Miacalcic® Nasal Spray

Regulator of calcium homeostasis

DESCRIPTION AND COMPOSITION

Active substance

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.

Active moiety

Salmon calcitonin

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.

Certain dosage strengths may not be available in all countries.

INDICATIONS

Miacalcic Nasal Spray is indicated for the treatment of:

Bone pain associated with osteolysis and/or osteopenia

Paget's disease of bone (osteitis deformans) only in patients who do not respond to alternative treatments or for whom such treatments are not suitable

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

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

DOSAGE AND ADMINISTRATION

Dosage

Adults

All indications

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

Due to the association between occurrence of malignancies and long term calcitonin use (see section WARNINGS AND PRECAUTIONS), the treatment duration in all indications should be limited to the shortest period of time possible and using the lowest effective dose.

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.

Dosage should 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 the association of the 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.

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. Subsequently, 200 IU may be administered every second day for up to 6 weeks depending on clinical progress.

Development of antibodies

Antibodies to calcitonins may develop in patients under long-term therapy; however clinical efficacy is usually not affected. 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.

Special populations

Renal impairment

There is no evidence of reduced tolerance or altered dosage requirements of Miacalcic Nasal Spray in patients with renal impairment; although no formal studies have been carried out in this specific patient population.

Hepatic impairment

There is no evidence of reduced tolerance or altered dosage requirements of Miacalcic Nasal Spray in patients with hepatic impairment; although no formal studies have been carried out in this specific patient population.

Paediatric patients (below 18 years of age)There is limited experience with the use of Miacalcic Nasal Spray in children, therefore no recommendations can be given for this patient population.

Geriatric patients (65 years of age and above)

Extensive experience with the use of Miacalcic Nasal Spray in the elderly has shown no evidence of reduced tolerance or altered dosage requirements.

CONTRAINDICATIONS

Known hypersensitivity to synthetic salmon calcitonin or to any of the excipients (see section WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS and DESCRIPTION AND COMPOSITION -EXCIPIENTS).

WARNINGS AND PRECAUTIONS

Allergic reactions

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.

Risk of Malignancy

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 section ADVERSE DRUG REACTIONS). These meta-analyses demonstrated an increase in the absolute rate of occurrence of malignancies for patients treated with calcitonin compared to placebo which varied between 0.7% and 2.36%. Numerical imbalances between calcitonin and placebo were observed after 6 to 12 months of therapy. A mechanism for this observation has not been identified. Patients in these trials were treated with oral or intra-nasal formulations. The benefits for the individual patient should be carefully evaluated against possible risks (see section ADVERSE DRUG REACTIONS).

INTERACTIONS

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

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY

Women of childbearing potential

There are no data to support special recommendations for women of child-bearing potential.

Pregnancy

Since there is insufficient documented experience with Miacalcic Nasal Spray 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.

Breast-feeding

Since there is insufficient documented experience with Miacalcic in nursing mothers and it is not known whether salmon calcitonin is excreted into human milk, breast-feeding during treatment is not recommended.

Fertility

There are no data regarding a potential influence of Miacalcic on human fertility.

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 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.

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

Tabulated summary of adverse drug reactions

Adverse drug reactions from multiple sources including clinical trials and post-marketing experience (Table 1) 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. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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 (frequency cannot be estimated from the available data).

Table 1 Adverse drug reactions reported from multiple sources including clinical trials and post-marketing experience

Immune system disorders	
Rare:	Hypersensitivity.
Very rare:	Anaphylactic and anaphylactoid reactions, anaphylactic shock.
Metabolism and nutrition disorders	
Not known:	Hypocalcaemia.
Nervous system disorders	
Common:	Headache, dizziness, dysgeusia.
Not known:	Tremor
Eye disorders	
Uncommon:	Visual impairment.
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 illness, oedema (facial, extremities and generalised).
Rare:	Pruritus.

Description of selected adverse drug reactions

Malignancies

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 patients treated with placebo. A mechanism for this observation has not been identified (see section WARNINGS AND PRECAUTIONS).

OVERDOSAGE

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.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA) / PHARMACODYNAMICS (PD)

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 exocrinepancreatic secretion.

PHARMACOKINETICS (PK)

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.

CLINICAL STUDIES

Not applicable.

NON-CLINICAL 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 tumors 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 7,000 times greater than that in humans following a dose of 200 IU, suggested that pituitary tumor 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 tumors in patients.

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

EXCIPIENTS

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

INCOMPATIBILITIES

None.

STORAGE

See also folding box.

