

Miacalcic

Nasal Spray 200 i.u.

Composition:

Active component	Nasal Spray bottle (at least 14 metered doses)
Synthetic Salmon Calcitonin	200 IU/dose

Properties

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.

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 significantly suppress biochemical markers of bone turnover such as **pyridinoline-crosslinks** and skeletal isoenzymes of alkaline phosphatase.

Pharmacokinetic properties

The bioavailability of Miacalcic Nasal Spray relative to parenteral administration is between 2 and 15%. 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.

Preclinical Safety Data

Conventional long-term toxicity, reproduction, mutagenicity and carcinogenicity studies have been performed in laboratory animals. In addition, nasal tolerance was investigated.

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.

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% 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. Reproduction studies have shown that 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.**

Indications

Postmenopausal Osteoporosis

Miacalcic Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years post menopause with low bone mass relative to healthy pre menopausal females.

Miacalcic Nasal Spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.

Use of Miacalcic Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 IU per day) intake to retard the progressive loss of bone mass.

The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo controlled trials were conducted in 325 postmenopausal females (227 Miacalcic Nasal Spray treated and 98 placebo treated) with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal females. These studies conducted over two years demonstrated that 200 I.U. daily of Miacalcic Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Miacalcic Nasal Spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as six months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of Miacalcic Nasal Spray on cortical bone of forearm or hip were demonstrated.

However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after one year treatment changing to a trend at 2 years that was no longer statistically significant.”

Dosage and administration

Osteoporosis

The recommended dosage of Miacalcic Nasal Spray **in postmenopausal osteoporotic females is one spray (200 IU) per day administered intranasally, alternating dosing daily.**

Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of Miacalcic Nasal Spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to Miacalcic Nasal Spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, Miacalcic Nasal Spray should not be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostrils with the head in the upright position and the pump firmly depressed toward the bottle. The pump should not be primed before each daily dose.

Contraindications

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

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.

Patients with chronic rhinitis should be kept under regular medical surveillance since the absorption of the drug from the inflamed nasal mucosa may be increased.

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

Interaction with other medicinal product 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.

Pregnancy and Lactation

Salmon calcitonin has been shown to cause a decrease in fetal birth weight in rabbits when given in doses of 14 to 56 times the parenteral doses recommended for human use.

Since calcitonin does not cross the placental barrier, this findings may be due to metabolic effects on the pregnant animal. Studies have not been carried out in pregnant women, hence Miacalcic Nasal Spray should not be administered to pregnant women.

Calcitonin has been shown to inhibit lactation animals. It is not known whether this drug is excreted in human breast milk, therefore Miacalcic Nasal Spray should not be administered to

nursing mothers.

Effect on the Ability to Drive and Use Machines

No studies exists on the effect 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.

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 (Table 1) are ranked under heading of frequency estimates, the most frequent first, using the following convention: very common ($\geq 1/10\%$); common ($\geq 1/100, \%$ to $< 1/10\%$); uncommon ($\geq 1/1,000$, 0.1% and $< 1/100\%$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Immune system disorders	
Rare:	Hypersensitivity.
Very rare:	<u>Anaphylactic and anaphylactoid reactions, anaphylactic shock.</u>
Nervous system disorders	
Common:	Dizziness, <u>headache, dysgeusia.</u>
Eye disorders	
Uncommon:	<u>Visual disturbance.</u>
Vascular disorders	
Common:	Flushing.
Uncommon:	<u>Hypertension.</u>
Respiratory, thoracic and mediastinal disorders	
Very common	<u>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).</u>
Common	Epitaxis, sinusitis, <u>rhinitis ulcerative, pharyngitis</u>
Uncommon	<u>Cough</u>
Gastrointestinal disorders	
Common:	Nausea, <u>diarrhoea, abdominal pain.</u>
Uncommon:	Vomiting.
Skin and subcutaneous tissue disorders	
Rare:	<u>Rash generalised.</u>
Musculoskeletal and connective tissue disorders	
Common:	<u>Arthralgia.</u>
Uncommon:	<u>Musculoskeletal pain.</u>
Renal and urinary disorders	

Table 1

Uncommon:	Polyuria, chills
<u>General disorders and administration site conditions</u>	
<u>Common:</u>	<u>Fatigue.</u>
<u>Uncommon:</u>	<u>Influenza-like symptoms,</u>
	<u>oedema (facial, peripheral</u>
	<u>and generalised).</u>
<u>Rare:</u>	<u>Pruritus.</u>

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.

