NOVARTIS

Drug Regulatory Affairs

MIACALCIC® NASAL SPRAY

(synthetic salmon calcitonin)

50 IU, 100 IU and 200 IU nasal spray solution

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

MIACALCIC® NASAL SPRAY 50 IU

MIACALCIC® NASAL SPRAY 100 IU

MIACALCIC® NASAL SPRAY 200 IU

2 Qualitative and quantitative composition

The active substance is synthetic salmon calcitonin (INN name Calcitonin).

One metered dose delivers 50 IU, 100 IU or 200 IU of synthetic salmon calcitonin.

One International Unit (= IU) corresponds to about 0.2 micrograms of synthetic salmon calcitonin.

For excipients see section 6.1 List of excipients.

3 Pharmaceutical form

Nasal Spray solution in bottles fitted with a metering pump delivering at least 14 doses of 50 IU, 100 IU or 200 IU salmon calcitonin per actuation.

4 Clinical particulars

4.1 Therapeutic indications

Miacalcic Nasal Spray is indicated for:

Treatment of postmenopausal osteoporosis

Bone pain associated with osteolysis and/or osteopenia

Paget's disease of bone (osteitis deformans)

Neurodystrophic disorders (synonymous with algodystrophy or Sudeck's disease)

Neurodystrophic disorders caused by various aetiological and predisposing factors such as post-traumatic painful osteoporosis, reflex dystrophy, shoulder-arm syndrome, causalgia, drug-induced neurotrophic disorders.

4.2 Posology and method of administration

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

Osteoporosis

The recommended dosage of Miacalcic Nasal Spray for treatment of osteoporosis is 200 IU per day.

It is recommended that use of Miacalcic Nasal Spray be accompanied by adequate calcium and vitamin D intake to prevent progressive loss of bone mass.

For the treatment of postmenopausal osteoporosis Miacalcic is to be administered on a long-term basis (see section 5.1 Pharmacodynamic properties).

Bone pain associated with osteolysis and/or osteopenia

In bone pain associated with osteolysis and/or osteopenia the recommended dose is 200-400 IU daily. Up to 200 IU may be administered as a single dose; in cases where a higher dosage is required, it should be given in divided doses.

Dosage should be adjusted to the individual patient's needs.

It may take several days of treatment until the analgesic effect is fully developed. For continuing therapy, the initial daily dosage can usually be reduced and/or the interval between administrations prolonged.

Paget's disease

In Paget's disease the recommended dose is 200 IU daily in a single dose or in divided doses. In some cases 400 IU in divided doses may be necessary at the beginning of therapy.

Treatment should be continued for at least 3 months, or longer if required. Dosage should be adjusted to the individual patient's needs.

In Paget's disease, treatment with Miacalcic should be given for periods ranging from at least several months to a few years. Treatment with Miacalcic markedly reduces serum alkaline phosphatase and urinary hydroxyproline excretion, often to normal levels. However, in rare cases, alkaline phosphatase and hydroxyproline excretion levels may rise after an initial fall; the physician must then judge from the clinical picture whether treatment should be discontinued and when it may be resumed.

Disorders of bone metabolism may recur one or several months after treatment has been discontinued, necessitating a new course of Miacalcic therapy.

Neurodystrophic disorders

Early diagnosis of neurodystrophic disorders is essential and treatment should start as soon as the diagnosis is confirmed.

The recommended dose is 200 IU daily in a single dose over a period of 2 to 4 weeks. An additional 200 IU may be administered every second day for up to 6 weeks depending on clinical progress.

Long-term therapy

Antibodies to calcitonins may develop in patients under long-term therapy; clinical efficacy is usually not affected, however. Escape phenomena, which occur in particular in patients with Paget's disease receiving long-term therapy, may be due to saturation of the binding sites and are apparently not related to the development of antibodies. Following interruption of treatment, the therapeutic response to Miacalcic is restored.

Use in children

There is limited experience with the use of Miacalcic Nasal Spray in children, therefore no recommendations can be given for this patient population.

Use in elderly patients / special patient populations

Extensive experience with the use of Miacalcic Nasal Spray in the elderly has shown no evidence of reduced tolerance or altered dosage requirements. The same applies to patients with altered renal or hepatic function, although no formal studies have been carried out in this specific patient population.

4.3 Contraindications

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see section 4.4 special warnings and precautions for use, 4.8. Undesirable effects and 6.1 List of excipients).

4.4 Special warnings and precautions for use

Because salmon calcitonin is a peptide, the possibility of systemic allergic reactions exists and allergic-type reactions including single cases of anaphylactic shock have been reported in patients receiving Miacalcic Nasal Spray. Skin testing with diluted sterile solution from Miacalcic Ampoules should be considered prior to treatment with Miacalcic in patients with suspected sensitivity to salmon calcitonin.

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 Pregnancy and lactation

Pregnancy

Since no studies have been carried out in pregnant women, Miacalcic should not be administered to such patients. Animal studies have, however, shown that Miacalcic is devoid of embryotoxic and teratogenic potential. It appears that salmon calcitonin does not cross the placental barrier in animals.

Lactation

Since no studies have been carried out in nursing mothers and it is not known whether salmon calcitonin is excreted into human milk, breast-feeding during treatment is not recommended.

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 reactions. Patients must therefore be warned that these effects may occur, in which case they should not drive or use machines

4.8 Undesirable effects

Local adverse events are generally mild (in about 80% of reports) and require discontinuation of the treatment in less than 5% of cases.

Adverse reactions (Table 1) are ranked under heading of frequency , the most frequent first, 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), including isolated reports.

