PRODUCT MONOGRAPH

[Pr]Calcitonin Salmon Injection USP

Synthetic Salmon Calcitonin

Solution, 200 IU / mL

Intramuscular or Subcutaneous Injection

Calcium Regulator

SteriMax Inc.
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NAME OF DRUG

Calcitonin Salmon Injection USP
(Calcitonin-Salmon)

THERAPEUTIC OR PHARMACOLOGICAL CLASSIFICATION

Calcium Regulator

ACTIONS

Calcitonin-Salmon participates in the regulation of the homeostasis of calcium by acting primarily on the bone; in Paget's disease presumably by an initial blocking effect on accelerated bone resorption. The rate of bone turnover appears to be decreased.

Calcitonin-Salmon participates in the regulation of urinary excretion of phosphate and calcium. Administration of Calcitonin-Salmon decreases the volume and acidity of the gastric juice and decreases the volume as well as trypsin and amylase content of the pancreatic juice.

(For further details see CLINICAL PHARMACOLOGY section).

INDICATIONS

1. Paget's Disease:

Treatment of symptomatic Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable.

2. Hypercalcemia:

Early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents. Calcitonin may be used in patients with azotemia and those with limited cardiac reserve in whom intravenous fluids may be contraindicated.

Due to evidence of an increased risk of malignancies with the long term calcitonin use, the treatment duration should be limited to the shortest period of time possible and using the minimum effective dose.

CONTRAINDICATIONS

Patients who are hypersensitive to Calcitonin Salmon Injection USP or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS and PHARMACEUTICAL INFORMATION, Composition sections of the Product Monograph.

WARNINGS

Risk of cancer: Analyses of randomized controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that calcitonin is associated with a statistically significant increase in the absolute risk of new malignancies (between 0.7% (oral route) to 2.4% (intranasal route)) in patients treated with calcitonin therapy compared to patients treated with placebo. Patients in these trials were treated with long-term oral and intra-nasal formulations however it is likely that an increased risk also applies when calcitonin is administered subcutaneously, intramuscularly or intravenously especially for long-term use, as systemic exposure to calcitonin in such patients is expected to be higher than for other formulations.

Pregnancy: Reproduction studies in two species (rats and rabbits) have revealed decreases in fetal birth weight, and data in humans are not available to exclude a possible adverse effect on the fetus. Use of this drug in women who are or may become pregnant requires a determination that the potential benefit to the patient outweighs the possibility of risk to the fetus.

Nursing Mothers: Calcitonin-Salmon has been shown to inhibit lactation in animals and should not be administered to nursing mothers.

Children (< 18 years of age): The safe use of Calcitonin-Salmon in children has not been established.

PRECAUTIONS

Potential allergenicity of Calcitonin Salmon Injection USP:

Skin testing should be considered prior to treatment of patients with suspected sensitivity to calcitonin. The following procedure is suggested:

Prepare a dilution of 10 I.U. per mL by withdrawing 1/20 mL (0.05 mL) in a tuberculin syringe and filling it to 1.0 mL with Dextrose Injection 5%, U.S.P. (or Saline Injection U.S.P.). Mix well, discard 0.9 mL and inject intracutaneously 0.1 mL (approximately 1 I.U.) on the inner aspect of the forearm. Observe the injection site 15 minutes after injection. The appearance of more than mild erythema or wheal constitutes a positive response.

Because calcitonin is protein in nature, the possibility of a systemic allergic reaction cannot be overlooked. Administration of Calcitonin-Salmon has been reported in a few cases to cause serious allergic-type reactions (for example, bronchospasms, swelling of the tongue or throat and anaphylactic shock), and in one case, death due to anaphylaxis. The usual provisions should be made for the emergency treatment of such a reaction should it occur.

Allergic reactions should be differentiated from generalized flushing and hypotension.

Possibility of hypocalcemic tetany:

The administration of calcitonin may lead to hypocalcemic tetany (i.e. muscle cramps, twitching). Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.

In patient's with active Paget's disease, a decrease in serum calcium was observed after the injection of up to 100 units of subcutaneous calcitonin, which can be asymptomatic, was evident by the end of the first hour and maximal from 4 to 6 hours.

