NOVARTIS

Miacalcic® nasal spray

Composition

Active substance
Salmon calcitonin

Excipients
Benzalkonium chloride, sodium chloride, hydrochloric acid (for pH adjustment), water (purified, Eur.P.).

Pharmaceutical form and quantity of active substance per unit

1 bottle of mite 100 nasal spray contains at least 14 metered 100 IU doses of salmon calcitonin.
1 bottle of nasal spray 200 contains at least 14 metered 200 IU doses of salmon calcitonin.

Indications / Potential uses

Miacalcic nasal spray is indicated for the treatment of:
Prevention of osteoporosis
In acute bone loss due to sudden immobilization such as in patients with osteoporotic fractures (see "**Properties / Actions**"). Miacalcic should be supplemented with adequate doses of calcium and vitamin D, as needed by the individual patient, to prevent further loss of bone mass. The maximum duration of treatment is 3 months.

Paget's disease (osteitis deformans):
Only in patients who do not respond to alternative treatments or for whom alternative treatments are not suitable: The duration of treatment is normally 3 months (also refer to "Dosage / Administration").

Algodystrophy or Sudeck's disease (neurodystrophic disorders): Neurodystrophic disorders due to various causes and predisposing factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia and drug-induced neurotrophic disorders. The duration of treatment is up to 6 weeks.

Dosage / Administration

It is recommended that the patient alternate between the right and left nostrils as sites of administration for the individual metered doses of nasal spray. In comparison to calcitonin ampoules, the bioavailability of the nasal spray is considerably lower at up to 25%, whereas bioavailability of around 70% is reached with the parenteral solution.
Due to the association between long-term calcitonin use and the occurrence of malignancies (see "**Warnings and precautions**"), treatment with calcitonin in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

Osteoporosis
200 IU (= 2 metered doses of Miacalcic mite 100 or 1 metered dose of Miacalcic 200) daily, if necessary in several divided doses.
The bioequivalence of the 1 × 200 IU and 2 × 100 IU dosages has not been studied, but data from clinical studies demonstrate the efficacy of both.

Paget's disease
In Paget's disease, the recommended dose is 200 IU (= 2 metered doses of Miacalcic mite 100) daily in two divided doses. In a few cases, 200 IU twice daily may be necessary at the beginning of therapy. Dose reduction may also be attempted during the course of treatment in patients using this dosage form.
The duration of treatment depends on the therapeutic indication and the patient's response. In exceptional circumstances (contraindication of bisphosphonates, severe renal impairment or pathological fractures), treatment may be given for up to 6 months. Thereafter, further treatment is only permissible following careful assessment of the benefits and risks (tumour risk).

Algodystrophy (neurodystrophic disorders)
Early diagnosis of neurodystrophic disorders is important, and treatment should start as soon as the diagnosis is confirmed.
The recommended dose is 200 IU daily in 2 divided doses for 2-4 weeks. Thereafter, 200 IU may be administered three times a week for up to 6 weeks, depending on the patient's clinical response.

Special remarks
Treatment with Miacalcic markedly reduces serum alkaline phosphatase and urinary hydroxyproline excretion, often even to normal levels. Pain is fully or partially alleviated.
In rare cases, alkaline phosphatase and hydroxyproline excretion levels rise after an initial fall. If this happens, the physician must decide on the basis of the clinical picture whether treatment should continue.
Disorders of bone metabolism may recur one to several months after treatment with Miacalcic has been discontinued, necessitating a new course of Miacalcic therapy.
Antibodies to calcitonin may develop in some patients during long-term calcitonin therapy; clinical efficacy is usually not affected, however. Signs of loss of efficacy ("escape phenomenon"), sometimes observed in pagetic patients receiving long-term therapy, are probably due to saturation of the receptors and are apparently not related to the development of antibodies. Following interruption of treatment, the therapeutic response to Miacalcic is restored.
There have been no reports of any pathological changes occurring in the nasal mucosa during long-term treatment with the nasal spray.

