CALCINASE Nasal Spray (Calcitonin)

Composition

CALCINASE Nasal Spray
Each spray delivers:
Calcitonin (Salmon) IP ....................... 200 IU
(Synthetic origin)
Each ml contains:
Calcitonin (Salmon) IP ..................... 2,200 IU
(Synthetic origin)
Preservatives:
Benzalkonium Chloride IP ........... 0.01% w/v
Phenylethyl Alcohol IP........................ 0.2% w/v
Aqueous Base................................. q.s.

Dosage Form

Nasal spray

Pharmacology

Pharmacodynamics

Salmon calcitonin is a calcitonin receptor agonist that acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Salmon calcitonin appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with injectable salmon calcitonin. The mean bioavailability of salmon calcitonin nasal solution is approximately 3% of that of injectable salmon calcitonin in healthy subjects and, therefore, the conclusions concerning the clinical pharmacology of this preparation may be different.

The actions of calcitonin on bone and its role in normal human bone physiology are still not completely elucidated, although calcitonin receptors have been discovered in osteoclasts and osteoblasts.

**Bone**

Single injections of salmon calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity.

In healthy adults, who have a relatively low rate of bone resorption, the administration of exogenous salmon calcitonin results in decreases in serum calcium within the limits of the normal range. In healthy children and in patients whose
bone resorption is more rapid, decreases in serum calcium are more pronounced in response to salmon calcitonin. *In vitro* studies have shown that salmon calcitonin causes inhibition of osteoclast function, with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of salmon calcitonin from the test system. There is some evidence from the *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in the formation of normal bone. Calcitonin nasal solution, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

**Calcium Homeostasis**

In two clinical studies designed to evaluate the pharmacodynamic response to salmon calcitonin nasal solution, administration of 100–1,600 IU salmon calcitonin to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 IU did not produce any further biological response to the drug. The development of hypocalcaemia has not been reported in studies in healthy volunteers or postmenopausal females.

**Kidneys**

Studies with injectable salmon calcitonin show increases in the excretion of filtered phosphate, calcium and sodium by decreasing their tubular reabsorption. Comparable studies have not been carried out with calcitonin nasal solution.

**Gastrointestinal Tract**

Some evidence from studies with injectable preparations suggests that salmon calcitonin may have effects on the gastrointestinal tract. Short-term administration of injectable salmon calcitonin results in marked transient decreases in the volume and acidity of gastric juice, and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of salmon calcitonin during long-term therapy has not been investigated. These studies have not been conducted with calcitonin nasal solution.

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**Pharmacokinetics**

The bioavailability of calcitonin nasal solution relative to intramuscular administration in healthy subjects is between 3% and 5%. Calcitonin nasal solution is absorbed by the nasal mucosa with a mean T$_{\text{max}}$ of about 13 minutes. The terminal half-life of salmon calcitonin has been calculated to be around 18 minutes and no evidence of accumulation was observed with multiple dosing. Plasma exposure was higher following administration of 400 IU nasal spray compared to that after a 200 IU dose. 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 should be evaluated by using clinical parameters of efficacy.

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**Indications**

**Treatment of Postmenopausal Osteoporosis**

CALCINASE is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years post-menopause. Fracture reduction efficacy has not been demonstrated. CALCINASE should be reserved for patients who refuse or cannot tolerate oestrogens or in whom oestrogens are contraindicated.

Due to the possible association between malignancy and salmon calcitonin use, the need for continued therapy should be re-evaluated on a periodic basis. Salmon calcitonin nasal solution has not been shown to increase spinal bone mineral density in early postmenopausal women.
Dosage And Administration

CALCINASE is for intranasal use only. CALCINASE delivers 200 IU salmon calcitonin per actuation. The recommended dosage of CALCINASE for the treatment of established postmenopausal osteoporosis is 1 spray (200 IU) once a day administered intranasally, alternating nostrils daily. Use of CALCINASE is recommended in conjunction with an adequate calcium (at least 1,000 mg elemental calcium per day) and vitamin D (400 IU per day) intake to retard the progressive loss of bone mass.

Contraindications

Hypersensitivity to salmon calcitonin or to any of the excipients of the formulation. Hypocalcaemia.