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

Once opened (see section 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 not be used after the date marked "EXP" on the pack.

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

INSTRUCTIONS FOR USE AND HANDLING

The instructions for use and handling of the Miacalcic Nasal Spray included in the section INFORMATION FOR PATIENTS 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.

INFORMATION FOR PATIENTS

When and how to use Miacalcic Nasal Spray

This medicine is for administration into the nostrils only. You should switch between each nostril every time you use Miacalcic Nasal Spray.

Your pharmacist has stored Miacalcic Nasal Spray in a refrigerator. Before you start using it, you should let the spray reach room temperature.

Instructions for use/handling of Miacalcic Nasal Spray

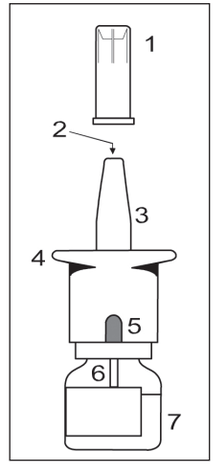
Please read the instructions carefully so that you know how to use your nasal spray.

These instructions tell you about:

- The different parts of the nasal spray
- How to prepare a new nasal spray for use
- Using the nasal spray
- If the spray mechanism should become blocked, this may be resolved by pressing down firmly on the pump; do not attempt to unblock it by using a sharp pointed object as this may cause damage.

  If you think your nasal spray is not working properly, take it back to your pharmacist. **Never** try to fix the nasal spray yourself or take it apart, as this may affect your dose.
- Always follow your doctor's instructions regarding dosage carefully.
- Keep this leaflet in a safe place so that you can read it again.

The different parts of your nasal spray

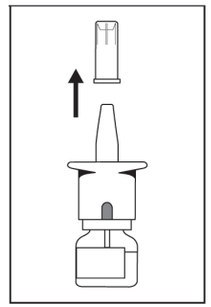


1. **Protective cap:** Keeps the nozzle clean and protects the jet. Always replace the protective cap after you have used the nasal spray.
2. **Jet:** The tiny hole from which the solution sprays out.
3. **Nozzle:** The part you insert into your nostril.
4. **Pump:** The part you press down to operate the spray.
5. **Counter:** The dose counter window on a new nasal spray shows , as shown in this picture. The display will change as you use the pump (see below).
6. **Dip tube:** The tube inside the spray bottle that draws up the solution when you press the pump.
7. **Bottle:** Contains enough solution for at least 14 doses.

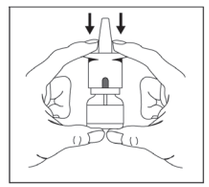
Preparing a new nasal spray bottle for use

NEVER shake the nasal spray bottle as this could cause air bubbles, which may affect your dose.

The dose counter window of a new nasal spray bottle is in the position marked as shown in the picture



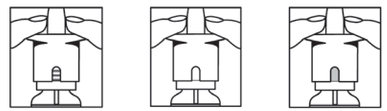
- First, remove the protective cap.



- Hold the nasal spray upright in one or two hands and press down firmly on the pump **3 times**.

This primes the new spray by clearing air out of the dip tube. You will only need to do this once when you start a **new** spray.

Do not worry if a little solution sprays out; this is normal.



- As you press the pump, watch the changes in the dose counter window. to to to
- When green is showing in the dose counter window, your new nasal spray is ready to use.
- Follow the instructions for 'Using your nasal spray'.

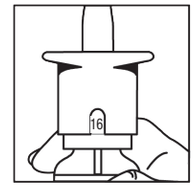
Using your nasal spray

- With the protective cap removed, bend your head forward slightly and insert the nozzle into one of your nostrils. Try to hold the nasal spray upright, as shown in the picture.
- Press the pump firmly **once only**.
- Remove the nasal spray from your nose and breathe in deeply through your nostril to help keep the solution in your nose.
- If your doctor has told you to take two puffs at a time, repeat this procedure in your other nostril.
- After use, clean the nozzle with a dry tissue and replace the protective cap.

Checking the counter:

Every time you use the nasal spray the number in the dose counter window will change. The number displayed tells you how many puffs you have already taken. The Nasal Spray is guaranteed to deliver 14 metered doses. You may be able to obtain 2 extra doses.

When the dose counter window shows a red 16 as shown in this picture, 16 puffs have been used and the nasal spray is finished. You may notice that a little liquid is left in the nasal spray bottle, but this is normal.



If you are not sure how to use your spray bottle, ask your doctor or pharmacist.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May 2018.SIN

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