Use in children
Miacalcic should not be administered to children for more than a few weeks unless the physician sees compelling reasons for a longer period of treatment. Experience relating to long-term treatment in children is insufficient.

Use in elderly patients / special patient populations
Extensive experience with the use of Miacalcic in elderly patients has shown no evidence of reduced tolerability or of the need for dosage adjustment. The same applies to patients with renal or hepatic impairment, although no specific studies have been carried out in this patient population.

Contraindications

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see "**Warnings and precautions**" and "**Adverse effects**").

Warnings and precautions

Because salmon calcitonin is a polypeptide, the possibility of allergic reactions exists. Allergic-type reactions, including isolated cases of anaphylactic shock, have been reported in patients receiving Miacalcic. In patients with suspected hypersensitivity to calcitonin, skin testing using diluted, sterile solution from Miacalcic ampoules should be considered prior to initiating treatment. 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 "**Adverse effects**"). Patients in these trials were treated with oral or intranasal formulations. The meta-analyses demonstrated an increase in the absolute rate of occurrence of tumours in patients treated with calcitonin compared to placebo, which varied between 0.7% (oral formulation) and 2.36% (nasal spray). Numerical imbalances between calcitonin and placebo were observed after 6 to 12 months of therapy. A mechanism for this observation could not be identified. The benefits for the individual patient should be carefully evaluated against possible risks (see "**Adverse effects**").

Interactions

Concomitant use of calcitonin and lithium may lead to a reduction of up to 30% in plasma lithium concentrations. The dose of lithium may need to be adjusted.

Pregnancy / Lactation

Miacalcic does not cross the placental barrier in animals. Reproductive toxicity studies in animals have shown that Miacalcic is devoid of embryotoxic and teratogenic potential. However, there have been no controlled studies in pregnant women. For this reason, Miacalcic should be used with caution during pregnancy.
Breast-feeding during treatment is not recommended. It is not known whether Miacalcic is excreted in breast milk.

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 transient fatigue, dizziness and visual disturbances, which may impair the patient's reactions. Patients must therefore be warned that these effects may occur, in which case they must not drive or use machines.

Adverse effects

Frequencies
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), including isolated reports; in post-marketing use: frequency not known.

Immune system disorders
Rare: Hypersensitivity.
Very rare: Anaphylactic and anaphylactoid reactions, anaphylactic shock.

Nervous system disorders
Common: Headache, dizziness, dysgeusia.
Frequency not known: Tremor.

Eye disorders
Uncommon: Visual disturbance.
Vascular disorders
Common: Flushing.
Uncommon: Hypertension.

Respiratory disorders
Very common: Nasal discomfort, nasal congestion, nasal oedema, sneezing, rhinitis, nasal dryness, allergic rhinitis, nasal irritation, nasal odour, nasal mucosal erythema, mucosal excoriation.
Common: Epistaxis, sinusitis, ulcerative rhinitis, pharyngitis.
Uncommon: Cough.

Gastrointestinal disorders
Common: Nausea, diarrhoea, abdominal pain.
Uncommon: Vomiting.
Skin and subcutaneous tissue disorders
Rare: Generalized rash.

Musculoskeletal disorders
Common: Arthralgia.
Uncommon: Musculoskeletal pain.

*General disorders and administration site reactions (see **Respiratory disorders**)*
Common: Fatigue.
Uncommon: Influenza-like symptoms, oedema (facial, peripheral or generalized).
Rare: Pruritus.
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. A mechanism for this observation could not be identified (see "**Warnings and precautions**").

Overdose

Signs and symptoms
Depending on the dose, parenteral administration may give rise to nausea, vomiting, flushing and dizziness. Such effects might therefore also be expected to occur in association with an overdose of Miacalcic nasal spray. However, Miacalcic nasal spray has been administered at up to 1,600 IU as a single dose and up to 800 IU per day for three days without causing any serious adverse effects. Isolated cases of overdose have been reported.

