Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Miacalcic 50 IU/ml solution for injection and infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution contains 50 IU of calcitonin as calcitonin (salmon, synthetic) where one IU corresponds to 0.167 micrograms of the drug substance.

Excipient(s) with known effect
Each 1 ml solution contains 3.3 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion.
Miacalcic 50 IU/ml is a clear, colourless aqueous solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Calcitonin is indicated for:

- Prevention of acute bone loss due to sudden immobilisation such as patients with recent osteoporotic fractures.
- For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment.
- Treatment of hypercalcemia of malignancy

4.2 Posology and method of administration

Posology
Salmon calcitonin may be administered at bedtime to reduce the incidence of nausea or vomiting which may occur, especially at the initiation of therapy.

Due to evidence of an increased risk of malignancies and long term calcitonin use (see section 4.4), the treatment duration in all indications should be limited to the shortest period of time possible and using the minimum effective dose.

Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
The recommended dosage is 100 IU daily or 50 IU twice daily administered subcutaneously or intramuscularly. The dose may be reduced to 50 IU daily at the start of remobilisation. The recommended treatment duration is 2 weeks and should not exceed 4 weeks in any case due to the association of the increased risk of malignancies and long term calcitonin use.

Paget's disease
The recommended dosage is 100 IU per day administered subcutaneously or intramuscularly, however, a minimum dosage regimen of 50 IU three times a week has achieved clinical and biochemical improvement. Dosage is to be adjusted to the individual patient's needs. Treatment should be discontinued once the patient has responded and symptoms have resolved. Duration of treatment should not normally exceed 3 months due to evidence of an increased risk of malignancies with long term calcitonin use. Under exceptional circumstances, e.g. in patients with impending pathologic fracture, treatment duration may be extended up to a recommended maximum of 6 months.
Periodic re-treatment may be considered in these patients, and should take into account the potential benefits and evidence of an increased risk of malignancies and long term calcitonin use (see section 4.4).
The effect of calcitonin may be monitored by measurement of suitable markers of bone remodelling, such as serum alkaline phosphatase or urinary hydroxyproline or deoxypyridinoline. The dose may be reduced after the condition of the patient has improved.

Hypercalcemia of malignancy
The recommended starting dose is 100 IU every 6 to 8 hours by subcutaneous or intramuscular injection. In addition, salmon calcitonin could be administered by intravenous injection after previous rehydration.

If the response is not satisfactory after one or two days, the dose may be increased to a maximum of 400 IU every 6 to 8 hours. In severe or emergency cases, intravenous infusion with up to 10 IU/kg body weight in 500ml 0.9% w/v sodium chloride solution may be administered over a period of at least 6 hours.

As salmon calcitonin is a peptide, adsorption onto the plastic of the infusion set may occur. This has the potential to reduce the total dose delivered to the patient. Frequent monitoring of the clinical and laboratory response including the measurement of serum calcium is recommended especially in the early phases of treatment. The dosing of Miacalcic should be individualized to the patient's specific requirements.

Elderly population
Experience with the use of calcitonin in the elderly has shown no evidence of reduced tolerability or altered dosage requirements.

Patients with hepatic impairment
Experience with the use of calcitonin in patients with altered hepatic function has shown no evidence of reduced tolerability or altered dosage requirements.

Patients with renal impairment
The metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known (see section 5.2).

Paediatric population
There is insufficient evidence to support the use of salmon calcitonin in conditions associated with paediatric osteoporosis. Use of salmon calcitonin in children 0 to 18 years is therefore not recommended.

Method of administration
Intravenous, subcutaneous, or intramuscular use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Calcitonin is also contraindicated in patients with hypocalcaemia.

4.4 Special warnings and precautions for use

Because calcitonin is a peptide, the possibility of systemic allergic reactions exists andallergic-type reactions including isolated cases of anaphylactic shock have been reported in patients receiving calcitonin. Such reactions should be differentiated from generalised or local flushing, which are common non-allergic effects of calcitonin (see section 4.8). Skin testing should be conducted in patients with suspected sensitivity to calcitonin prior to their treatment with calcitonin.