Antibody development:

Calcitonin administration can and does lead to antibody development. This is minimal when the hormone is injected in the absence of an adjuvant or when it is not complexed with a larger protein. Gelatin and acetate buffer solutions have been shown to have little or no adjuvant-like action in comparison to Freund's adjuvant.

The antibodies which develop when calcitonin is administered repeatedly with Freund's adjuvant are measurable in the circulation by radio-immunoassay techniques. In no instance has any systemic allergic or anaphylactic effect been reported in animal studies with calcitonin, in spite of the known development of circulating antibodies.

Laboratory Tests:

Periodic examinations of serum calcium and urine sediment of patients on chronic therapy are recommended.

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given salmon calcitonin to study its effect on immobilization osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped.

Instructions for the patient:

Careful instruction in sterile injection technique should be given to the patient and to other persons who may administer Calcitonin Salmon Injection USP.

INTERACTIONS

Concomitant use of Calcitonin Salmon Injection USP and lithium may lead to a reduction in plasma lithium concentrations. The dose of lithium may need to be adjusted; blood monitoring of lithium is recommended.

ADVERSE REACTIONS

Central and peripheral nervous system disorders:
Paresthesia (tingling of the hands), dizziness, seizures, visual and hearing impairment, headache, tremor, tinnitus.

Endocrine disorders:
Secondary hyperparathyroidism did not develop in patients with Paget's disease as a result of the transient hypocalcemia following calcitonin administration.

Eye disorders:
Pain in the eyes.

Gastrointestinal disorders:
Nausea with or without vomiting has been noted in about 10% of patients treated with Calcitonin-Salmon. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration. Abdominal pain, diarrhea.

General and administration site disorders:
Local inflammatory reactions at the site of injection have been reported in about 10% of patients. Feverish sensation.

Immune system disorders:
Evidence of systemic allergic reactions was minimal. Administration of Calcitonin-Salmon has been reported in a few cases to cause serious allergic-type reactions (for example, bronchospasms, swelling of the tongue or throat and anaphylactic shock), and in one case, death due to anaphylaxis (see PRECAUTIONS, Potential allergenicity of Calcitonin Salmon Injection USP). Skin rashes and pruritus of the ear lobes have also been reported.

The usual laboratory parameters of liver and kidney function and of hematologic status remained within normal limits. In approximately one-half the patients tested after six months or more of treatment, indications of circulating antibodies to calcitonin were obtained. In most of the patients the level of antibodies was not high enough to interfere with the effect of exogenous calcitonin. In a few patients resistance to calcitonin was attributed to high levels of antibodies.

Metabolism and nutrition disorders:
Decreased appetite, anorexia, and a metallic and/or salty taste.

Neoplasms; benign, malignant and unspecified (including cysts and polyps):
Malignancy was seen with long term use, and frequency was common (between 0.7% for the oral formulation to 2.4% for the nasal formulation).

Urinary disorders:
Nocturia, polyuria.

Vascular disorders:
Flushing of the face, ears, hands and feet occurred in about 2-5% of patients. Hypertension.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: The pharmacologic actions of Calcitonin Salmon Injection USP suggest that hypocalcemic tetany could occur in overdose. Therefore, provisions for the parenteral administration of calcium should be available for the treatment of overdose (see PRECAUTIONS).

Dose-dependent adverse effects such as nausea, vomiting, flushing, and dizziness can occur when calcitonin is administered for parenteral use (see ADVERSE REACTIONS).

Treatment: There is no specific antidote. In the event of a suspected overdose, discontinue treatment temporarily, maintain the patient under observation and implement supportive treatment as indicated.

For management of a suspected drug overdose, contact your regional poison control centre.

DOSAGE AND ADMINISTRATION

Due to evidence of an increased risk of malignancies with long term calcitonin use, the treatment duration should be limited to the shortest period of time possible and using the minimum effective dose.

Adults:

1. Paget's Disease:

The recommended dosage is 100 I.U. per day administered subcutaneously or intramuscularly, however in many patients a minimum dosage regimen of 50 I.U. three times a week is sufficient to maintain clinical and biochemical improvement.

Dosage is to 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 evidence of an 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.