Table 1

Immune system disorders		
	Rare:	Hypersensitivity.
	Very rare:	Anaphylacticand anaphylactoid reactions, anaphylactic shock.
Nervous system disorders		
	Common:	Headache, dizziness, dysgeusia.
Eye disorders		
	Uncommon:	Visual disturbance.
Vascular disorders		
	Common:	Flushing.
	Uncommon:	Hypertension.
Respiratory, thoracic and mediastinal 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, rhinitis ulcerative, pharyngitis.
	Uncommon:	Cough.
Gastrointestinal disorders		
	Common:	Nausea, diarrhoea, abdominal pain.
	Uncommon:	Vomiting.
Skin and subcutaneous tissue disorders		
	Rare:	Rash generalised.
Musculoskeletal and connective tissue disorders		
	Common:	Arthralgia.
	Uncommon:	Musculoskeletal pain.
General disorders and administration site conditions		
	Common:	Fatigue.
	Uncommon:	Influenza like symptoms, oedema (facial, extremities and generalised).
	Rare:	Pruritis.

4.9 Overdose

Nausea, vomiting, flushing and dizziness are known to be dose dependent when Miacalcic is administered parenterally. Such events 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 1600 IU as a single dose and up to 800 IU per day for three days without causing any serious adverse event. Isolated cases of overdose have been reported. Treatment would be symptomatic.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Regulator of calcium homeostasis (ATC code H05B A01).

All calcitonin structures consist of 32 amino acids in a single chain with a ring of seven amino-acid residues 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.

By inhibiting osteoclast activity via its specific receptors, salmon calcitonin markedly reduces bone turnover to a normal level in conditions with an increased rate of bone resorption such as osteoporosis. Salmon calcitonin has also been shown both in animal models and in humans to have analgesic activity, probably primarily via a direct effect on the central nervous system.

Miacalcic Nasal Spray 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 re-uptake) and a decrease in the urinary excretion of hydroxyproline. Long-term administration of Miacalcic Nasal Spray (up to 5 years of treatment) significantly suppresses biochemical markers of bone turnover such as serum C-telopeptides (sCTX) and skeletal isoenzymes of alkaline phosphatase.

Miacalcic Nasal Spray results in a statistically significant 1.0-2.0 % 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.

Administration of 200 IU/day Miacalcic Nasal Spray results in a statistically and clinically significant 36% decrease in the risk of developing new vertebral fractures relative to treatment with vitamin D and calcium alone ("placebo"). Additionally, the incidence of multiple new vertebral fractures is reduced by 35%, also compared to "placebo".

Calcitonin reduces gastric and exocrine secretion pancreatic secretion.

5.2 Pharmacokinetic properties

The bioavailability of Miacalcic Nasal Spray relative to parenteral administration is between 3 and 5%. Miacalcic 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, Miacalcic activity should be evaluated by using clinical parameters of efficacy.

5.3 Preclinical safety data

Conventional long-term toxicity, reproduction, mutagenicity and carcinogenicity studies have been performed in laboratory animals.

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 daily by intranasal administration for 4 weeks did not reveal any relevant abnormal findings in the nasal cavity and upper respiratory tract. Miacalcic Nasal Spray with 0.01% benzalkonium chloride did not change the nasal ciliary beat frequency of guinea-pigs or of Pagetic patients over 4 weeks and 6 months of treatment, respectively.

Minor effects in toxicity studies are attributable to the pharmacological action of salmon calcitonin. Salmon calcitonin is devoid of embryotoxic, teratogenic and mutagenic potential. Toxicity and carcinogenicity studies have shown that salmon calcitonin increases the

incidence of pituitary tumours in rats at exposures lower than those likely from clinical use. However, further preclinical studies, particularly a mouse carcinogenicity study, in which the maximum exposure was more than 7000 times greater than that in humans following a dose of 200 IU, suggested that pituitary tumour induction is specific to the rat.

Clinical data including for patients treated for up to 24 months in a study with matched controls, failed to show any pituitary-related changes. In addition, calcitonin receptors in the human pituitary have been shown to be very few in number or even to be completely absent.

Furthermore, there have been no reports of adverse events relating to pituitary tumours in patients.

There is therefore enough evidence to conclude that pituitary tumour induction is a rat-specific event and that rat pituitary tumours have no relevance for the clinical use of Miacalcic.

6 Pharmaceutical particulars

6.1 List of excipients

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

6.2 Incompatibilities

None.

6.3 Shelf life

3 years, if unopened.

6.4 Special precautions for storage

Miacalcic Nasal Spray bottles must be stored at 2-8°C. Do not freeze.

Once opened (see section 6.6 Instructions for use and handling), they must be kept at room temperature (not above 25°C) and used within a maximum of 4 weeks.

Keep the bottle upright at all times to reduce the risk of air bubbles entering the dip tube.

Miacalcic Nasal Spray should be kept out of the reach and sight of children.

6.5 Nature and content of container

The device consists of a clear, uncoloured glass bottle (glass type I) and a spray mechanism with an integrated, automatic dose-counting mechanism and a built-in mechanical stop. The pack contains one bottle with 2 mL of nasal spray solution, fitted with a metering pump delivering at least 14 doses of 50 IU, 100 IU or 200 IU.

6.6 Instructions for use and handling

The instructions for use and handling of the Miacalcic Nasal Spray included in the Basic Patient Leaflet must be read carefully before the spray is used for the first time.

The pump must be primed before first use: Pull up the protective cap, holding the bottle in an upright position, press down the upper part until it clicks. Repeat 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.