SALCATONIN™ 200 NSS
(Calcitonin salmon)
Nasal Spray Solution (NSS)
200 I.U. /dose
SALCATONIN™
(Calcitonin salmon)
Nasal Spray Solution (NSS) 200 I.U./dose
If a patient has been diagnosed with osteoporosis and

- likes the ease of a nasal spray to treat osteoporosis?
- suffers from heartburn or stomach pain
- has difficulty swallowing?
- takes multiple medications?
- starts the day with breakfast, juice, coffee or tea?
- has difficulty sitting upright?
- wants a medicine with a convenient dosing schedule?

Why SALCATONIN 200 NSS?

Effective way

A nasal spray is an effective way to treat osteoporosis especially for patients who have problems using other types of medications. SALCATONIN 200 NSS is a prescription medication recommended for the treatment of postmenopausal osteoporosis in women. The medicine from a nasal spray enters the bloodstream rapidly. The tiny blood vessels lining the nasal passages quickly absorb the fine mist of medication that it sprayed in the nostril, where it works to stop bone loss and helps bones become stronger.
It’s easy to use

**SALCATONIN 200 NSS** is an easy-to-use type of medicine that accommodates active lifestyles. It can be used before, during, and after meals, and with multiple medications.
A very fine mist of medication is sprayed into the nostril.
Just one spray, once a day in alternate nostrils.

It’s convenient

The medicine from a nasal spray does not enter the stomach.
Therefore, **SALCATONIN 200 NSS** is unlikely to cause unpleasant side effects such as discomfort of the stomach or oesophagus, or other problems in the digestive system such as upset stomach or other digestive complaints.
Other medications that have to be swallowed, such as tablets and pills, must first be absorbed by the digestive system.
Using **SALCATONIN 200 NSS** is easy and convenient because it can be used before, during, and after meals, and with other medications.
There’s no need to wait for long periods before eating, drinking, or taking other medications.
Other treatments may have limits on when a patient can eat, drink, and take other medications. These strict rules may be difficult for some people to follow.

It’s safe and well-tolerated

**SALCATONIN 200 NSS** is an appropriate choice for many patients:

- refusing or not tolerating estrogens or are contraindicated [1]
Salcatonin 200 NSS is not an estrogen hormonal medication
Salcatonin 200 NSS does not show any estrogenic activity

- with GI or drug-induced problems [2]
Salcatonin 200 NSS bypasses the digestive system
Salcatonin 200 NSS has no serious drug-related GI or oesophageal side effects

- taking multiple medications [3]
Salcatonin 200 NSS can be used safely in patients taking GI and other
drugs (eg, aspirin, ibuprofen, NSAIDs)
Salcatonin 200 NSS can be administered concomitantly with calcium
and vitamin D dietary supplements or drugs

in long-term care facilities (who are unable to follow
complicated daily or weekly dosing instructions)
Salcatonin 200 NSS has no restrictions on time of administration,
food intake, or other medications
Salcatonin 200 NSS is administered with just one spray, once a day

with limited mobility or renal impairment
Salcatonin 200 NSS has no requirements for remaining upright
Salcatonin 200 NSS has no drug-related venous thromboembolic
events

**It’s an adjuvant**

**SALCATONIN 200 NSS** is a suitable adjuvant for drug-induced
osteoporosis of concomitant to other health conditions:

- glucocorticoids induced osteoporosis [3][4]
- antiepileptic drugs-induced bone loss [3][5]
- increased risk of vertebral fractures in patients with
  Intestinal Inflammatory Disease [6]
- increased risk of vertebral fractures in patients with Crohns
  Disease, Ulcerative Colitis and Celiac Syndrome [6]
- premenopausal women with depression-induced bone loss [7]
- female anorexia-induced osteoporosis [8]
**Composition characteristics and advantages**

**Trometamol (THAM): physiological absorption enhancer**
* it’s the absorption enhancer which physiologically depolarizes the cell membrane thus enhancing the peptide absorption through the tiny blood vessels lining the nasal mucosa, which promptly resumes its original biological balance
* biological buffer, alkalizer, very soluble in water

**Meglumine: stabilizing and buffering agent**
* amino-glucitol which ameliorate the buffering properties of the solution to yield a pH range to optimally stabilize the dissolved calcitonin salmon

**Citric acid: stabilizing and buffering agent**
* buffering agent, antioxidant deprived of allergenic properties, suitably formulated to yield a pH range to optimally stabilize calcitonin in aqueous solution
* naturally found in the body, mainly in the bones, is a widely used buffer in pharmaceutical formulations