Storage Conditions

Before using Miacalcic Nasal Spray for the first time, store in refrigerator between 2 and 8° C. do not freeze.

After priming Miacalcic Nasal Spray (see Instruction for use/handling) use within 4 weeks, store below 25° C, but do not store in refrigerator. To ensure correct delivery, the bottle should be kept in an upright position.

Shelf Life: 3 years if unopened.

HARUS DENGAN RESEP DOKTER

Package and Registration Number

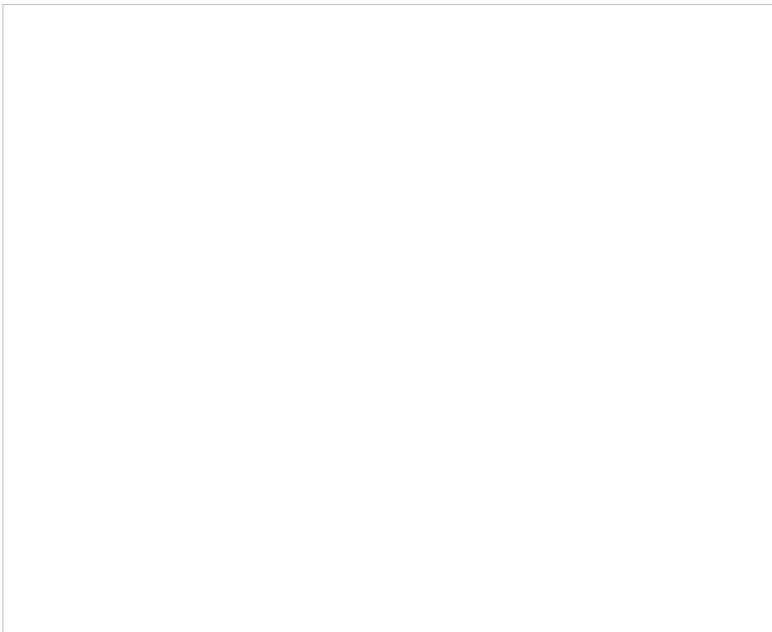
Miacalcic Nasal Spray, bottle of at least 14 metered doses of 200 IU/doses Reg No. DK10169900156A1

Available as a metered dose solution in 2 ml fill glass bottles.

Manufactured by Novartis Pharma S.A.S, Huningue, France for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia

INSTRUCTION FOR USE/HANDLING



1. Remove the protective cap
2. First time of use only: holding the device as shown, depress the plunger sharply until it clicks, then release. Do this three times. The window at the bottom of the actuator will now show green and the spray is ready for use.
3. Bend your head slightly forward and insert the applicator nozzle into one of your nostrils. Make sure it is in a straight line with the nasal passage to allow the spray mist to spread more evenly. Depress the plunger once and release (see drawing). In the counter window you will now see the number 1.
4. After taking a dose, sniff vigorously several times to prevent the solution from running out of your nose. Do not blow your nose immediately after taking a dose.
5. If your doctor has told you to take two puffs of Miacalcic at a time, repeat the application in the other nostril.
6. Always replace the protective cap to prevent the jet from becoming blocked.
7. When a red marker appears in the counter window and there is noticeable resistance to further movement of the plunger (warning stop), 16 doses have been delivered. A small remainder (technical overfill) remains in the bottle.
8. Under no circumstances attempt to enlarge the jet with a needle or sharp object. This will destroy the function completely. Do not dismantle the pump. If in doubt, consult your supplier. To ensure even dosage, store or carry the bottle in an upright position. Avoid shaking and extremes of temperature.
9. Once opened the nasal spray bottle must be kept at room temperature and used for a maximum of 4 weeks.