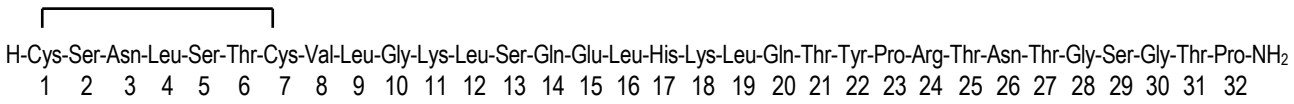
MIACALCIC®
(salcatonin)

NAME OF THE MEDICINE

Salcatonin is a synthesised polypeptide hormone structurally identical with salmon calcitonin. It contains 32 amino-acids in linear sequence with a disulphide bridge at position 1 and 7 and a molecular weight of 3431.9 (free peptide). Salcatonin is a white or grey-tinged white amorphous powder. It is very soluble in water and very slightly soluble in alcohol.

Chemical structure: CAS number: 47931-85-1



Naturally-occurring calcitonin is synthesised by parafollicular cells in the thyroid gland of mammals and the ultimobranchial gland of birds and fish. The potency of salmon calcitonin is standardised according to its ability to lower plasma calcium levels of rats as compared to the International Reference standard.

DESCRIPTION

Each mL MIACALCIC injection contains 50 or 100 I.U. salcatonin (present as polyacetate polyhydrate), sodium acetate 0.2%, glacial acetic acid 0.2% and sodium chloride 0.75%.

PHARMACOLOGY

Pharmacotherapeutic group, ATC code: Regulator of calcium homeostasis, H05BA01.

The secretion and biosynthesis of calcitonin in both animals and man are regulated by the concentration of calcium in plasma. When the calcium concentration is high the amount of the hormone increases.

The pharmacological activity of salmon calcitonin is the same as that of mammalian calcitonin. In man, data on relative potency are sparse, but salcatonin is thought to be at least 10-40 times as potent by weight as porcine or human calcitonin in producing hypocalcaemia depending on methodology. Presumably due to its greater affinity for receptor binding sites in bone and kidney, and slower rate of metabolism, salcatonin has a longer duration of action.

Calcitonin inhibits osteoclastic bone resorption, altering both the number and/or resorptive activity of osteoclasts. There is suggestive evidence in animals and man that calcitonin may promote bone and collagen formation via an increase in osteoblastic activity. However, the exact role of calcitonin on osteoblastic activity has not been fully established.

Calcitonin decreases the rate of bone turnover in conditions with an increased rate of bone resorption and formation, such as active Paget's disease, malignant osteolysis and some forms of osteoporosis characterised by a high bone turnover. This can be measured biochemically as a decrease in urine hydroxyproline excretion and a decrease in serum alkaline phosphatase levels.

Calcitonin treatment of Paget's disease may relieve bone pain, lower skin temperature over involved bone, decrease excessive cardiac output, stabilise hearing and allow radiographic and histological regression of bone lesions. Clinical experience demonstrates that salcatonin possesses analgesic activity. Investigations have shown binding sites specific to salcatonin in some areas of the central nervous system.

Calcitonin increases the excretion of phosphate, calcium and sodium by decreasing their tubular reabsorption.

Calcitonin is effective in diminishing hypercalcaemia in patients with hyperparathyroidism, vitamin D intoxication and osteolytic bone metastases.

The gastrointestinal effects attributed to calcitonin include the inhibition of gastric acid secretion, stimulation of the intestinal secretion of water and electrolytes, inhibition of pancreatic enzyme secretion and modifications of glucose-insulin relationships. Calcitonin probably has no major effects on the intestinal absorption of calcium and does not affect gastrointestinal motility.

Mechanism of Action

It has been postulated that cyclic AMP is involved in the secretion of calcitonin, which binds specifically to the membrane receptors of the target tissue and stimulates cyclic AMP accumulation.

Pharmacokinetics

Absorption:

Due to its polypeptide nature, salcatonin is not administered by the oral route as intestinal proteases inactivate the drug. It is administered by s.c., i.m., or i.v. routes. The onset of action is immediate after intravenous administration and occurs in about 15 minutes following intramuscular or subcutaneous administration, with peak plasma levels being attained within one hour. After subcutaneous administration, peak plasma levels are reached in about 23 minutes. The bioavailability of salcatonin is about 70% following both i.m. and s.c. administration.
Protein binding: 30 - 40%.
Volume of distribution: 0.15 - 0.30 litres/kg.