**pH range**
* the harmonic balance of the above physiological buffers yields a pH range comprised between 3.6 and 4.2, which is the optimal pH range to stabilize and preserve calcitonin solution

**Preserving efficacy**
* methyl parahydroxybenzoate and propyl parahydroxybenzoate are admixed in such a proportion to achieve the desired preserving efficacy required for a multidose nasal solution
* broad spectrum antimicrobial preservatives, exhibiting their activity at a pH range from 4.0 to 7.0
Salcatonin ™
(Calcitonin salmon)
Nasal Spray Solution (NSS) 200 I.U./dose
(Concentration 2200 I.U./ml)

Summary of Product Characteristics (SPC) as approved by CPMP/EMEA for Calcitonin products (November 2002).

1. NAME OF THE MEDICINAL PRODUCT
Salcatonin 200 I.U. Nasal Spray, Solution (SALCATONIN 200 NSS)

PHARMACEUTICAL FORM AND CONTENTS
- Nasal Spray bottle (200 I.U./dose) 14 doses
- Nasal Spray bottle (200 I.U./dose) 28 doses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml solution containing : Calcitonin salmon (Salcatonin) 2200 I.U.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM
Nasal Spray, Solution

4. CLINICAL PARTICULARS

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

4.2 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 (see point 5.1, Pharmacodynamic properties).
[FDA/USA Approved indication: SALCATONIN 200 NSS is indicated for the treatment of osteoporosis in women more than 5 years after menopause with low bone mass. SALCATONIN 200 NSS should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated.]
**Use in elderly patients, in hepatic impairment and in renal insufficiency**

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**

As intranasal calcitonin is indicated for post-menopausal women, its use in children is not appropriate.

**Note**

Full instructions for use by the patient are given in the package leaflet.

### 4.3 Contra-indications

Hypersensitivity to calcitonin (see section 4.8 Undesirable effects) or to any of the excipients of the formulation (see section 6.1 List of excipients).

Calcitonin is also contra-indicated in patients with hypocalcaemia.

### 4.4 Special warnings and special precautions for use

Nasal examination is to be performed before treatment begins and in the case of nasal complaints, medication should not be started. If severe ulceration of the nasal mucosa occurs (e.g. penetration below the mucosa or association with heavy bleeding), intranasal 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 systemic 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

No drug interactions with intranasal salmon calcitonin have been reported.

### 4.6 Pregnancy and lactation

As intranasal calcitonin is indicated for postmenopausal women, no studies have been carried out in pregnant women or nursing mothers. Therefore, intranasal calcitonin is not to be administered to such patients. However, animal studies have shown no embryotoxic and teratogenic potential. It appears that salmon calcitonin does not cross the placental barrier in animals.

It is not known whether salmon calcitonin is excreted into human breast milk. In animals, salmon calcitonin has been shown to decrease lactation and to be excreted in milk.

### 4.7 Effects on ability to drive and use machines

No data exist on the effects of intranasal calcitonin on the ability to drive and use machines. Intranasal calcitonin may cause transient dizziness (see section 4.8 Undesirable effects) which may impair the reaction of the patient. Patients must therefore be warned that transient dizziness may occur, in which case they are not to drive or use machines.

### 4.8 Undesirable effects

Frequency estimates:
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.

**Gastrointestinal disorders**
Common: nausea, diarrhoea, abdominal pain
Uncommon: vomiting

**Vascular disorders**
Common: flushing
Uncommon: hypertension

**Respiratory disorders**
Very common: rhinitis (including dry nose, nasal oedema, nasal congestion, sneezing, allergic rhinitis), unspecified symptoms of the nose (e.g. nasal passage irritation, rash papular, parosmia, erythema, abrasion)
Common: rhinitis ulcerative, sinusitis, epistaxis, pharyngitis
Uncommon: cough
These events are generally mild (in about 80% of reports) and require discontinuation of the treatment in less than 5% of cases.