Drug effect should be monitored by periodic measurement of bone remodeling markers such as serum alkaline phosphatase and 24-hour urinary hydroxyproline or deoxypyridinoline and evaluation of symptoms. A decrease toward normal of the biochemical abnormalities is usually seen, if it is going to occur, within the first few months. Bone pain may also decrease during that time.
In any patient with a good initial response who later relapses, either clinically or biochemically, the possibility of antibody formation should be explored to detect titers that interfere with the action of calcitonin.

In patients who relapse, whether because of antibodies or for unexplained reasons, a dosage increase beyond 100 I.U. per day does not usually appear to elicit an improved response.

After overnight fasting, a sample of the patient's blood is taken for determination of serum calcium and 100 I.U. of Calcitonin Salmon Injection USP are injected IM. The patient is then permitted to eat his usual breakfast. At 3 & 6 hours post-injection additional blood samples are drawn and the patient is released. The serum calcium values are then compared. A decrease of 0.12 mmol/L (0.5 mg/dL) or more from fasting level at 3 and 6 hours is usually seen in the responsive patient. Decreases of 0.07 mmol/L (0.3 mg/dL) or less constitute an inadequate response to calcitonin in the patient with active Paget's disease. If the hypocalcemic action of calcitonin is lost, further therapy with Calcitonin Salmon Injection USP will not be effective.

2. Hypercalcemia:

The recommended starting dose of calcitonin in hypercalcemia is 4 I.U. /kg body weight every 12 hours by subcutaneous or intramuscular injection. If the response to this dose is not satisfactory after one or two days, the dose may be increased to 8 I.U. /kg every 12 hours. If the response remains unsatisfactory after two more days, the dose may be further increased to a maximum of 8 I.U./kg every 6 hours.

If the volume of Calcitonin Salmon Injection USP to be injected exceeds 2 mL, intramuscular injection is preferable and multiple sites of injection should be used.

In clinical trials, Calcitonin-Salmon has been shown to lower the elevated serum calcium of patients with carcinoma (with or without demonstrated metastases) multiple myeloma or primary hyperparathyroidism (lesser response). Patients with higher values for serum calcium tend to show greater reduction during Calcitonin-Salmon therapy. The decrease in calcium occurs about 2 hours after the first injection and lasts for about 6-8 hours. Calcitonin-Salmon given every 12 hours maintained a calcium lowering effect for about 5-8 days, the time period evaluated for most patients during the clinical studies. The average reduction of 8-hour post-injection serum calcium during this period was about 9 percent.

The use of Calcitonin Salmon Injection USP in the management of hypercalcemia should be limited to patients under close supervision in hospitals.

DOSAGE FORMS

Calcitonin Salmon Injection USP is available as a sterile solution, containing 200 International Units per mL, or 400 International Units per 2 mL vial, with 0.5% phenol as a conservation agent. Sodium chloride, sodium acetate and acetic acid have been added to regulate tonicity.

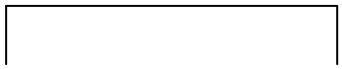
(NOTE: 1 International Unit is equivalent to 1 MRC unit).

PHARMACEUTICAL INFORMATION

Common name: Calcitonin (salmon)

Chemical Name: L -Cysteinyl-L -seryl-L -asparaginyl-L -leucyl-L -seryl-L –threonyl-L- cysteinyl-L -valyl-L -leucyl-glycyl-L -lysyl-L -leucyl-L -seryl-L-gIutaminyl-L -gIutamyl-L -leucyl-L -histidyl-L -lysyl-L –leucyl-L-glutaminyl-L-threonyl-L-tyrosyl-L-prolyl-L-arginyl-L-threonyl-L-asparaginyl-L-threonyl-glycyl-L-seryl-glycyl-L-threonyl-L-proline amide 3, 7-3,1 disulfide

Structural Formula-Calcitonin



Cys-Ser-Asn-Leu-Ser-Thr-Cys-Val-Leu-Gly-Lys-Leu-Ser-Gln-Glu-Leu-His-Lys-Leu-Gin-Thr-Tyr-Pro-Arg-Thr-Asn-Thr-Gly-Ser-Gly-Thr-Pro-NH_2

Using the one letter code for the amino acids the structural formula is abbreviated as

Molecular Formula: $C_{145}H_{240}N_{44}O_{48}S_2$

Molecular Weight: The molecular weight of calcitonin (salmon) is 3431.9 and the monoisotopic mass of calcitonin (salmon) is 3429.7.