Metabolism:

Studies suggest that salcatonin is rapidly metabolised to unidentified and inactive metabolites primarily in the kidneys, but also in the blood and peripheral tissues. The metabolic clearance rate of salcatonin appears to be lower than either porcine or synthetic human calcitonin.

Excretion:

Up to 95% of salcatonin and its metabolites are excreted by the kidney, of which less than 2% is unchanged drug.

Half-life:

The absorption half-life is reported to be 8 - 22 minutes. The elimination half-life is about 60 minutes following i.m. administration and 60 - 90 minutes following s.c. or i.v. administration. The apparent biological half-life is several hours.

INDICATIONS

Active Paget's disease in patients who do not respond to alternative treatments or for whom such treatments are not suitable.
Hypercalcaemia.

CONTRAINDICATIONS

Pregnancy and Lactation (see 'PRECAUTIONS-Use in Pregnancy and Lactation').
Hypersensitivity to salcatonin or to any of the excipients in the formulation.

PRECAUTIONS

Hypersensitivity Reactions

Being a polypeptide, calcitonin may give rise in rare cases to localised or generalised hypersensitivity reactions. Allergic-type reactions, including single cases of anaphylactic shock, have been reported. If such symptoms are observed and can definitely be ascribed to the effect of the drug, treatment should be discontinued. (see "PRECAUTIONS - Escape Phenomena").

Malignancies

Meta-analyses of randomised 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 Adverse 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. The increased malignancy risk with the meta-analysis was heavily influenced by a single large 5-year trial, which had an observed risk difference of 3.4%. Imbalances in risk were still observed when analyses excluded basal cell carcinoma. There

were several limitations with the meta-analysis data and it is not clear how these limitations affect the results. 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 subcutaneously, intramuscularly or intravenously. The benefits for the individual patient should be carefully evaluated against possible risks (see Adverse effects).

Sensitivity Testing

It is advisable to perform a scratch or intradermal skin test to determine sensitivity before administration, as calcitonin is a protein. A 1 in 100 dilution should be used.

Escape Phenomena

Escape phenomena seen sometimes in long-term therapy are usually due to a saturation of the binding sites rather than to the development of antibodies. After an interruption of treatment, the therapeutic response to Miacalcic is restored. (see "ADVERSE REACTIONS - Immunological").

Use in Children

Long-term safety and efficacy have not been established in children, and therefore calcitonin is not recommended for paediatric use except in exceptional circumstances. Calcitonin has been used in familial hyperphosphatasaemia. Unless the physician considers that prolonged treatment is indicated on compelling medical grounds, prolonged treatment should be avoided as calcitonin may interfere with bone growth. In the absence of specific dosage experience in children, the doses relating to body weight should be used cautiously. Dosage should be adjusted to desired effect.

Use in Pregnancy and Lactation (B2)

There is no information on the drug's use in pregnancy and therefore the drug should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh any potential risk.

Animal studies suggest that calcitonin might suppress lactation in nursing mothers. Treatment during lactation is not recommended.

Effects on Ability to Drive and Use Machines

Miacalcic may cause fatigue, dizziness and visual disturbances (see " ADVERSE REACTIONS") which may impair the reactions of the patient. Patients should be warned that these effects may occur, in which case they should not drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

For Miacalcic ampoules no recent frequency estimations based on clinical trials are available. Estimations based on the number of post-marketing reports received lead to frequencies lower than those reported in controlled clinical trials with Miacalcic nasal spray. For events attributed to the systemic administration of salcatonin therefore the same (higher) frequency categories as used for the nasal spray was also used for Miacalcic ampoules.

Adverse reactions (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)

Table 1

Immune system disorders:	
Rare:	Hypersensitivity[+].
Very rare:	Anaphylactic and anaphylactoid reactions^, anaphylactic shock.
Nervous system disorders:	
Common:	Dizziness, headache, dysgeusia.
Uncommon:	Paraesthesia.
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:	Pruritus, rash generalised (including maculopapular eruption urticaria)
Musculoskeletal and connective tissue disorders:	
Common:	Arthralgia.
Uncommon:	Musculoskeletal pain, muscle spasms.
Renal and urinary disorders:	
Rare:	Polyuria.