Analyses of randomised controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that calcitonin is associated with a statistically significant increase in the risk of cancer compared to patients treated with placebo. These trials demonstrated an increase in the absolute risk of cancer occurrence for patients treated with calcitonin compared to placebo which varied between 0.7% and 2.4% with long term therapy. Patients in these trials were treated with oral or intra-nasal formulations however it is likely that an increased risk also applies when calcitonin is administered subcutaneously, intramuscularly or intravenously especially for long-term use, as systemic exposure to calcitonin in such patients is expected to be higher than for other formulations.

This medicinal product contains 3.3 mg sodium per ml, equivalent to 0.16% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Serum calcium levels may be transiently decreased to below normal levels following administration of calcitonin, notably upon initiation of therapy in patients with abnormally high rates of bone turnover. This effect is diminished as osteoclastic activity is reduced. However, care should be exercised in patients receiving concurrent treatment with cardiac glycosides or calcium channel blocking agents. Dosages of these drugs may require adjustment in view of the fact that their effects may be modified by changes in cellular electrolyte concentrations.

The use of calcitonin in combination with bisphosphonates may result in an additive calcium-lowering effect.

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

Pregnancy
Calcitonin has not been studied in pregnant women. Calcitonin should be used during pregnancy only if treatment is considered absolutely essential by the physician.

Breast-feeding
It is not known if the substance is excreted in human milk. In animals, salmon calcitonin has been shown to decrease lactation and to be excreted in milk (see section 5.3). Therefore, breast-feeding is not recommended during treatment.

Fertility
There are no data regarding a potential influence of calcitonin 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 usemachines. Miacalcic may cause fatigue, dizziness and visual disturbances (see section 4.8) which may impair the patient's reaction. Patients must therefore be warned that these effects may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

The most frequently observed undesirable effects are nausea, vomiting and flushing. They are dose-dependent and are more frequent after intravenous than after intramuscular or subcutaneus administration.

Adverse drug reactions from multiple sources including clinical trials and post-marketing experience 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.

Adverse reactions have been ranked under headings of frequency using the following convention: 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), not known (cannot be estimated from the available data).

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Common: *Malignancy (with long term use).*

Immune system disorders
Uncommon: Hypersensitivity.
Very rare: Serious allergic-type illness, such as bronchospasm, swelling of the tongue and throat, anaphylactic shock.

Metabolism and nutrition disorders
Rare: Transient decrease of calcemia.[3]
Not known: Hypocalcemia.

Nervous system disorders
Common: Dizziness, headache, dysgeusia.
Not known: Tremor.

Eye disorders
Uncommon: Visual disturbance.

Vascular disorders
Very common: Flushing (facial or upper body)[4]
Uncommon: Hypertension.

Gastrointestinal disorders
Very common: Nausea with or without vomiting.[2]
Common: Diarrhoea, abdominal pain.

Skin and subcutaneous tissue disorders
Uncommon: Rash generalised, pruritus.
Not known: Urticaria

Musculoskeletal and connective tissue disorders
Common: Musculoskeletal pain including arthralgia.

Renal and urinary disorders
Uncommon: Polyuria.

General disorders and administration site conditions
Common: Fatigue.
Uncommon: Influenza-like symptoms, oedema (facial, peripheral and generalised), injection site reaction.

Investigations
Rare: Development of neutralising antibodies to calcitonin.[1]

The frequencies of the above listed undesirable effects are partly based on results from clinical trials with calcitonin nasal spray.

[1]Development of neutralising antibodies to calcitonin. The development of these antibodies is not usually related to loss of clinical efficacy, although their presence in a small percentage of patients following long-term therapy with calcitonin may result in a reduced response to the product. The presence of antibodies appears to bear no relationship to allergic reactions, which are rare. Calcitonin receptor down-regulation may also result in a reduced clinical response in a small percentage of patients following long-term therapy.
[2]Nausea with or without vomiting is noted in approximately 10% of patients treated with calcitonin. The effect is more evident on initiation of therapy and tends to decrease or disappear with continued administration or a reduction in dose. An antiemetic may be administered, if required. Nausea/vomiting are less frequent when the injection is done in the evening and after meals.
[3]In case of patients with high bone remodelling (Paget's disease and young patients) a transient decrease of calcemia may occur between the 4th and the 6th hour after administration, usually asymptomatic.
[4]Flushing (facial or upper body) is not an allergic reaction but is due to a pharmacological effect, and is usually observed 10 to 20 minutes after administration.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

Nausea, vomiting, flushing and dizziness are known to be dose dependent when calcitonin is administered parenterally. Single doses (up to 10,000 IU) of injectable salmon calcitonin have been administered without adverse reactions, other than nausea and vomiting, and exacerbation of pharmacological effects.
Should symptoms of overdose appear, treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

The pharmacological properties of the synthetic and recombinant peptides have been demonstrated to be qualitatively and quantitatively equivalent.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiparathyroid hormone, ATC code: H05BA01 (calcitonin, salmon, synthetic).