**Nervous system disorders**
Common: dizziness, headache, dysgeusia,

**Sense organ disorders**
Uncommon: vision disturbance

**Skin and subcutaneous tissue disorders**
Uncommon: oedema (face oedema, oedema peripheral and ansarca)

**Musculoskeletal disorders**
Common: musculoskeletal pain
Uncommon: arthralgia

**Immune system disorders**
Uncommon: hypersensitivity reactions such as generalised skin reactions, flushing, oedema (face oedema, oedema peripheral and ansarca), hypertension, arthralgia and pruritus
Very rare: allergic and anaphylactoid-like reactions such as tachycardia, hypotension, circulatory collapse and anaphylactic shock

**Investigations**
Rare: development of neutralising antibodies to calcitonin. The development of these antibodies is not usually related to loss of clinical efficacy, although their presence in a small percentage of patients following long-term therapy with high doses of calcitonin may result in a reduced response to the product. The presence of antibodies appears to bear no relationship to allergic reactions, which are rare. Calcitonin receptor down-regulation may also result in a reduced clinical response in a small percentage of patients following long-term therapy with high doses.

**General disorders**
Common: fatigue
Uncommon: influenza-like illness

### 4.9 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 1,600 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiparathyroid hormone, ATC code: H05BA01 (calcitonin, salmon).

5.1 Pharmacodynamic properties

Calcitonin is a calcitropic 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 mineralisation 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 postmenopausal osteoporosis is 200 IU once a day. Higher dosages were not more effective.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters of intranasally administered salmon calcitonin are difficult to quantitate due to the inadequate sensitivity and uncertain specificity of the available immunoassay methods used in the studies performed to date. 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. The half-life of elimination has been calculated to be approximately 16 to 43 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%.

5.3 Preclinical safety data

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

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Trometamine
- Meglumine
- Citric acid
- Methyl parahydroxybenzoate
- Propyl parahydroxybenzoate
- Water for injections.

6.2. Incompatibilities

None.

6.3. Shelf life

The shelf life of the product is 24 months when it is preserved in the original spraying bottle (not opened) and at the recommended storage conditions. Preserve in refrigerator between +2°C and +8°C. Do not freeze.

In any case the container shall not be used after one month from the opening date.

6.4. Special precautions for storage

After opening keep the spraying bottle at a temperature not exceeding 25°C.

After the recommended administration of one single daily dose during 14 or 28 consecutive days, the bottle shall be disposed.

6.5. Nature and content of container

Multidose spraying bottle containing solution for intranasal administration, dispensing.

- 14 individual doses
- 28 individual doses

each delivering 200 I.U. of calcitonin, placed inside the try-holder and packed individually in a lithographed card-board box together with the patient inside leaflet (PIL) and the pushing device.
6.6. **Instructions for use/handling**

1. Remove the spraying bottle from the try-holder and instal the pushing device on the protective cap of the nasal actuator as directed in the instructions.

2. Remove the protection cap and pull it out from the nasal applicator.

3. **IMPORTANT:**

   **14 doses bottle:** when starting and opening a new spraying bottle, press 5 consecutive fold the pushing device. These 5 initial doses (marked with an arrow \(<\) ) shall be withdrawn until the symbol "P" appears on the applicator screen to indicate that the pump is "ready" to be used.

   **28 doses bottle:** when starting and opening a new spraying bottle, press 5 consecutive fold the pushing device. These 5 initial doses (marked with an arrow) shall be withdrawn until the complete spray dose (as from 6 to 28 cumulative doses).

4. To dispense the daily dose follow the instructions on the cartoons: maintain the spraying bottle in the up-right position, insert the nasal applicator inside a nostril and press vigorously the pushing device until the actuation stroke is completed. The delivery of the daily dose is confirmed from the discharge from the applicator of the nebulized solution.

   For 14 doses bottle: at the same time a progression of one number appears on the applicator screen (from 1 to 14).

   After delivering each dose replace the protective cap on the actuator.

   **See enclosed cartoons for 14 and 28 doses spray bottles.**

7. **MARKETING AUTHORISATION HOLDER**

   Company specific.

8. **MARKETING AUTHORISATION NUMBER**

   Company-specific.

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION**

   Company specific.

10. **DATE OF REVISION OF THE TEXT**

    Company-specific.
Bibliographic references


[2] As for other current approved therapy: alendronate sodium, raloxifene hydrochloride, risedronate sodium, along with concomitant calcium and vitamin D supplements.


24th Annual meeting of the American Society for Bone and Mineral Research (ASBMR)


2) "Exploring the depression-bone connection. A new study finds that antidepressant use doubles fracture risk. Other research point to links between depression and bone loss” Harw Womens Health Watch. 14 (10), 1-3, June 2007 (PMID:18018314).
3) “SSRIs and osteoporosis” Med Lett Drugs Ther. 49 (1274), 95-6, Nov. 2007 (PMID: 17910572).