General disorders and administration site conditions:

Common:	Fatigue.
Uncommon:	Injection site reaction (including pain on injection), influenza-like illness (including chills and fever), oedema (facial, peripheral and generalised).

^ Reactions resulting in tachycardia, hypotension and collapse.

***** Facial flushing accompanied by a sensation of heat.

[+] Allergic reactions manifested in some cases by rash, hypertension or peripheral oedema.

The gastrointestinal disorder may include nausea, abdominal pain, diarrhoea and vomiting and is usually a transient, dose-related phenomenon, and occurs more frequently after i.v. than i.m. or s.c. administration. This problem may be overcome either by concomitant anti-emetic therapy or by subdividing the daily dose. A temporary dose reduction may be necessary in a few cases.

Immunological: Salcatonin binding antibodies may develop in some patients after several months (generally of low titre, and more likely to occur with higher doses). However, the development of antibodies does not necessarily cause clinical resistance but may do so in a small number of cases.

Malignancies: Meta-analyses of randomised 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 Precautions).

Post-marketing Experience

The following reactions have been identified through post-marketing reporting and literature review. Because this adverse drug reaction has been reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency which is therefore categorised as not known.

Central and peripheral nervous system: Tremor
Metabolism and nutrition disorders: Hypocalcaemia
Skin and subcutaneous tissue disorders: Urticaria

DOSAGE AND ADMINISTRATION

Note: 1 I.U. = 1 MRC unit. One unit corresponds to 0.2 μg of the pure peptide.

Miacalcic may be administered subcutaneously, intramuscularly or intravenously; local and systemic tolerance is generally good with all 3 routes of administration at recommended dosages.

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

Hypercalcaemia

Treatment should be limited to the shortest duration possible. The recommended dose is 5 - 10 I.U. per kg daily, administered by slow i.v. infusion in 500 mL normal saline over at least six hours, or by slow intravenous injection in 2 to 4 divided doses spread over the day.

Alternatively, the same daily dose may be given by one or more s.c. or i.m. injections. If the volume of Miacalcic for injection exceeds 2 mL, i.m. injection is preferable and multiple sites of injection should be used.

Rehydration should be considered. Emergency treatment is followed by specific treatment of the underlying disease, if required.

Paget's Disease

80 - 100 I.U. daily by s.c. or i.m. injection. In some cases the injections may be given only every second day. In particular after improvement of the objective and subjective symptoms, an injection of 50 I.U. per day may be sufficient.

The duration of treatment depends on the therapeutic indication and the patient’s response. The need for ongoing therapy should be assessed by a health practitioner on a regular basis. Following cessation of chronic treatment return of biochemical values to pretreatment levels may take weeks or years.

Mode of Administration

For intramuscular or subcutaneous use:

The solution requires no further dilution. See "Presentation and Packaging".
Patients who are instructed in the self-administration of subcutaneous injections must receive precise directions from the physician or the nurse.

For intravenous infusion:

Intravenous infusion is the most effective method of administration and should always be used in emergency or severe cases of hypercalcaemia. Dilute the required amount of salcatonin in 500 mL of 0.9% sodium chloride and infuse over at least 6 hours.

Geriatric

Use adult dosage with care. It should be noted that most patients with Paget's disease are elderly.

With impaired liver function

No information available.

With impaired renal function

A smaller dose may be required in renal impairment, as calcitonin is metabolised and excreted predominantly by the kidneys.

OVERDOSAGE

Clinical features:
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.

Contact the Poison Information Centre on 131 126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentation:

- 100 I.U.: each ampoule of 1 mL contains 100 I.U. = 100 MRC units salcatonin (present as polyacetate polyhydrate)
- 50 I.U.: each ampoule of 1 mL contains 50 I.U. = 50 MRC units salcatonin (present as polyacetate polyhydrate)

The ampoules are ready for injection.

Storage: Store between 2° - 8°C. Refrigerate. Do Not Freeze.

NAME AND ADDRESS OF THE SPONSOR

Emerge Health Pty Ltd
Suite 3, 22 Gillman Street,
Hawthorn East, VIC. 3123

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE ARTG

21 August 1991 (grandfathered)

DATE OF MOST RECENT AMENDMENT

9 August 2018

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