Mechanism of action
Calcitonin is a calciotropic hormone, which inhibits bone resorption by a direct action on osteoclasts. By inhibiting osteoclast activity via its specific receptors, salmon calcitonin decreases bone resorption.In pharmacological studies, calcitonin has been shown to have analgesic activity in animal models.

Pharmacodynamic effects
Calcitonin markedly reduces bone turnover in conditions with an increased rate of bone resorption such as Paget's disease and acute bone loss due to sudden immobilisation.
The absence of mineralisation defect with calcitonin has been demonstrated by bone histomorphometric studies both in man and in animals.

Decreases in bone resorption as judged by a reduction in urinary hydroxyproline and deoxypyridinoline are observed following calcitonin treatment in both normal volunteers and patients with bone-related disorders, including Paget's disease and osteoporosis.

The calcium-lowering effect of calcitonin is caused both by a decrease in the efflux of calcium from the bone to the ECF and inhibition of renal tubular reabsorption of calcium.

5.2 Pharmacokinetic properties

Absorption
Salmon calcitonin is rapidly absorbed. Calcitonin has a short absorption half-life of 10-15 minutes.
Peak plasma concentrations are attained within the first hour of administration. After subcutaneous administration, peak plasma levels are reached in about 23 minutes.
Bioavailability following subcutaneous and intramuscular injection in humans is high and similar for the two routes of administration (71% and 66%, respectively).

Distribution
Plasma protein binding is 30 to 40%.

Biotransformation
Animal studies have shown that calcitonin is primarily metabolised via proteolysis in the kidney following parenteral administration. The metabolites lack the specific biological activity of calcitonin.

Elimination
Salmon calcitonin is rapidly eliminated. The elimination half-life is about 1 hour for intramuscular administration and 1 to 1.5 hours for subcutaneous administration. Salmon calcitonin is primarily and almost exclusively degraded in the kidneys, forming pharmacologically inactive fragments of the molecule. Therefore, the metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known.

Pharmacokinetic/pharmacodynamic relationship
There is a relationship between the subcutaneous dose of calcitonin and peak plasma concentrations. Following parenteral administration of 100 IU calcitonin, peak plasma concentration lies between about 200 and 400 pg/ml. Higher blood levels may be associated with increased incidence of nausea and vomiting.

5.3 Preclinical safety data

Conventional long-term toxicity, reproduction, mutagenicity, and carcinogenicity studies have been performed in laboratory animals. Salmon calcitonin is devoid of embryotoxic, teratogenic and mutagenic potential.

An increased incidence of pituitary adenomas has been reported in rats given synthetic salmon calcitonin for 1 year. This is considered a species-specific effect and of no clinical relevance.

It is not known whether salmon calcitonin crosses the placental barrier.

In lactating animals given calcitonin, suppression of milk production has been observed. Calcitonin is secreted into the milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Sodium acetate trihydrate
Sodium chloride
Water for injection

6.2 Incompatibilities

Glass or hard plastic IV containers should not be used.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.

From a microbiological point of view, this medicine should be used immediately after it has reached room temperature if it is to be injected or immediately after dilution in 0.9% w/v sodium chloride in soft PVC bags only, if it is to be infused.

For additional instructions please refer to section 6.3 and 6.6.

6.5 Nature and contents of container

Type I, clear glass ampoule containing 1ml of solution. Miacalcic ampoules 50 IU/ml are supplied as packs containing 5, 10, 50 and 100 ampoules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Miacalcic ampoules 50 IU/ml should be inspected visually. If the liquid is not clear and colourless, or contains any particles, or the ampoule is damaged, do not use the medicine.

Solutions for infusion should be prepared immediately before use in soft plastic PVC infusion bags. Glass or hard plastic IV containers should not be used.

The ampoules are for single use only. Remaining contents should be discarded. Allow to reach room temperature before intramuscular or subcutaneous use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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