two routes of administration (71% and 66%, respectively). Calcitonin has a short absorption half-life of 10-15 minutes. The elimination half-life is about 1 hour following intramuscular administration and 1 to 1.5 hours following subcutaneous administration.

After subcutaneous administration, peak plasma levels are reached in about 23 minutes.

The apparent volume of distribution is 0.15 to 0.3 litres/kg and protein binding amounts to 30 to 40%.

Elimination

The elimination half-life is about 1 hour following intramuscular administration and 1 to 1.5 hours following subcutaneous administration. Up to 95% of salmon calcitonin and its metabolites are excreted via the kidneys, the fraction of parent drug being 2%.

PRECLINICAL DATA

Toxicological findings from long-term studies are attributable to the pharmacological action of salmon calcitonin.

Salmon calcitonin is devoid of embryotoxic, teratogenic and mutagenic potential. Toxicity and carcinogenicity studies in rats have shown that salmon calcitonin increases the incidence of pituitary tumours. Further preclinical studies, particularly a mouse carcinogenicity study in which the maximum exposure was more than 760 times greater than that in humans following a dose of 50 IU, suggest that this elevated incidence of pituitary tumours is species-specific to rats.

In vivo preclinical safety data do not indicate any association of salmon calcitonin treatment with malignancies and do not provide any evidence for tumour progression.

INCOMPATIBILITIES

None.

STORAGE

See also folding box.

Miacalcic Ampoules should be stored at temperatures of 2 - 8°C. Do not freeze.

Once opened, the ampoules should be used immediately and not stored, since they do not contain a preservative.

Miacalcic should not be used after the date marked “EXP” on the pack.

Miacalcic must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Miacalcic Ampoules should be inspected visually prior to use. If the solution is not clear and colourless, or contains any particles, or if the ampoule is damaged, do not administer the solution.

The ampoules are for single use only. Leftover solution must be discarded. Allow to reach room temperature before intramuscular or subcutaneous administration.

MANUFACTURER

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