Description

The active ingredient of Calcitonin Salmon Injection USP is a synthetic calcitonin consisting of 32 amino acids in the same linear sequence as that found in salmon calcitonin. It is a white or slightly yellowish powder. It is provided in sterile injectable form and its calcitonin activity is stated in International Units.

Equivalency of M.R.C.U. and I.U.
An International Unit for Calcitonin, salmon, is defined as the activity contained in 0.02525 mg of the International Reference Preparation of Calcitonin, salmon, for Bioassay[1].

[1]From 26th Report: Expert Committee on Biological Standardization World Health Organization, December 1974.

By agreement, the International Unit is identical to the pre-existing Medical Research Council (MRC) unit.

Composition

Each mL of Calcitonin Salmon Injection USP contains 200 IU Calcitonin-Salmon, and the following non-medicinal ingredients: acetic acid (2.25 mg), phenol (5.0 mg), sodium acetate (2.0 mg), sodium chloride (7.5 mg), and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Store at refrigerator temperature - between 2 and 8°C. Protect from light. Discard unused portion 28 days after initial puncture (when stored under refrigeration).

Unopened vials of the product are stable for 2 weeks at room temperature 15-30°C.

Do not use product if solution shows haziness, particulate matter, discolouration, or leakage.

AVAILABILITY OF DOSAGE FORMS

Calcitonin Salmon Injection USP is available as a sterile solution containing 200 International Units per mL, or 400 International Units per 2 mL multidose vial, for intramuscular or subcutaneous injection with 0.5% phenol, as preservative. Sodium chloride, sodium acetate and acetic acid, have been added to adjust the tonicity and pH.

Calcitonin Salmon Injection USP is supplied in packages of 1 x 2 mL, 5 x 2mL and 10 x 2 mL multidose vials.

(NOTE: 1 International Unit is equivalent to 1 MRC unit).

PHARMACOLOGY

Summary of Major Points from Experimental Studies:
The following represents a summary of the more important aspects of the animal pharmacology of calcitonin.

Calcitonin is a group of polypeptide hormones secreted by the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

It is of physiological importance in the regulation of calcium metabolism in certain animal species, and may also have physiological importance in certain extra-skeletal systems (e.g., 0.1 and renal function).

Because of its chemical nature (a peptide of 32 amino acids), calcitonin is usually administered parenterally to achieve maximum absorption. Small percentages of the dose given are apparently

absorbed after administration by buccal, oral, topical (to the skin) or inhalation routes, but no practical use of these non-parenteral routes has been made thus far.

Calcitonin, particularly the salmon form, is extremely potent. As little as 1 nanogram given subcutaneously to young rats lowers the serum calcium by 0.25-0.49 mmol/L (1-2 mg/dL). Standardization of potency is based upon rat bioassay versus standards prepared by the Medical Research Council, Mill Hill, London. Recently an official standard has been prepared, (International Reference Preparation of Calcitonin, Salmon, for Bioassay) One International Unit (I.U.) = 1 MRC Unit.

Following parenteral administration, calcitonin is rapidly absorbed into the blood. Its half-life in the circulation, like that of other peptide hormones, is measured in minutes rather than hours. Salmon calcitonin, however, exhibits a relatively longer half-life than does porcine or human calcitonin. Immediately after introduction into the circulation, calcitonin is present in the free form. Later it is largely protein bound, but this does not appear to interfere with either its biological or immunological activity. The duration of action of calcitonin, administered subcutaneously or intramuscularly, is somewhat prolonged by the use of a gelatin vehicle.

The primary action of calcitonin is on bone, and in that tissue it is the osteoclasts which have most consistently been shown to be affected. These cells show decreased function, altered morphology and decreased numbers under the influence of calcitonin. Osteocytic osteolysis also appears to be depressed by this hormone. These effects result in the well known inhibition of bone resorption by calcitonin. Calcitonin may also stimulate osteoblastic bone formation, but decreases in osteoblastic function have also been reported.

By virtue of its ability to inhibit bone resorption, calcitonin decreases the flow of calcium from bone to blood and thus tends to lower blood calcium. The hypocalcemic effect of calcitonin is most marked when bone turnover proceeds at a high rate. Thus, decreases in serum calcium in young animals are more pronounced than those in adults.