Warnings And Precautions

General

Hypersensitivity Reactions

Serious hypersensitivity reactions have been reported in patients receiving salmon calcitonin nasal solution, e.g. bronchospasm, swelling of the tongue or throat, anaphylaxis and anaphylactic shock. Reports of serious hypersensitivity reactions with injectable salmon calcitonin have also been reported, including reports of death attributed to anaphylaxis. The usual provisions should be made for the emergency treatment if such a reaction occurs. Hypersensitivity reactions should be differentiated from generalized flushing and hypotension. For patients with suspected hypersensitivity to salmon calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of salmon calcitonin injection.

Hypocalcaemia

Hypocalcaemia associated with tetany (i.e. muscle cramps, twitching) and seizure activity has been reported with calcitonin therapy. Hypocalcaemia must be corrected before initiating therapy. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should also be effectively treated. In patients with these conditions, serum calcium and symptoms of hypocalcaemia should be monitored during therapy.

Periodic Nasal Examinations

Adverse reactions related to the nose including rhinitis and epistaxis have been reported. Development of mucosal alterations may occur. Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended periodically during the course of therapy, and at any time nasal symptoms occur.

The development of mucosal alterations or transient nasal conditions occurred in up to 9% of patients who received calcitonin nasal solution and in up to 12% of patients who received placebo nasal solution in studies in postmenopausal females. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

In all postmenopausal patients, the most commonly reported nasal adverse events included rhinitis (12%), epistaxis (3.5%), and sinusitis (2.3%). Smoking was shown not to have any contributory effect on the occurrence of nasal adverse events. One patient (0.3%) treated with calcitonin nasal solution who was receiving 400 IU daily developed a small nasal wound. In clinical trials in another disorder (Paget's disease), 2.8% of patients developed nasal ulcerations.

If severe ulceration of the nasal mucosa occurs, as indicated by ulcers greater than 1.5 mm in diameter or penetrating...
below the mucosa, or those associated with heavy bleeding, calcitonin nasal solution should be discontinued. Although smaller ulcers often heal without withdrawal of the spray, medication should be discontinued temporarily until healing occurs.

**Malignancy**

In a meta-analysis of 21 randomized, controlled clinical trials with salmon calcitonin (nasal spray or investigational oral formulations), the overall incidence of malignancies reported was higher among salmon calcitonin treated patients (4.1%) compared with placebo treated patients (2.9%). This suggests an increased risk of malignancies in salmon calcitonin treated patients compared to placebo treated patients. Although a definitive causal relationship between salmon calcitonin use and malignancies cannot be established from this meta-analysis, the benefits for the individual patient should be carefully evaluated against all possible risks.

**Antibody Formation**

Circulating antibodies to salmon calcitonin have been reported with salmon calcitonin nasal solution. The possibility of antibody formation should be considered in any patient with an initial response to salmon calcitonin nasal solution who later stops responding to treatment.

**Laboratory Tests**

Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin salmon nasal solution. Coarse granular casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest, who were given injectable calcitonin salmon to study the effect of immobilization on osteoporosis. There was no evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Periodic examinations of urine sediment should be considered. Urine sediment abnormalities have not been reported in ambulatory volunteers treated with calcitonin salmon nasal solution.

**Drug Interactions**

Formal studies designed to evaluate drug interactions with salmon calcitonin nasal solution have not been done. Concomitant use of salmon calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

The effects of prior use of diphosphonates in postmenopausal osteoporosis patients have not been assessed; however, in patients with Paget’s disease, prior diphosphonate use appears to reduce the anti-resorptive response to calcitonin nasal solution.

The use of calcitonin in combination with bisphosphonates may result in an additive calcium-lowering effect.

**Renal Impairment**

There is no evidence of reduced tolerability or altered dosage requirements in such patients.

**Hepatic Impairment**

There is no evidence of reduced tolerability or altered dosage requirements in such patients.

**Pregnancy**

*Pregnancy Category C*

Salmon Calcitonin has been shown to cause a decrease in foetal birth weights in rabbits when given by subcutaneous injection in doses 4-18 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area. Since calcitonin does not cross the placental barrier, this finding may be due to the metabolic effects on the pregnant animal. No embryo/foetal toxicities related to salmon calcitonin nasal solution were reported from maternal subcutaneous daily doses in rats up to 80 IU/kg/day from gestation day 6-15. There are no adequate and well-controlled studies in pregnant women with salmon calcitonin. Nasal salmon calcitonin solution is not
indicated for use in pregnancy.

