Miacalcic® Ampoules 50 IU/mL and 100 IU/mL (1 mL) solution for injection or infusion

Miacalcic® Multidose Vials 200 IU/mL (2 mL) solution for injection or infusion

Regulator of calcium homeostasis

DESCRIPTION AND COMPOSITION

Active substance

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

One millilitre contains 50 IU, 100 IU or 200 IU of synthetic salmon calcitonin.

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

Active moiety

Salmon calcitonin Pharmaceutical forms

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

- ampoules (1 mL) containing 50 IU/mL or 100 IU/mL
- multidose vials* (2 mL) containing 200 IU/mL
- The amount of solution contained in each multidose vial is sufficient for 4 injections of 0.5 mL (four times 100 IU).

Certain dosage strengths may not be available in all countries.

INDICATIONS

Miacalcic solution for injection or infusion is indicated for the treatment of:

Bone pain associated with osteolysis and/or osteopenia

Paget's disease of bone (osteitis deformans) only in patients who do not respond to alternative treatments or for whom such treatments are not suitable

Hypercalcemia and hypercalcemic crisis due to

- tumoral osteolysis secondary to breast, lung or kidney carcinoma, myeloma and other malignancies,
- hyperparathyroidism, immobilization or vitamin D intoxication,

for both the acute treatment of emergencies and the prolonged treatment of chronic hypercalcemia, until specific therapy of the underlying condition proves effective.

Neurodystrophic disorders (synonymous with algodystrophy or Sudeck's disease)

Caused by various etiological and predisposing factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia, drug-induced neurotrophic disorders.

Adjuvant therapy of acute pancreatitis

DOSAGE AND ADMINISTRATION

Dosage

Adults

All indications

The solution in the multidose vials can be used for subcutaneous (s.c) or intramuscular (i.m), injection or for continuous intravenous (i.v) infusion, but is not suitable for i.v. bolus injection as it contains phenol (5 mg/mL) as a preservative.

Patients who will administer Miacalcic by themselves should first receive precise instruction in the self-administration of subcutaneous injections from the physician or the nurse.

Due to the association between occurrence of malignancies and long term calcitonin use (see section WARNINGS AND PRECAUTIONS), the treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

Bone pain associated with osteolysis and/or osteopenia

In bone pain associated with osteolysis and/or osteopenia the recommended dose is 100 to 200 IU daily by slow i.v. infusion in physiological saline, or by s.c. or i.m. injection in divided doses spread over the day, until a satisfactory response is achieved.

Dosage should be adjusted to the individual patient's needs.

It may take several days of treatment until the analgesic effect is fully developed. For continuing therapy the initial daily dosage can usually be reduced and/or the interval between administrations prolonged.

Paget's disease

In Paget's disease the recommended dose is 100 IU daily or every second day by s.c. or i.m. injection. Dosage should be adjusted to the individual patient's needs. Treatment should be discontinued once the patient has responded and symptoms have resolved. Duration of treatment should not normally exceed 3 months due to the association of the increased risk of malignancies with long term calcitonin use. Under exceptional circumstances, e.g. in patients with impending pathologic fracture, treatment duration may be extended up to a recommended maximum of 6 months.

Treatment markedly reduces serum alkaline phosphatase and urinary hydroxyproline excretion, often to normal levels. However, in rare cases, alkaline phosphatase and hydroxyproline excretion levels may rise after an initial fall; the physician must then judge from the clinical picture whether treatment should be discontinued and when it may be resumed.

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

Hypercalcemia

Emergency treatment of hypercalcemic crisis

Intravenous infusion is the most effective method of administration and should therefore be preferred in the treatment of emergencies or other severe conditions.

The recommended dose is 5 to 10 IU per kg body weight in 500 mL physiological saline daily by i.v. infusion over at least six hours, or by slow i.v. injection in 2 to 4 divided doses spread over the day.

Treatment of chronic hypercalcemic states

The recommended dosage in treatment of chronic hypercalcemic states is 5 to 10 IU per kg body weight daily by s.c. or i.m. injection as a single dose or in two divided doses. Treatment should be adjusted to the patient's clinical and biochemical response. If the volume of Miacalcic to be injected exceeds 2 mL, i.m. administration is preferable and multiple sites of injection should be used.