The lowering of serum calcium with calcitonin can, under certain conditions, be as much as 0.75 to 1.00 mmol/L (3 to 4 mg/dL), which may lead to hypocalcemic tetany (see PRECAUTIONS, Possibility of hypocalcemic tetany).

The chronic treatment of animals with calcitonin has not led to a generalized increase in skeletal density, as some might earlier have predicted. When changes in density have been noted they have nearly always been in the upward direction, but these have usually been local rather than general in nature. Increased density in the metaphyseal area of long bones and vertebrae has been reported from several studies, while increased cortical density has been reported only infrequently. In other studies calcitonin has been shown to reduce bone resorption stimulated by vitamin D, vitamin A or parathyroid hormone.

Actions of calcitonin on gastrointestinal function have clearly been shown, though these are not fully understood as yet. Variable effects on calcium absorption by the G.I. tract have been reported, with an increase in absorption the effect most frequently noted. In this regard calcitonin

could be acting directly; alternatively the hormone may invoke increased formation of 1,25-dihydroxychole-calciferol which in turn would increase the absorption of calcium.

Finally, the effect could be mediated by a secondary parathyroid mechanism, whereby PTH, either directly or via the vitamin D mechanism, would act to enhance calcium absorption.

Other actions of calcitonin on G.I. function include an ability to decrease the volume and acidity of gastric secretion as well as an inhibition of exocrine volume and enzyme secretion by the pancreas. Attempts to inhibit ulcer formation in animal experiments by reducing gastric secretion with calcitonin were successful in each of the two studies.

Renal effects of calcitonin are now well documented and the mechanisms better understood than earlier. It appears that calcitonin decreases the tubular reabsorption of calcium, leading to increased excretion of this ion when other factors are not involved. Analogous effects of calcitonin are seen in magnesium handling, though the mechanism of this effect is somewhat less clear than for calcium. Sodium and phosphorus also experience decreased tubular reabsorption due to calcitonin. For these ions the effects appear to involve the proximal tubules. Actions of calcitonin on the handling of calcium and sodium by the kidney seem to be separate.

Salmon calcitonin appears to be markedly more natriuretic than porcine or human calcitonin in animal studies though the effects of these different species of the hormone on calcium excretion are relatively similar. Potassium excretion is sometimes increased and sometimes unchanged by calcitonin. Increased excretion of water also occurs. Calcitonin appears to have little effect on glomerular filtration rate.

There are two modifying factors which are important in any consideration of the renal effects of calcitonin. The first involves a decrease in filtered load of calcium due to the hypocalcemic effect on the hormone. In acute situations especially, the decrease in tubular reabsorption of this ion results in a decrease rather than an increase in urinary calcium excretion. The second factor is increased PTH secretion, secondary to the hypocalcemic effect of calcitonin. PTH acts directly on the kidney to increase the tubular reabsorption of calcium and magnesium and to decrease the reabsorption of phosphorus. The first two actions of PTH oppose those of calcitonin, while the effect on phosphorus complements the action of calcitonin. In any given situation the overall effects of calcitonin on urinary excretion are dependent upon several factors and the results can vary accordingly.

The dose level of calcitonin may also influence renal excretion, at least as regards calcium. The effect of calcitonin on bone resorption appears to be more sensitive than is the effect on the renal tubular reabsorption of calcium. Thus, at low doses, calcitonin can sometimes lower urinary calcium excretion because of its effect on filtered load. At high doses the direct renal effect tends to predominate which results in an increased excretion of urinary calcium.

PTH secretion is directly controlled by levels of serum calcium, and acute decreases in the latter, caused by calcitonin, result in immediate increases in circulating levels of PTH. Chronic treatment with calcitonin could, therefore, conceivably give rise to hyperplasia of the parathyroids and increased levels of basal PTH secretion (secondary hyperparathyroidism). Certain animal data appear to support this possibility. There is also reason to believe that the

enhanced secretion of PTH during calcitonin administration modifies the effects that would otherwise be produced. For some effects, PTH may tend to antagonize and minimize the actions of calcitonin. In other instances in the same animal, the effects of PTH and calcitonin may complement and reinforce one another. For example, as explained above, calcitonin and PTH have opposite effects on the tubular reabsorption of calcium but reinforce each other in their actions on phosphate excretion. On bone the interactions of PTH and calcitonin are perhaps more important but less well understood. Increased parathyroid hormone levels lead to enhanced osteoclastic activity, while calcitonin has the opposite effect. But the outcome when both are present in continuing high levels has not been clarified. Interactions of these hormones on other bone cells are even less well understood. Increased levels of PTH have been implicated as causing enhanced bone formation as well as increased bone resorption; both may prove to be significant factors in the long-term skeletal effects with chronic calcitonin treatment. Cessation of calcitonin treatment appears to be associated with a return toward the pretreatment level of PTH secretion, based on indirect evidence.

