MIACALCIC®
(salcatonin)

DESCRIPTION

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.

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%.

H-Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-Gln-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH₂

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.

PHARMACOLOGY

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, stabilize 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.
Hypercalcaemia.

CONTRAINDICATIONS
Pregnancy and Lactation (see 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”).

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 hyperphosphatasemia. 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. Salcatonin does not cross the placental barrier in animals.

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.

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

ADVERSE REACTIONS
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.

The adverse reactions below are listed according to the following frequency values: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1,000, <1/100); rare (≥ 1/1,000, 1/10,000) and very rare (< 1/10,000).
Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity^</td>
<td>Anaphylactic and anaphylactoid reactions^, anaphylactic shock.</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness, headache, dysgeusia.</td>
<td>Paraesthesia.</td>
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<tr>
<td>Eye disorders</td>
<td>Visual disturbance.</td>
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<tr>
<td>Vascular disorders</td>
<td>Flushing*.</td>
<td>Hypertension.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, abdominal pain, diarrhoea.</td>
<td>Vomiting.</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus, rash generalised (including maculopapular eruption and urticaria).</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia.</td>
<td>Musculoskeletal pain, muscle spasms.</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Frequency, polyuria.</td>
<td></td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue.</td>
<td>Injection site reaction (including pain on injection), influenza-like symptoms (including chills and fever), oedema (facial, peripheral and generalized).</td>
</tr>
</tbody>
</table>

^ 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.

**Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following reaction has 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 categorized as not known.

**Central and peripheral nervous system:** Tremor

**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.

**Hypercalcaemia**

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.

Treatment should be given for periods ranging from a few months to a few years. 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

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.
Schedule: Schedule 4.

SPONSOR
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