℞ For the use of a Registered Medical Practitioner or a Hospital only

Calcitonin (Salmon) Nasal Solution USP

AMERICAN Calcican Nasal Spray

Composition: Each actuation delivers:

Calcitonin (Salmon) IP (Synthetic Origin)	200 IU
Each ml contains:	
Calcitonin (Salmon) IP (Synthetic Origin)	2200 IU
Preservative:	
Benzalkonium Chloride IP	0.01% w/v
Phenyl Ethyl Alcohol IP	0.2% w/v
Aqueous base	q.s.

Therapeutic Indication

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

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. It is recommended to administer **Calcican** 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 pediatric osteoporosis. Use of salmon calcitonin in children 0 to 18 years is therefore not recommended.

Contraindication

Calcitonin is also contraindicated in patients with hypocalcaemia.

Special warning and precaution for use

Nasal examinations are to be performed before treatment beings and in the case of nasal complains, medication should not be started. If severe ulceration of the case of nasal mucosa occurs (e.g. penetration below the mucosa), internasal 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 sustemic 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.

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.

Pregnancy and lactation

NA

Effect on ability to drive and use machine

No effect

Undesirable effects

Dizziness, Headache, Cough, Nasal oedema, Nasal congestion, Sneezing, Allergic, Nausea, Diarrhoea
Abdominal pain, Vomiting, Flushing

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.

Pharmaceutical properties

Pharmacodynamic Properties

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 mineralization 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.

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%.

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 **Calcican** Nasal Spray (containing 0.01% w/v benzalkonium chloride).

However, daily intranasal administration for 26 weeks of a placebo containing 0.01% w/v benzalkonium chloride or of high doses of a calcitonin formulation containing 0.01% w/v benzalkonium chloride was well tolerated by monkeys.

No treatment related changes to the respiratory tract were observed. Dogs receiving salmon calcitonin with 0.01% w/v benzalkomium chloride did not reveal any relevant abnormal findings in the nasal cavity and upper respiratory tract.

Calcican Nasal Spray with 0.01% w/v benzalkonium chloride did not change the nasal ciliary beat frequency of guinea pigs and of Pagetic patients over 4 weeks and 6 months respectively.

Packaging Information: Calcitonin Salmon Nasal Solution USP is available as 3.7 ml fill in 10 ml amber bottle with pump and actuator. It delivers 30 metered doses.

Storage: Protect from light & moisture. Store unopened bottle in refrigerator at a temperature between 2°C to 8°C. Do not freeze.

Once opened the bottle it may be stored at room temperature below 25°C in an upright position for upto 9 weeks.

Keep out of reach of children.

Directions for use:



1. Remove the protective dust cap. Hold the bottle in upright position with your forefinger & middle finger on each side of the nozzle & your thumb underneath the base of the bottle as shown.



2. If using for the first time, test the spray with the nozzle pointing away from you, press down three times as shown until a fine mist comes out of the nozzle.



3. Bend your head forward slightly and insert the nozzle into one of your nostril. Try to hold the nasal spray upright. Press the pump firmly once only.



4. Remove the nasal solution from your nostril & breath in deeply through your nose to help keep the medicine in your nose. Repeat steps 3 & 4 in alternate nostril daily.

Cleaning of nozzle



Wipe the nozzle with a clean handkerchief / tissue and re-place the protective dust cap.

Nozzle spray should be cleaned at least once a week.



Pull the nozzle upwards to detach from the bottle.



Wash the nozzle & the dust cap in warm water.



Shake off all excess water and allow the nozzle & cap to attain room temperature before refitting into the bottle.

Note:
IF YOUR NOZZLE BECOMES BLOCKED, DO THE ABOVE PROCEDURE AS SHOWN, DO NOT USE PIN OR SHARP OBJECT TO UNBLOCK THE NOZZLE.

DO NOT USE AFTER 30 DOSES EVEN IF BOTTLE IS NOT COMPLETELY EMPTY, AS IT MAY NOT DELIVER CORRECT AMOUNT

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