Calcitonin administration can and does lead to antibody development. This is minimal when the hormone is injected in the absence of an adjuvant or when it is not complexed with a larger protein. Gelatin and acetate buffer solutions have been shown to have little or no adjuvant-like action in comparison to Freund's adjuvant. The antibodies which develop when calcitonin is administered repeatedly with Freund's adjuvant are measurable in the circulation by radio-immunoassay techniques. In no instances has any systemic allergic or anaphylactic effect been reported in animal studies with calcitonin, in spite of the known development of circulating antibodies.

Repeated treatment of animals with very high doses of calcitonin has led to several unexplained changes. In a one-month study in rabbits, Lupulescu reported histological changes in follicular cells of the thyroid indicative of a hypersecretory state; changes were also noted in the parafollicular cells. In studies by Armour treatment of young rats for seven days consistently lead to decreases in thyroid and heart weight and to increases in red cell counts.

Metabolism:
The patterns of tissue distribution seem to differ for the three forms of the hormone studied thus far, and these differences appear to correlate with information on sites of degradation. Thus porcine calcitonin tends to accumulate in the liver and kidney and both tissues degrade this form. Human calcitonin shows similar properties except that the kidney is relatively more important for the metabolism of human calcitonin than for porcine calcitonin. In the case of salmon calcitonin, accumulation and degradation seem to occur almost exclusively in the kidney. Degradation of all forms of calcitonin occurs by splitting the molecule into smaller fragments which are biologically and immunologically inactive. Very little renal excretion of the intact calcitonin molecule takes place. It appears that Calcitonin-Salmon cannot cross the placental barrier.

TOXICOLOGY

General:

Salmon calcitonin has been administered to animals acutely, subchronically and chronically by intravenous, subcutaneous and intramuscular routes. Rats, rabbits and dogs were used for these studies. Teratogenicity as well as perinatal and postnatal studies were conducted in rats and rabbits. The studies were carried out according to standard protocols. A sensitization study in guinea pigs was also completed because of the chemical nature of calcitonin.

Dogs given calcitonin subcutaneously for six months at dosage levels of 20 to 80 units/kg/day exhibited partial to total anorexia with concurrent body weight loss during the first few weeks of the study. Thereafter, food consumption was similar in control and treated dogs.

Calcitonin was administered subcutaneously at levels of 20 to 80 units/kg/day from day 25 of gestation through lactation in a perinatal and postnatal study. In this study there appeared to be a partial to complete failure in lactation in some treated dams. One litter in each of the treated groups gradually became cachectic before day 9 of lactation and died. Macroscopically the kidneys of several rats in both treated groups appeared mottled. Microscopically, hyaline casts in the medulla and cortex, dilatation of cortical tubules, interstitial nephritis (not associated with cast formation); and fat droplets and brown pigment in cortical tubular cells were seen. The following parameters in pups of treated dams were affected: pup weight at 24 hours, 4 days and 21 days, and lactation index.

In a repeat of the perinatal and postnatal study in rats, body weight of pups in treated groups was less than control pups, and the rate of stillbirth was more for pups of treated dams than for control pups. No macroscopic kidney changes were noted in dams. Microscopically the kidneys of several of the dams treated with 20 or 80 units/kg/day exhibited dilatation of renal collecting tubules with homogeneous casts. No such kidney changes were noted in dams treated with 5 units/kg/day.

In a third perinatal and postnatal study in rats, treatment with 320 units/kg/day from day 15 of pregnancy through the lactation period caused renal tubule dilatation and associated hyaline cast formation in 3 of 10 dams. No significant effect was noted in pups.