Neurodystrophic disorders

Early diagnosis of neurodystrophic disorders is essential and treatment should start as soon as the diagnosis is confirmed.

The recommended dosage is 100 IU daily by s.c. or i.m. injection for 2 to 4 weeks. Subsequently, 100 IU may be given every second day for up to 6 weeks depending on clinical progress.

Acute pancreatitis

Miacalcic is a useful adjunct in conservative management of acute pancreatitis when administered at the recommended dosage of 300 IU by i.v. infusion in physiological saline over a 24 hours period for up to 6 consecutive days.

Development of antibodies

Antibodies to calcitonins may develop in patients under long-term therapy; however, clinical efficacy, is usually not affected. Escape phenomena, which occur in particular in pagetic patients receiving long-term therapy, may be due to saturation of the binding sites and are apparently not related to the development of antibodies. Following interruption of treatment, the therapeutic response to Miacalcic is restored.

Special populations

Renal impairment

There is no evidence of reduced tolerance or altered dosage requirements of Miacalcic in patients with renal impairment, although no formal studies have been carried out in this specific patient population.

Hepatic impairment

There is no evidence of reduced tolerance or altered dosage requirements of Miacalcic in patients with hepatic impairment, although no formal studies have been carried out in this specific patient population.

Paediatric patients (below 18 years of age)There is limited experience with the use of parenteral Miacalcic in children, therefore no recommendations can be given for this patient group.

Geriatric patients (65 years of age and above)

Extensive experience with the use of parenteral Miacalcic in the elderly has shown no evidence of reduced tolerance or altered dosage requirements.

CONTRAINDICATIONS

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see sections WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS and DESCRIPTION AND COMPOSITION- EXCIPIENTS).

WARNINGS AND PRECAUTIONS

Allergic reactions

Because salmon calcitonin is a peptide, the possibility of systemic allergic reactions exists and allergic-type reactions including single cases of anaphylactic shock have been reported in patients receiving Miacalcic. Skin testing with diluted, sterile solution from Miacalcic Ampoules should be considered prior to treatment with Miacalcic in patients with suspected sensitivity to salmon calcitonin.

Risk of malignancy

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 section ADVERSE DRUG REACTIONS). These meta-analyses demonstrated an increase in the absolute rate of occurrence of malignancies for patients treated with calcitonin compared to placebo which varied between 0.7% and 2.36%. Numerical imbalances between calcitonin and placebo were observed after 6 to 12 months of therapy. A mechanism for this observation has not been identified. Patients in these trials were treated with oral or intra-nasal formulations however it cannot be excluded that an increased risk also applies when calcitonin is administered long-term subcutaneously, intramuscularly or intravenously. The benefits for the individual patient should be carefully evaluated against possible risks (see section ADVERSE DRUG REACTIONS).

INTERACTIONS

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

WOMEN OF CHILD-BEARING POTENTIAL (WOCBP), PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of childbearing potential

There are no data to support special recommendations for women of child-bearing potential.

Pregnancy

Since there is insufficient documented experience with Miacalcic in pregnant women, Miacalcic should not be administered to such patients. Animal studies have, however, shown that salmon calcitonin is devoid of embryotoxic and teratogenic potential.

Breast-feeding

Since there is insufficient documented experience with Miacalcic in nursing mothers and it is not known whether salmon calcitonin is excreted in human milk, breast-feeding during treatment is not recommended.

Fertility

There are no data regarding a potential influence of Miacalcic on human fertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

ADVERSE DRUG REACTIONS

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 necessary in a few cases only.

