NOVARTIS

Drug Regulatory Affairs

# MIACALCIC®

(synthetic salmon calcitonin)

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

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

## Basic Prescribing Information

**NOTICE**

**The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.**

**National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.**


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| Author(s): | Liesbeth Hof |
| GLCapproval: | 06 July 2006 |
| Release date: | 15 September 2006 |
| Tracking number | 2006–PSB/GLC-0009-s |
| Document status: | Final |
| Number of pages: | 9 |

# 1 Name of the medicinal product

MIACALCIC® AMPOULES

MIACALCIC® MULTIDOSE VIALS

# 2 Qualitative and quantitative composition

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.

For excipients see section 6.1 List of excipients.

# 3 Pharmaceutical form

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).

# 4 Clinical particulars

## 4.1 Therapeutic indications

Miacalcic solution for injection or infusion is indicated for:

**Osteoporosis**

- Primary osteoporosis, e.g. early and advanced stages of postmenopausal osteoporosis and senile osteoporosis in women and men.
- Secondary osteoporosis, e.g. caused by corticosteroid therapy or immobilisation.

**Bone pain associated with osteolysis and/or osteopenia**

**Paget's disease of bone (osteitis deformans)**

**Hypercalcaemia and hypercalcaemic crisis due to**

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

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

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

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

#### Adjuvant therapy of acute pancreatitis

## 4.2 Posology and method of administration

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

#### 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 Miacalcic be accompanied by an 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 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. Treatment should be continued for at least 3 months, or longer if required. Dosage should be adjusted to the individual patient’s needs.

In Paget's disease and other chronic conditions with high bone turnover, treatment with Miacalcic should be given for periods ranging from at least several months to a few years. 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.

### 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 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.

#### Prolonged treatment of chronic hypercalcaemic states

The recommended dosage in prolonged treatment of chronic hypercalcaemic 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. An additional 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.

### Long-term treatment

Antibodies to calcitonins may develop in patients under long-term therapy; clinical efficacy, is usually not affected, however. 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.

**Use in children**

There is limited experience with the use of parenteral Miacalcic 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.

## 4.3 Contraindications

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see sections 4.4 Special warnings and precautions for use, 4.8 Undesirable effects and 6.1 List of excipients).

## 4.4 Special warnings and precautions for use

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.

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

## 4.5 Interaction with other medicinal products and other forms of interaction

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

## 4.6 Pregnancy and lactation

### Pregnancy

Since no studies have been carried out 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. It appears that salmon calcitonin does not cross the placental barrier in animals.

### Lactation

Since no studies have been carried out in nursing mothers and it is not known whether salmon calcitonin is excreted in human milk, breast-feeding during treatment is not recommended.

## 4.7 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 4.8. 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.

## 4.8 Undesirable 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 necessary in a few cases only.

*Adverse reactions (Table 1) are ranked under heading of frequency estimates, the most frequent first, using the following convention: very common (≥ 1/10%),; common (≥ 1/100,% to < 1/10%),; uncommon (≥ 1/1,000, 0.1% and < 1/100%); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.*

**Table 1**

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| **Immune system disorders** | |
| Rare: | Hypersensitivity. |
| Very rare: | Anaphylactic and anaphylactoid reactions, anaphylactic shock. |
| **Nervous system disorders** | |
| Common: | Dizziness, headache, dysgeusia. |
| **Eye disorders** | |
| Uncommon: | Visual disturbance. |
| **Vascular disorders** | |
| Common: | Flushing. |
| Uncommon: | Hypertension. |
| **Gastrointestinal disorders** | |
| Common: | Nausea, diarrhoea, abdominal pain. |
| Uncommon: | Vomiting. |
| **Skin and subcutaneous tissue disorders** | |
| Rare: | Rash generalised. |
| **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 symptoms, oedema (facial, peripheral and generalised). |
| Rare: | Injection site reactions, pruritus. |

### 4.9 Overdose

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.

## 5 Pharmacological properties

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Regulator of calcium homeostasis (ATC code H05B A01).

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.

### 5.2 Pharmacokinetic properties

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%.

### 5.3 Preclinical 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 tumours 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 tumours in patients.

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

# 6 Pharmaceutical particulars

## 6.1 List of 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.

## 6.2 Incompatibilities

None.

## 6.3 Shelf life

Ampoules: 5 years, if unopened.

Multidose vials: 3 years, if unopened.

## 6.4 Special precautions for storage

Miacalcic Ampoules and Multidose Vials should be stored at temperatures of 2-8°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 Ampoules and Multidose Vials should be kept out of the reach and sight of children.

## 6.5 Nature and content of container

Colourless glass OPC (One-Point-Cut) ampoules (glass type I).

Colourless glass vials (glass type I) with a stopper and a cap.

## 6.6 Instructions for use and handling

Miacalcic Ampoules and Multidose Vials should be inspected visually. If the solution is not clear and colourless, 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.