The sensitization study in guinea pigs indicated that calcitonin had no sensitizing potential.

Carcinogenicity:

A one-year toxicological study was conducted in Japan with salmon calcitonin administered subcutaneously to 153 male and female Sprague-Dawley rats respectively, in doses ranging from 1.25 to 80 IU/kg/day. An increased incidence of pituitary adenomas was observed in male and to a lesser extent in female rats. Histopathological examination revealed a significant ($p<0.01$) increase in pituitary chromophobe cell adenomas in males receiving 20 IU/kg/day or more.

Several toxicological and mechanistic studies have been undertaken to assess these findings. In two further one-year studies in rats, salmon calcitonin did not induce the hyperplastic/neoplastic process as evidenced by the similar incidences of total proliferative lesions observed in control and treated (80 IU/kg/day) animals. It did however reduce the latency period for development of pituitary adenomas, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Continuous administration of

80 IU/kg/day of salmon calcitonin with osmotic pumps appeared to decrease the latency period for the development of hyperplastic foci compared to daily subcutaneous injection of the same dose.

Mechanistic studies in rats, using salmon calcitonin administered subcutaneously at 20 IU/kg/day, either alone or in combination with diethylstilbestrol and/or bromocriptine, for 8 weeks, suggested that salmon calcitonin does not act directly or indirectly on lactotrophs to stimulate a proliferative response in the pituitary. Findings from a 3-month subcutaneous toxicity study of calcitonin (5 or 160 IU/kg/day) and disodium EDTA (150 mg/kg/day) revealed that it is not the calcium lowering activity of the drug which is responsible for the increased incidences of pituitary lesions in rats. A combination of serum assays, immunohistochemical and Northern blot analyses have determined that the majority of proliferative lesions in rats are non-functional and composed of cells which produce alpha subunit common to glycoprotein hormones (LH, TSH, FSH). Moreover, the histomorphology of these proliferative non-functional lesions was consistent with that which occurs spontaneously in aged laboratory rats.

The results of extensive testing indicate that calcitonin would have no effect in the rat pituitary if the spontaneous proliferative lesions did not occur. Furthermore, all evidence suggests that proliferative response in the pituitary of rats is species specific, as similar findings have not been observed in studies in mice treated with subcutaneous salmon calcitonin in doses ranging from 0.625 to 160 IU/kg/day for periods of 13 weeks to 18 months, and in dogs treated with subcutaneous salmon calcitonin in doses of 5 to 80 IU/kg/day for 16 weeks.

Teratology:

In a teratogenicity study in rats wherein calcitonin was administered from day 6 through day 20 of gestation at 20 to 80 units/kg/day subcutaneously, two of 20 dams receiving the higher dosage level exhibiting coarse tan mottling of both kidneys. In a repeat study in the same strain of rats no such macroscopic kidney changes were noted, and there were no microscopic pathologic changes in the kidneys related to treatment with calcitonin.

In a teratogenicity study in rabbits, the mean fetal weight was decreased at 80 and 20 units/kg/day and the mean placental weight was decreased at 80 units/kg/day.

CLINICAL PHARMACOLOGY

Calcitonin-Salmon acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract have also been recognized. Calcitonin-Salmon 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 actions of calcitonin on bone and its role in normal human bone physiology are still incompletely understood.

Bone-single injections of Calcitonin-Salmon 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. Decreased osteocytic resorption may also be

involved. There is some evidence that bone formation may be augmented by Calcitonin-Salmon through increased osteoblastic activity.

Animal studies indicate that endogenous calcitonin, primarily through its action on bone, participates with parathyroid hormone in the homeostatic regulation of blood calcium. Thus, high blood calcium levels cause increased secretion of calcitonin which, in turn, inhibits bone resorption. This reduces the transfer of calcium from bone to blood and tends to return blood calcium to the normal level. The importance of this process in humans has not been determined. In normal adults, who have a relatively low rate of bone resorption, the administration of exogenous calcitonin results in only a slight decrease in serum calcium. In normal children and in patients with generalized Paget's disease, bone resorption is more rapid and decreases in serum calcium are more pronounced in response to calcitonin.

