MIACALCIC®
Ampoules

Description and composition

Pharmaceutical form
Ampoules (1 mL) contains 50 and 100 IU of synthetic salmon calcitonin.

Active substance
Active ingredients: Synthetic salmon calcitonin

One International Unit (=IU) corresponds to about 0.2 micrograms of the drug substance.

Active moiety
Salmon calcitonin.

Excipients
Glacial acetic acid, sodium acetate trihydrate, sodium chloride, water for Injection.

Indications

Miacalcic solution for injection is indicated for the treatment of:

Osteoporosis in patients for whom alternative treatments are not suitable
Primary osteoporosis, e.g. early and advanced stages of postmenopausal osteoporosis and senile osteoporosis in women and men.

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

Hypercalcaemia and hypercalcaemic 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 states, until specific therapy of the underlying condition proves effective.

Neurodystrophic disorders (synonymus with algodystrophy or Sudeck's disease)
Due to various aetiological factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia, drug-induced neurotrophic disorders.

Dosage and administration

Dosage

All indications

Patients should 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 Special warnings and precautions for use), the treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

**Osteoporosis**
In osteoporosis, the recommended dose is 50 IU daily or 100 IU daily or every second day by s.c. or i.m. injection, depending on the severity of the disease.

It is recommended that use of Micalcic be accompanied by adequate intake of calcium and vitamin D to prevent progressive loss of bone mass.

**Bone pain associated with osteolysis and/or osteopenia**
In bone pain associated with osteolysis and/or osteopenia, the recommended dose is 100-200 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 administration prolonged.

**Paget’s disease**
100 IU daily or every second day by s.c. or i.m. injection.

The duration of treatment depends on the therapeutic indication and the patient’s response. Dosage should be adjusted to the individual patient’s needs.

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

**Hypercalcaemia**

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

5-10 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 dose spread over the day.

**Treatment of chronic hypercalcaemic states**
Treatment should be limited to the shortest duration possible (see above section “all indications”). The recommended dosage in treatment of chronic hypercalcemic states is 5-10 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 Micalcic to be injected exceeds 2 mL, i.m. administration is preferable and multiple sites of injection should be used.
Neurodystrophic disorders
Early diagnosis is essential 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. An additional 100 IU may be given every second day for up to 6 weeks depending on clinical progress.

Note
Patients should receive precise instruction in the self-administration of subcutaneous injections from the physician or nurse.

Development in antibiotics
Treatment should be limited to the shortest duration possible (see above section “all indications”). Antibodies to calcitonins may develop in patients under long-term therapy; clinical efficacy, however, is usually not affected. Escape phenomena, which occur in particular in pagetic patients receiving long-term therapy, may be due to the saturation of the binding sites and are apparently not related to the development of antibodies. After interruption of treatment, the therapeutic response to Miacalcic is restored.

Use in children
There is limited experience with the use of Miacalcic Ampoules in children, therefore no recommendations can be given for this patient group.

Use in elderly patients/special patient population
Extensive experience with the use of parenteral Miacalcic in the elderly has shown no evidence of reduced tolerance or altered dosage requirements. The same applies to patients with altered renal or hepatic function, although no formal studies have been carried out in this specific patient population.

Contraindications
Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see 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. In patients with suspected sensitivity to salmon calcitonin, skin testing should be considered prior to treatment, using a dilute, sterile solution of Miacalcic Ampoules.

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 Undesirable effects). 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 Undesirable effects).

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

**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 Adverse drug reactions), 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, dizziness, slight facial flushing accompanied by a sensation of heat, and arthralgia have been reported. 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 0.1 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); 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

<table>
<thead>
<tr>
<th>Immune system disorders</th>
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<tbody>
<tr>
<td>Rare:</td>
<td>Hypersensitivity.</td>
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<tr>
<td>Very rare:</td>
<td>Anaphylactic and anaphylactoid reactions, anaphylactic shock.</td>
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<tr>
<th>Metabolism and nutrition disorders</th>
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<tr>
<td>Not known:</td>
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<table>
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<tr>
<th>Nervous system disorders</th>
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<tr>
<td>Common:</td>
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<td>Not known:</td>
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<th>Eye disorders</th>
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<tr>
<td>Uncommon:</td>
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<tr>
<th>Vascular disorders</th>
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<tbody>
<tr>
<td>Common:</td>
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<td>Uncommon:</td>
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<tr>
<th>Gastrointestinal disorders</th>
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<tr>
<td>Common:</td>
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<td>Uncommon:</td>
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<tr>
<th>Skin and subcutaneous tissue disorders</th>
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<tbody>
<tr>
<td>Rare:</td>
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<td>Not known:</td>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tr>
<td>Common: Musculoskeletal pain including arthralgia.</td>
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<th>Renal and urinary disorders</th>
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<tr>
<td>Rare:</td>
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<tr>
<th>General disorders and administration site conditions</th>
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<tbody>
<tr>
<td>Common: Fatigue.</td>
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<tr>
<td>Uncommon: Influenza-like illness, oedema (facial, peripheral and generalized).</td>
</tr>
<tr>
<td>Rare: Injection site reactions, pruritus.</td>
</tr>
</tbody>
</table>

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 increase in the incidence of malignancies compared to patients treated with placebo. A mechanism for this observation has not been identified (see section Warnings and precautions).
**Overdosage**
Nausea, vomiting, flushing and dizziness are known to be dose dependent when Miocalcic is administered parenterally.

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

**Clinical Pharmacology**

*Pharmacotherapeutic group, ATC code*

**Pharmacotherapeutic group:** Regulator of calcium homeostasis

**ATC code H05B A01.**

**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 calcitomin 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 human to have analgesic activity, probably primarily via a direct effect on the central nervous system.

Miocalcic produces a clinically relevant biological response in humans after only a single dose, as shown by an increase in the urinary excretion of calcium, phosphorous and sodium (by reducing their tubular re-uptake) and a decrease in the urinary excretion of hydroxyproline. Long-term administration of parenteral Miocalcic significantly suppresses biochemical markers of bone turnover such as pyridinoline-crosslinks and skeletal isoenzymes of alkaline phosphatase.

Calcitonin reduces gastric and exocrine pancreatic secretion.

**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 0.15-0.3 L/kg, and protein binding amounts to 30-40%.

**Clinical studies**

*Not applicable.*
Non-clinical 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. In vivo nonclinical safety data do not support an association of salmon calcitonin treatment with malignancies and do not provide any evidence for tumor progression.

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.

Pharmaceutical information

Incompatibilities
None

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

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

Miacalcic ampoules should be kept out of reach of children.

Shelf-life
60 months

Package
Miacalcic® injectable forms:
Boxes of 5 ampoules @ 50 IU/mL, No. Reg. DKI8767500143A1
Boxes of 5 ampoules @ 100 IU/mL, No. Reg. DKI8767500143B1

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

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