

MIACALCIC AMPOULES

Salmon Calcitonin

100 IU Injection

1 PRODUCT NAME

MIACALCIC 100 IU synthetic salmon calcitonin (INN name Calcitonin) solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

One millilitre contains 100 IU of synthetic salmon calcitonin. One International Unit (= IU) corresponds to about 0.2 micrograms of synthetic salmon calcitonin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MIACALCIC is available as a solution for injection or infusion in ampoules (1 mL) containing 100 IU/mL.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

MIACALCIC solution for injection or infusion is indicated for the treatment of:-

Acute bone pain associated with hip arthroplasty osteolysis and osteoporotic vertebral compression fracture.

Paget's disease of bone (osteitis deformans), only in patients with the following conditions and who do not respond to alternative treatments or for whom such treatments are not suitable:

- Bone pain
- Neurological complications
- Increased bone turnover reflected in elevated serum alkaline phosphatase and urinary hydroxyproline excretion
- Progressive extension of bone lesions
- Incomplete or repeated fractures

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, Sudeck's disease or complex regional pain syndrome), in conjunction with physiotherapy:

- Caused by various aetiological and predisposing factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia, drug-induced neurotrophic disorders.
- In patients who do not respond to alternative treatments or for whom such treatments are not suitable

Adjuvant therapy of acute pancreatitis.

4.2 Dosage and method of administration

All indications

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 4.4 *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.

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.

Acute bone pain associated with hip arthroplasty osteolysis and osteoporotic vertebral compression fracture

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. Treatment should normally be for up to four weeks.

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

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.

Treatment of hypercalcaemia:

Treatment should be limited to the shortest duration possible. The recommended dosage in treatment of 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. Subsequently, 100 IU may be given every second day for up to 6 weeks depending on clinical progress.

Acute pancreatitis

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

Treatment should be limited to the shortest duration possible. 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

Use in 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.

Use in geriatric patients (65 years of age and older)

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

Use in renal or hepatic impairment

There is no evidence of reduced tolerance or altered dosage requirements for patients with renal or hepatic impairment, although no formal studies have been carried out in these specific patient populations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 4.8 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 4.8 Undesirable effects*).

4.5 Interaction with other medicines 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 Fertility, pregnancy and lactation

Women of child-bearing 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.

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 *Adverse 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.

NEW ZEALAND DATA SHEET

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

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.
Investigations	
Rare:	Development of neutralising antibodies to calcitonin

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 section 4.4 *Special warnings and precautions for use*).

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

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. *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 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.

6.2 Incompatibilities

None.

6.3 Shelf life

Ampoules: 5 years, if unopened.

6.4 Special precautions for storage

MIACALCIC Ampoules should be stored at temperatures of 2-8°C. Refrigerate do not freeze.

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

MIACALCIC Ampoules should be kept out of the reach and sight of children.

6.5 Nature and contents of container

Colourless glass OPC (One-Point-Cut) ampoules (glass type I). Each ampoule contains 100IU/mL. Each pack of MIACALCIC contains five ampoules.

6.6 Special precautions for disposal and other handling

MIACALCIC Ampoules should be inspected visually. 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. Remaining contents should be discarded. Allow to reach room temperature before intramuscular or subcutaneous use.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Emerge Health New Zealand Ltd
 58 Richard Pearse Drive
 Airport Oaks
 Mangere 2022
 New Zealand
 Phone: +61 3 9077 4486
 Email: customerservice@emergehealth.com.au

9 DATE OF FIRST APPROVAL

29 October 2014

10 DATE OF REVISION OF THE TEXT

4 September 2018

11 SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Data Sheet reformatted for compliance with the Medsafe "Guideline on the Regulation of Therapeutic Products in New Zealand" (Part 10, Section 2).
8	Update of Sponsor details following Change of Sponsor from Novartis to Emerge Health