### Lactation

It is not known whether this drug is excreted in human milk. No studies have been conducted to assess the impact of salmon calcitonin nasal solution on milk production in humans, its presence in human breast milk, or its effects on the breastfed child. Because many drugs are excreted in human milk, caution should be exercised when salmon calcitonin nasal solution is administered to a nursing woman. Calcitonin has been shown to inhibit lactation in animals.

### Paediatric Use

Safety and effectiveness in paediatric patients have not been established. There are no data to support the use of nasal salmon calcitonin solution in children. Disorders of bone in children, referred to as idiopathic juvenile osteoporosis, have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established, and experience with the use of calcitonin in these disorders is very limited.

### Geriatric Use

In one large multicentre, double-blind, randomized clinical study of salmon calcitonin nasal solution, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old, and 196 patients were aged 75 years and over. Compared with subjects less than 65 years old, the incidence of nasal adverse events (rhinitis, irritation, erythema and excoriation) was higher in patients over the age of 65 years, particularly those over the age of 75 years. Most events were mild in intensity. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out.

### Undesirable Effects

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to salmon calcitonin nasal solution (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of salmon calcitonin nasal solution treated patients are presented below in the following table. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to salmon calcitonin nasal solution has not been established.

#### Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Salmon Calcitonin Nasal Solution N=341 % of Patients</th>
<th>Placebo N=131 % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Symptoms of the nose †</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Back pain</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

† Symptoms of the nose include the following: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across the bridge of nose.
In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with calcitonin nasal solution. Adverse events reported in 1–3% of patients are identified with an asterisk (*). The remainder occurred in less than 1% of patients.

Body as a Whole: General Disorders: influenza-like symptoms*, fatigue*, oedema (facial, peripheral, and generalized), fever.

Integumentary: erythematous rash*, skin ulceration, eczema, alopecia, pruritus, increased sweating.

Musculoskeletal/Collagen: arthrosis*, myalgia*, musculoskeletal pain, including arthritis, polymyalgia rheumatica, stiffness.

Respiratory/Special Senses: sinusitis*, upper respiratory tract infection*, bronchospasm*, pharyngitis, bronchitis, pneumonia, coughing, dyspnoea, taste perversion, parosmia, nasal congestion, sneezing, allergic rhinitis, nasal odour, mucosal excoriation, rhinitis ulcerative.

Cardiovascular: hypertension*, angina pectoris*, tachycardia, palpitation, bundle-branch block, myocardial infarction.

Gastrointestinal: dyspepsia*, constipation*, abdominal pain*, nausea*, diarrhoea*, vomiting, flatulence, increased appetite, gastritis, dry mouth.

Liver/Metabolic: cholelithiasis, hepatitis, thirst, weight increase.

Endocrine: goitre, hyperthyroidism, transient decrease in calcaemia.

Urinary System: cystitis*, pyelonephritis, haematuria, renal calculus, polyuria.

Central and Peripheral Nervous System: dizziness*, paraesthesia*, vertigo, migraine, neuralgia, agitation, dysgeusia, tremor.

Hearing/Vestibular: tinnitus, hearing loss, earache.

Vision: abnormal lacrimation*, conjunctivitis*, blurred vision, vitreous floater, visual disturbance.

Vascular: flushing, cerebrovascular accident, thrombophlebitis.


Psychiatric: depression*, insomnia, anxiety, anorexia.

immune System Disorders: hypersensitivity, anaphylaxis and anaphylactic shock.

Common adverse reactions associated with the use of injectable salmon calcitonin occurred less frequently in patients treated with calcitonin nasal solution than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients treated with the nasal spray (and 1.5% of those receiving placebo nasal spray), occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the salmon calcitonin nasal solution, occurs in 2–5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of salmon calcitonin injectable and nasal spray are comparable (50–100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range: 0.3–30.6%) and, therefore, provides less drug to the systemic circulation, possibly accounting for the decrease in the frequency of adverse reactions.

Neutralizing antibodies to calcitonin rarely develop. 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 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.

Malignancy

The overall incidence of malignancies reported in 21 trials was higher among salmon calcitonin treated patients (4.1%) compared with placebo treated patients (2.9%) and is as mentioned in the below mentioned table.