Management
Management of overdose should be symptomatic.

Properties / Actions

ATC code: H05BA01

Mechanism of action / Pharmacodynamics
All calcitonins consist of 32 amino acids in a single chain, with a ring of 7 amino acids 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.
Salmon calcitonin inhibits the activity of osteoclasts via their specific receptors. It markedly reduces, and may even normalize, bone turnover in conditions with an increased rate of bone resorption, such as osteoporosis. Salmon calcitonin has been shown both in animal models and in humans to have analgesic activity, presumably via a direct effect on the central nervous system.

Clinical efficacy
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 reuptake) and a decrease in the urinary excretion of hydroxyproline.
Controlled studies with smaller patient collectives with Miacalcic nasal spray have shown that there is a significant reduction in markers of bone turnover such as serum C-telopeptides (sCTx), osteocalcin and skeletal isoenzymes of alkaline phosphatase, at least for the first three months.
Miacalcic produces beneficial effects with a bone-stabilizing effect particularly in postmenopausal women with high bone turnover, alongside analgesia, which is especially beneficial in osteoporotic fractures.
A meta-analysis published in mid-2011, which focussed on pain prevention following vertebral compression fractures (data with nasal spray and ampoules), found significant effects for calcitonin compared to placebo in the first 4 weeks in resting state. For mobile groups, there was also still a small (but statistically significant) effect after 6 months.
In a collective of 467 patients (10 studies), the average age was about 67 years and 90% were women; these data thus show that efficacy is demonstrated especially in postmenopausal women, while use in men and younger patients is only documented in a limited manner.
Calcitonin inhibits gastric and exocrine pancreatic secretion.

Pharmacokinetics

Intranasal administration
Various authors have provided divergent data on bioavailability, which is likely to be 25% maximum. As is the case with other polypeptide hormones, plasma levels of salmon calcitonin are not predictive of therapeutic response.

Preclinical data

Daily intranasal administration for 26 weeks of a placebo solution 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. Daily intranasal administration of salmon calcitonin with 0.01% benzalkonium chloride to dogs for 4 weeks did not reveal any relevant abnormal findings in the nasal cavity or upper respiratory tract. Miacalcic nasal spray with 0.01% benzalkonium chloride did not change nasal ciliary beat frequency following 4 weeks of use in guinea pigs or 6 months of treatment in pagetic patients.
Toxicological findings from long-term studies are attributable to the pharmacological action of salmon calcitonin. Salmon calcitonin is devoid of embryotoxic, teratogenic and mutagenic potential. Toxicity and carcinogenicity studies in rats have shown that salmon calcitonin increases the incidence of pituitary tumours. Further preclinical studies, particularly a mouse carcinogenicity study in which the maximum exposure was more than 7,000 times greater than that in humans following a dose of 200 IU, suggest that this elevated incidence of pituitary tumours is species-specific to rats and not clinically relevant.
In vivo preclinical safety data do not indicate any association of salmon calcitonin treatment with malignancies and do not provide any evidence for tumour progression.

Other information

Shelf life
Do not use after the expiry date (= EXP) printed on the pack.
Opened spray bottles: Store upright at room temperature (15-25°C) and use within a maximum of 4 weeks.

Special precautions for storage
Unopened spray bottles: Store at 2-8°C (in a refrigerator). Do not freeze.
Keep out of the reach of children.

Instructions for use and handling
The pump must be primed before using the nasal spray for the first time: Remove the protective cap. Holding the bottle in an upright position, press down the upper part until it clicks. Repeat twice. The dose-counter window shows white and red lines the first time, white ones the second time, and green ones the third time. If the nozzle becomes blocked, try to expel the blockage by pressing down firmly on the pump. Do not use sharp objects that may damage the pump mechanism.

Pack sizes

Country specific pack sizes.

Manufacturer

See folding box.

Information last revised

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® = registered trademark

Novartis Pharma AG, Basle, Switzerland

This is a medicament

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists