Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Miacalcic 200 IU Nasal Spray, solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One metered dose delivers 200 IU of calcitonin as calcitonin (salmon, synthetic) where one IU corresponds to 0.167 micrograms of the drug substance.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal Spray, solution.
Miacalcic 200 IU Nasal Spray is a liquid dosage form for local application using a spray device. The liquid takes the form of a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of established post-menopausal osteoporosis in order to reduce the risk of vertebral fractures. A reduction in hip fractures has not been demonstrated.

4.2 Posology and method of administration

The recommended dosage of intranasal calcitonin for the treatment of established post-menopausal osteoporosis is 200 IU once a day. Use of intranasal calcitonin is recommended in conjunction with an adequate calcium and vitamin D intake. Treatment is to be administered on a long-term basis, *(see section 5.1, Pharmacodynamic properties)*.

It is recommended to administer Miacalcic Nasal Spray per actuation to alternating nostrils.

Use in elderly, hepatic and renal impairment patients
Extensive experience with the use of intranasal calcitonin in the elderly has shown no evidence of reduced tolerability or altered dosage requirements. The same applies to patients with altered renal or hepatic function.

Use in children
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.

Note
Full instructions for use by the patient are given in the package leaflet.

4.3 Contraindications

Hypersensitivity to calcitonin (see section 4.8.) 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

Nasal examinations is to be performed before treatment begins and in the case of nasal complaints, medication should not be started. If severe ulceration of the nasal mucosa occurs (e.g. penetration below the mucosa or association with heavy bleeding), intranasal calcitonin is to be discontinued. In case of mild ulceration, medication is to be interrupted temporarily until healing occurs.

Because calcitonin is a peptide, the possibility of systemic allergic reactions exists and allergic-type reactions including isolated cases of anaphylactic shock have been reported in patients receiving intranasal calcitonin. In patients with suspected sensitivity to calcitonin, skin testing is to be considered prior to treatment.

The preservative (benzalkonium chloride) can cause swelling of the nasal mucosa, especially during long-term use. If such a reaction (i.e. persistent nasal congestion) is suspected, the use of another dosage form should be considered.

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 Fertility, pregnancy and lactation

As intranasal calcitonin is indicated for postmenopausal women, no studies have been carried out in pregnant women or nursing mothers. Therefore, intranasal calcitonin is not to be administered to such patients. However, animal studies have shown no embryotoxic and teratogenic potential *(see section 5.3, Preclinical safety data).*

It is not known whether salmon calcitonin is excreted into human breast milk. In animals, salmon calcitonin has been shown to decrease lactation and to be excreted in milk.

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 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 local reactions such as rhinitis and nasal discomfort. They are generally mild and rarely require discontinuation of the treatment.

Adverse reactions have been ranked under headings of frequency using the following convention:: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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

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

Eye disorders
Uncommon: Visual disturbance.

Respiratory, thoracic and mediastinal disorders [2]

Very common:	Rhinitis (including nasal dryness, nasal oedema, nasal congestion, sneezing, allergic rhinitis), nasal discomfort (e.g. nasal irritation, nasal odour, rash papular, parosmia, nasal mucosal erythema, mucosal excoriation).
Common:	Rhinitis ulcerative, sinusitis, epistaxis, pharyngitis.
Uncommon:	Cough.

Gastrointestinal disorders

Common:	Nausea, diarrhoea, abdominal pain.
Uncommon:	Vomiting.

Skin and subcutaneous tissue disorders

Uncommon:	Pruritus.
Rare:	Rash generalized.

Musculoskeletal and connective tissue disorders

Common:	Musculoskeletal pain including arthralgia.

Vascular disorders

Common:	Flushing.
Uncommon:	Hypertension.

General disorders and administration site conditions

Common:	Fatigue.
Uncommon:	Influenza-like symptoms, oedema (facial, extremities and generalized).

Immune system disorders

Uncommon:	Hypersensitivity reactions.
Very rare:	Anaphylactic and anaphylactoid reactions such as tachycardia, hypotension, circulatory collapse and anaphylactic shock.

[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 high doses of 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 with high doses.

[2] Respiratory, thoracic and mediastinal disorders are generally mild (in about 80% of reports) and require discontinuation of the treatment in less than 5% of cases.