Tabulated summary of adverse drug reactions

Adverse drug reactions from multiple sources including clinical trials and post-marketing experience (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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) and not known (frequency cannot be estimated from the available data)

Table 1 Adverse drug reactions reported from multiple sources including clinical trials and post-marketing experience

Immune system disorders	
Rare:	Hypersensitivity.
Very rare:	Anaphylactic and anaphylactoid reactions, anaphylactic shock.
Metabolism and nutrition disorders	
Not known:	Hypocalcaemia
Nervous system disorders	
Common:	Dizziness, headache, dysgeusia.
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:	Rash generalised.
Not known:	Urticaria
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia.
Uncommon:	Musculoskeletal pain.
Renal and urinary disorders	
Rare:	Polyuria.
General disorders and administration site conditions	
Common:	Fatigue.
Uncommon:	Influenza-like illness, oedema (facial, peripheral and generalised).
Rare:	Injection site reaction, pruritus.

Description of selected adverse drug reactions

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 patients treated with placebo. A mechanism for this observation has not been identified (see sectionWARNINGS AND PRECAUTIONS).

OVERDOSAGE

Nausea, vomiting, flushing and dizziness are known to be dose-dependent when Miacalcic is administered parenterally.

Nausea and vomiting have occurred following administration of Miacalcic as a parenteral overdose, but severe adverse reactions due to overdosage have so far not been reported. Treatment would be symptomatic.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) / Pharmacodynamics (PD)

All calcitonin structures consist of 32 amino acids in a single chain with a ring of seven amino-acid residues 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.

By inhibiting osteoclast activity via its specific receptors, salmon calcitonin markedly reduces bone turnover to a normal level in conditions with an increased rate of bone resorption such as osteoporosis. Salmon calcitonin has also been shown both in animal models and in humans to have analgesic activity, probably primarily via a direct effect on the central nervous system.

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 administration of parenteral Miacalcic significantly suppresses biochemical markers of bone turnover such as pyridinoline-crosslinks and skeletal isoenzymes of alkaline phosphatase.

Calcitonin reduces gastric and exocrine pancreatic secretion. Owing to these properties, Miacalcic has been shown to be beneficial in the medical treatment of acute pancreatitis.

PHARMACOKINETICS (PK)

The absolute bioavailability of salmon calcitonin is about 70% after either intramuscular (i.m.) or subcutaneous (s.c.) injection. Peak plasma concentrations are attained within one hour. After subcutaneous administration, peak plasma levels are reached in about 23 minutes. The elimination half-life is about 1 hour for i.m. administration and 1 to 1.5 hours for s.c. administration. Salmon calcitonin and its metabolites are excreted up to 95% by the kidney, the fraction of parent drug being 2%. The apparent volume of distribution is 0.15 to 0.3 L/kg, and protein binding amounts to 30 to 40%.

CLINICAL STUDIES

Not applicable.

NON-LINICAL SAFETY DATA

Conventional long-term toxicity, reproduction, mutagenicity and carcinogenicity studies have been performed in laboratory animals.

Minor effects in toxicity studies are attributable to the pharmacological action of salmon calcitonin. Salmon calcitonin is devoid of embryotoxic, teratogenic and mutagenic potential. Toxicity and carcinogenicity studies have shown that salmon calcitonin increases the incidence of pituitary tumors in rats at exposures lower than those likely from clinical use. However, further preclinical studies, particularly a mouse carcinogenicity study, in which the maximum exposure was about 760 times greater than that in humans following a dose of 50 IU, suggested that pituitary tumor induction is specific to the rat.

Furthermore, there have been no reports of adverse events relating to pituitary tumors in patients.

There is therefore enough evidence to conclude that pituitary tumor induction is a rat-specific event and that rat pituitary tumors have no relevance for the clinical use of Miacalcic.

EXCIPIENTS

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

Multidose vials: Acetic acid, phenol, sodium acetate trihydrate, sodium chloride, water for injections.

INCOMPATIBILITIES

None.

STORAGE

See also folding box.

Miacalcic Ampoules and Multidose Vials should be stored at temperatures of 2 to 8°C. Do not freeze.

Once opened, the multidose vials must be kept at room temperature (not above 25°C) and used within a maximum of 4 weeks.

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 and Multidose Vials should be inspected visually. If the solution is not clear and colorless, or contains any particles, or if the ampoule or vial is damaged, do not administer the solution.

The ampoules are for single use only. Remaining contents should be discarded. Allow to reach room temperature before intramuscular or subcutaneous use.

Manufacturer:

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International Package Leaflet

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