Paget's Disease of Bone (osteitis deformans) - Paget's disease is a disorder of uncertain etiology characterized by abnormal and accelerated bone formation and resorption in one or more bones. In most patients only small areas of bone are involved and the disease is not symptomatic. In a small fraction of patients, however, the abnormal bone may lead to bone pain and bone deformity, cranial and spinal nerve entrapment, or spinal cord compression. The increased vascularity of the abnormal bone may lead to high output congestive heart failure.

Active Paget's disease involving a large mass of bone may increase the urinary hydroxyproline excretion (reflecting breakdown of collagen-containing bone matrix) and serum alkaline phosphatase (reflecting increased bone formation).

Calcitonin-Salmon, presumably by an initial blocking effect on bone resorption, causes a decreased rate of bone turnover with a resultant fall in the serum alkaline phosphatase and urinary hydroxyproline excretion in approximately 2/3 of patients treated. These biochemical changes appear to correspond to changes toward more normal bone, as evidenced by a few well-documented examples of: 1) radiologic regression of Pagetic lesions, 2) improvement of impaired auditory nerve and other nerve and other neurologic function, 3) decreases (measured) in abnormally elevated cardiac output. These improvements occur extremely rarely, if ever, spontaneously (Elevated cardiac output may disappear over a period of years when the disease slowly enters a sclerotic phase; in the cases treated with Calcitonin-Salmon, however, the decreases were seen in less than one year).
Some patients with Paget's disease who have good biochemical and/or symptomatic responses initially, later relapse. Suggested explanations have included the formation of neutralizing antibodies and the development of secondary hyperparathyroidism, but neither suggestion appears to explain adequately the majority of relapses.

Although the parathyroid hormone levels do appear to rise transiently during each hypocalcemic response to Calcitonin-Salmon, most investigators have been unable to demonstrate persistent hypersecretion of parathyroid hormone in patients treated chronically with Calcitonin-Salmon.

Circulating antibodies to Calcitonin-Salmon after 2-18 months treatment have been reported in about half of the patients with Paget's disease in whom antibody studies were done, but Calcitonin-Salmon treatment remained effective in many of these cases. Occasionally patients with high antibody titers are found. These patients usually will have suffered a biochemical

relapse of Paget's disease and are unresponsive to the acute hypocalcemic effects of Calcitonin-Salmon.

Kidney – Calcitonin-Salmon increases the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. In some patients the inhibition of bone resorption by Calcitonin-Salmon is of such magnitude that the consequent reduction of filtered calcium load more than compensates for the decrease in tubular reabsorption of calcium. The result in these patients is a decrease rather than an increase in urinary calcium.

Transient increases in sodium and water excretion may occur after the initial injection of calcitonin. This is of no clinical consequences and in most patients these changes return to pretreatment levels with continued therapy.

Gastrointestinal tract – Increasing evidence indicates that Calcitonin-Salmon has significant actions on the gastrointestinal tract. Short-term administration 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 Calcitonin-Salmon during chronic therapy has not been investigated.

See section entitled “Metabolism”.

General:

At the present time effectiveness has been demonstrated principally in patients with moderate to severe disease characterized by polyostotic involvement with elevated serum alkaline phosphatase and urinary hydroxyproline excretion.

In these patients, the biochemical abnormalities are substantially improved (more than 30% reduction) in about 2/3 patients and bone pain is improved in a similar fraction. Well-documented instances of reversal of neurologic deficits have occurred, including improvement in hearing, improvement in the basilar compression syndrome, and improvement of spinal cord and spinal nerve lesions. At present there is too little experience to predict the likelihood of improvement of any given neurologic lesion, although hearing loss appears to improve in only 5% of patients.

Patients with increased cardiac output due to extensive Paget's disease have had measured decreases in cardiac output while receiving Calcitonin-Salmon. The number of treated patients in this category is still too small to predict how likely such a result will be.

The large majority of patients with localized, especially monostotic, disease do not develop symptoms and most patients with mild symptoms can be managed with analgesics. There is no evidence that the prophylactic use of Calcitonin-Salmon is beneficial in asymptomatic patients, although treatment may be considered in exceptional circumstances in which there is extensive involvement of the skull or spinal cord with the possibility of irreversible neurologic damage. In these instances treatment should be based on the demonstrated effect of Calcitonin-Salmon on Pagetic bone.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about Calcitonin Salmon Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://sterimaxinc.com/, or by calling 1-800-881-3550.

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