Risk Difference for Malignancies in Calcitonin-Salmon-Treated Patients Compared with Placebo-Treated Patients
<table>
<thead>
<tr>
<th>Patients</th>
<th>Malignancies</th>
<th>Risk Difference(^1) (%)</th>
<th>95% Confidence Interval(^2) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (nasal spray + oral)</td>
<td>All</td>
<td>1.0</td>
<td>(0.3, 1.6)</td>
</tr>
<tr>
<td>All (nasal spray + oral)</td>
<td>Excluding basal cell carcinoma</td>
<td>0.5</td>
<td>(-0.1, 1.2)</td>
</tr>
<tr>
<td>All (nasal spray only)</td>
<td>All</td>
<td>1.4</td>
<td>(0.3, 2.6)</td>
</tr>
<tr>
<td>All (nasal spray only)</td>
<td>Excluding basal cell carcinoma</td>
<td>0.8</td>
<td>(-0.2, 1.8)</td>
</tr>
</tbody>
</table>

\(^1\)The overall adjusted risk difference is the difference between the percentage of patients who had any malignancy (or malignancy excluding basal cell carcinoma in calcitonin-salmon and placebo treatment groups, using the Mantel-Haenszel (MH) fixed-effect method. A risk difference of 0 is suggestive of no difference in malignancy risks between the treatment groups.  
\(^2\)The corresponding 95% confidence interval for the overall adjusted risk difference also based on MH fixed-effect method.

### Postmarketing Experience

Because postmarketing adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been reported during post-approval use of salmon calcitonin nasal solution:

**Allergic/Hypersensitivity Reactions:** serious allergic reactions reported in patients receiving salmon calcitonin nasal solution, including anaphylaxis and anaphylactic shock.

**Hypocalcaemia:** hypocalcaemia with paraesthesia reported.

**Body as a Whole:** facial or peripheral oedema

**Cardiovascular:** hypertension, vasodilatation, syncope, chest pain

**Nervous system:** dizziness, seizure, visual or hearing impairment, tinnitus

**Respiratory/Special Senses:** cough, bronchospasm, dyspnoea, loss of taste/smell

**Skin:** rash/dermatitis, pruritus, alopecia, increased sweating

**Gastrointestinal:** diarrhoea

**Nervous system disorders:** tremor

### Overdosage

No instances of overdose with calcitonin nasal solution have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon. Single doses of calcitonin nasal solution up to 1,600 IU, doses up to 800 IU per day for 3 days, and continuous administration of doses up to 600 IU per day have been studied without serious adverse effects.

The pharmacologic actions of calcitonin nasal solution suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

### Storage And Handling Instructions

Store the unopened bottle in the refrigerator between 2°C and 8°C until ready to use. Protect from freezing. Bottle in use can be stored at room temperature between 15°C and 30°C for up to 35 days in an upright position. Keep out of the
reach of children. The protective cap should be on the bottle whenever it is not in use.

**Packaging Information**

CALCINASE Nasal Spray is available as a glass bottle......... 3.7 ml

**Patient Information**

**Different Parts of CALCINASE Nasal Spray**

The different parts of the nasal spray are as below:

- **Protective Cap:** Keeps the nozzle clean. Always replace the protective cap after you have used the nasal spray.
- **Nozzle:** The part you insert into your nostril. It has a tiny hole from which the medicine sprays out.
- **Pump:** The part you press down to operate the spray.
- **Dip Tube:** The tube inside the spray bottle that draws up the medicine when you press the pump.
- **Bottle:** Contains enough medicine for at least 30 metered doses.

**How to Use CALCINASE Nasal Spray**

**Step 1**
Remove the protective dust cap. Hold the bottle with your forefinger and middle finger on either side of the nozzle and your thumb underneath the bottle.

**Step 2**
Ensure that the bottle is at room temperature before use. The nasal spray must be primed before being used for the first time. To do this, hold the nasal spray with the nozzle pointing away from you; press the pump down firmly several times until a fine mist comes out of the nozzle. There is no need to prime the bottle before each daily use, as this will waste the medication.

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

**Step 4**
Remove the nasal spray nozzle from your nostril and breathe in deeply through your nose.

**Step 5**
Wipe the nozzle with a clean and dry cloth/tissue and replace the protective dust cap.

*Last Updated: Feb 2018*
*Last Reviewed: Feb 2018*

CALCINASE Nasal Spray

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