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 salmon calcitonin have been administered parenterally without adverse effects other than nausea and vomiting, and exacerbation of pharmacological effects. Such events might therefore also be expected to occur in association with an overdose of intranasal calcitonin. However, intranasal calcitonin has been administered at up to 1600 IU as a single dose and up to 800 IU per day for three days without causing any serious adverse event. If symptoms of overdose appear, treatment is to be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.
Calcitonin markedly reduces bone turnover in conditions with an increased rate of bone resorption such as osteoporosis.
The absence of mineralisation defect with calcitonin has been demonstrated by bone histomorphometric studies both in man and in animals.

In pharmacological studies, calcitonin has been shown to have analgesic activity in animal models. Intranasal calcitonin produces a clinically relevant biological response in humans , 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 intranasal calcitonin significantly suppresses biochemical markers of bone turnover such as serum C-telopeptides (sCTX) and skeletal isoenzymes of alkaline phosphatase .

Intranasal calcitonin results in a statistically significant 1-2% increase in lumbar spine Bone Mineral Density (BMD), which is evident from year 1 and is sustained for up to 5 years. Hip BMD is preserved.

In a 5-year trial in postmenopausal women (PROOF study), administration of 200 IU intranasal salmon calcitonin resulted in a reduction of 33% in the relative risk of developing vertebral fractures. The relative risk of developing vertebral fractures, compared to placebo (treatment with vitamin D and calcium alone) in all patients treated with daily doses of 200 IU was 0.67 (95% CI: 0.47-0.97). The absolute risk of developing vertebral fractures over 5 years was reduced from 25.9% in the placebo group to 17.8% in the 200 IU group. A reduction in hip fractures has not been demonstrated.

The recommended dosage of intranasal salmon calcitonin for the treatment of established post-menopausal osteoporosis is 200 IU once a day. Higher dosages were not more effective.

5.2 Pharmacokinetic properties

The bioavailability of a 200 IU dose relative to parenteral administration is between 2 and 15%. Intranasal calcitonin is absorbed rapidly through the nasal mucosa and peak plasma concentrations are attained within the first hour of administration (median about 10 minutes). The half-life of elimination has been calculated to be around 20 minutes and no evidence of accumulation was observed with multiple dosing. Doses higher than the recommended dose result in higher blood levels (as shown by an increase in AUC) but relative bioavailability does not increase. As is the case with other polypeptide hormones, there is very little value in monitoring plasma levels of salmon calcitonin since these are not directly predictive of the therapeutic response. Hence, calcitonin activity is to be evaluated by using clinical parameters of efficacy.

Plasma protein binding is 30 to 40%.

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.

Salmon calcitonin does not cross the placental barrier.

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

Preclinical data from the literature show that the excipient benzalkonium chloride produces a concentration- and time-dependent adverse effect on nasal cilia, including irreversible immobility, both in vitro and in vivo using rats as the animal model. Benzalkonium chloride induces histopathological changes in the nasal mucosa of rats at a concentration of 0.021% and higher, which is more than double the concentration of the commercially available Miacalcic Nasal Spray (containing 0.01% benzalkonium chloride).

However, daily intranasal administration for 26 weeks of a placebo containing 0.01% benzalkonium chloride or of high doses of a calcitonin formulation containing 0.01% benzalkonium chloride was well tolerated by monkeys.
No treatment related changes to the respiratory tract were observed. Dogs receiving salmon calcitonin with 0.01% benzalkonium chloride did not reveal any relevant abnormal findings in the nasal cavity and upper respiratory tract. Miacalcic Nasal Spray with 0.01% benzalkonum chloride did not change the nasal ciliary beat frequency of guinea pigs and of Pagetic patients over 4 weeks and 6 months respectively.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride
Sodium chloride
Hydrochloric acid
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened, 3 years.
After opening: it should be used within 4 weeks.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C). Do not freeze.
Once opened, store at room temperature. Do not store above 25°C.
Keep the bottle upright at all times to reduce the risk of air bubbles getting into the dip tube.

6.5 Nature and contents of container

The device is composed of a clear, uncoloured glass bottle (glass type I) and a spray mechanism containing an integrated, automatic dose-counting mechanism and a built-in mechanical stop. Miacalcic 200 IU Nasal Spray is supplied in packs containing one or two bottle(s) with 2 ml of spray solution, delivering at least 14 metered doses of 200 IU. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The pump should be primed before first use: pull up the protective cap and hold the bottle in the vertical direction, and press down the upper part until it clicks. Repeat this operation twice. After the first time the dose counter window shows white and red lines, after the second time white and after the third time green. It is now ready for use.

7 MARKETING AUTHORISATION HOLDER

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