NOVARTIS

Miacalcic® ampoules

Synthetic salmon calcitonin

COMPOSITION

Active substance: Salmon calcitonin
One 1 mL ampoule contains:
50 or 100 IU salmon calcitonin
(1 IU is equivalent to about 0.2 µg of the pure peptide.)
Excipients: Sodium acetate, sodium chloride, water to 1 mL

PROPERTIES/ACTIONS

All calcitonins consist of a chain of 32 amino acids, with a ring of 7 amino-acids at the N-terminus, that differ in sequence from species to species. Salmon calcitonin is more potent and longer acting than calcitonins from mammals due to its greater affinity for receptor binding sites.
Salmon calcitonin inhibits the activity of osteoclasts via their specific receptors. In conditions with an increased rate of bone resorption, such as osteoporosis, it brings about a striking reduction in – and may even normalize – bone turnover. Salmon calcitonin has been shown to have an analgesic effect in both animal models and humans, presumably as a result of direct action on the central nervous system.
Miacalcic produces a clinically relevant biological response in humans after only a single dose. This is shown by an increase in the urinary excretion of calcium, phosphorus, and sodium (by reducing their tubular reuptake) 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

The absolute bioavailability of salmon calcitonin following intramuscular or subcutaneous injection is approximately 70%. Peak plasma concentrations are attained within 1 hour of administration. The elimination half-life is 70–90 minutes.
Up to 95% of salmon calcitonin and its metabolites are excreted via the kidneys, the fraction of parent drug being 2%. The apparent volume of distribution is 0.15–0.3 litres/kg and protein binding reaches 30–40%.

INDICATIONS/POTENTIAL USES

Substantiated uses

Osteoporosis
Early and advanced stages of postmenopausal osteoporosis.
Miacalcic should be supplemented with adequate doses of calcium and vitamin D, as needed by the individual patient, to prevent further loss of bone mass.

Paget's disease of bone (Osteitis deformans)

Hypercalcaemia and hypercalcaemic crisis due to:
– Tumour-related osteolysis in patients with bone metastases from breast, lung or kidney carcinoma, myeloma or other malignant tumours;
– Hyperparathyroidism, immobilization or vitamin-D intoxication, in both emergency and long-term treatment.

Algoneurodystrophy or Sudeck's disease (neurodystrophic disorders) due to various causes and predisposing factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia and drug-induced neurotrophic disorders.

DOSAGE AND ADMINISTRATION

Osteoporosis

In view of its superior tolerability, it is recommended that preference be given to the nasal spray in the treatment of osteoporosis.
Parenteral administration should be considered in cases where the nasal spray is not well tolerated.
The exact figure for the lowest effective dose is not yet known. The following dosage is currently recommended:
The standard maintenance dose is 50 IU/day or 100 IU on alternate days, given by s.c. or i.m. injection.
Initially, 50 IU should be administered on alternate days. If treatment is well tolerated, the dosage can be increased to the standard maintenance dose of 50 IU/day or 100 IU on alternate days. Subsequently, a dose of 50 IU on alternate days is often adequate.

Paget's disease of bone

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 by the doctor or nurse). Injections can also be restricted to alternate days in certain cases. Daily administration of 50 IU may be considered, particularly following an improvement in clinical signs and symptoms. If necessary, the daily dosage can be raised to 200 IU.
Treatment should be given for at least 3 months, and longer if required.

Hypercalcaemia

Emergency management of hypercalcaemic crisis
Intravenous drip infusion is the most effective method of administration and should therefore always be used in emergencies or severe cases.
Intravenous infusion of 5–10 IU per kg bodyweight in 500 mL physiological saline for at least six hours per day, or by slow i.v. injection in 2–4 divided doses spread over the day.
The patient must be rehydrated. Where necessary, emergency management should be followed by specific treatment of the underlying disease.

Long-term management of chronic hypercalcaemic states
The dosage depends on the patient's clinical and biochemical response. The usual daily dose is 5–10 IU per kg bodyweight by s.c. or i.m. injection, given in a single dose or 2 divided doses. If the volume to be injected exceeds 2 mL, the i.m. route is preferable, with injections being given at different sites.

Algoneurodystrophy (neurodystrophic disorders)

Early diagnosis is important, and treatment should start as soon as the diagnosis is confirmed.
100 IU daily by s.c. or i.m. injection for 2–4 weeks, then 100 IU three times a week for up to 6 weeks, depending on the patient's clinical response.

Special remarks

In Paget's disease, treatment should be given for periods ranging from several months to a few years.

Treatment markedly reduces – and frequently even normalizes – serum alkaline phosphatase and urinary hydroxyproline excretion. 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 from one to several months after treatment with Miacalcic has been discontinued, necessitating a new course of Miacalcic therapy.

Although antibodies to calcitonin may develop in some patients undergoing long-term treatment with calcitonin, its clinical efficacy is not normally affected. Signs of loss of efficacy ("escape phenomenon"), sometimes observed in long-term use of the drug in patients with Paget's disease, are probably due to saturation of the binding sites and are apparently not related to the development of antibodies. Following interruption of treatment, the therapeutic response of the patient to Miacalcic is restored.

Use in children

Miacalcic should not be administered to children for more than a few weeks unless the physician thinks there are compelling reasons that necessitate 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 Miacalcic in elderly patients has shown no evidence of reduced tolerability or of the need for dosage adjustment. The same applies to patients with impaired hepatic or renal function, even though no special studies have been carried out in this population.

RESTRICTIONS ON USE

Contraindications

Hypersensitivity to synthetic salmon calcitonin or to any of the excipients.

Precautions

Allergic reactions may occur because salmon calcitonin is a polypeptide. Allergic-type reactions, including isolated cases of anaphylactic shock, have been reported in patients receiving Miacalcic. Skin testing – using dilute, sterile solution from Miacalcic ampoules (synthetic salmon calcitonin) – should be considered prior to initiating treatment in patients with suspected hypersensitivity to calcitonin.

Pregnancy/Lactation

Reproduction studies in animals have shown that Miacalcic has no embryotoxic or teratogenic potential, but there have been no controlled studies in pregnant women. Miacalcic does not cross the placental barrier in animals.
Breastfeeding during treatment is not recommended. It is not known whether Miacalcic is excreted in human milk.

ADVERSE EFFECTS

There have been reports of nausea, vomiting, dizziness, arthralgia and slight facial flushing accompanied by a sensation of heat. Nausea, vomiting, dizziness and flushing are dose dependent and are more frequent after i.v. than after i.m. or s.c. administration.
There have been rare reports of polyuria and chills. All these adverse effects normally stop spontaneously, with temporary dose reduction necessary only in exceptional cases.
In rare cases Miacalcic may give rise to hypersensitivity reactions, including local reactions at the injection site and generalized skin reactions. In isolated cases, allergic reactions took the form of rash, hypertension or peripheral oedema. Anaphylactoid-like reactions and isolated cases of anaphylactic shock have been reported.
Adverse effects are less common with intranasal administration than with injections (see **Dosage and Administration**).

INTERACTIONS

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

OVERDOSE

Depending on the dose administered, parenteral administration may give rise to nausea, vomiting, flushing and dizziness.
Nausea and vomiting have been reported following parenteral overdosing of Miacalcic, but no severe adverse reactions have been observed.
Management should be symptomatic.

OTHER INFORMATION

Storage conditions

Store the ampoules in a refrigerator (at 2–8°C).

PACK SIZES

Country specific pack sizes.

MANUFACTURER

See folding box.

Information last revised: November 2001
Approval date (text): April 2002

Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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