ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for calcitonin and related names. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

INJECTABLE SALMON CALCITONIN

1. NAME OF THE MEDICINAL PRODUCT

{(Trade) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Company- specific.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calcitonin is indicated for:

- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
- Paget's disease
- Hypercalcemia of malignancy

4.2 Posology and method of administration

For subcutaneous, intramuscular or intravenous (product specific) use in individuals aged 18 years or more.

Salmon calcitonin may be administered at bedtime to reduce the incidence of nausea or vomiting which may occur, especially at the initiation of therapy.

Prevention of acute bone loss:
The recommended dosage is 100 I.U. daily or 50 I.U. twice daily for 2 to 4 weeks, administered subcutaneously or intramuscularly. The dose may be reduced to 50 I.U. daily at the start of remobilisation. The treatment should be maintained until patients are fully mobilized.

Paget's disease:
The recommended dosage is 100 IU per day administered subcutaneously or intramuscularly, however, a minimum dosage regimen of 50 IU three times a week has achieved clinical and biochemical improvement. Dosage is to be adjusted to the individual patient's needs. The duration of treatment depends on the indication for treatment and the patient´s response. The effect of calcitonin may be monitored by measurement of suitable markers of bone remodeling, such as serum alkaline phosphatase or urinary hydroxyproline or deoxypyridinoline. The dose may be reduced after the condition of the patient has improved.

Hypercalcemia of malignancy:

The recommended starting dose is 100 IU every 6 to 8 hours by subcutaneous or intramuscular injection. In addition, salmon calcitonin could be administered by intravenous injection after previous rehydration.
If the response is not satisfactory after one or two days, the dose may be increased to a maximum of 400 IU every 6 to 8 hours. In severe or emergency cases, intravenous infusion with up to 10 IU/kg body weight in 500ml 0.9% w/v sodium chloride solution may be administered over a period of at least 6 hours.

Use in elderly, hepatic and renal impairment patients
Experience with the use of calcitonin in the elderly has shown no evidence of reduced tolerability or altered dosage requirements. The same applies to patients with altered hepatic function. The metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Calcitonin is also contraindicated in patients with hypocalcaemia.

4.4 Special warnings and special precautions for use

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 calcitonin. Such reactions should be differentiated from generalised or local flushing, which are common non-allergic effects of calcitonin (see 4.8). Skin testing should be conducted in patients with suspected sensitivity to calcitonin prior to their treatment with calcitonin.

4.5 Interaction with other medicinal products and other forms of interaction

Serum calcium levels may be transiently decreased to below normal levels following administration of calcitonin, notably upon initiation of therapy in patients with abnormally high rates of bone turnover. This effect is diminished as osteoclastic activity is reduced. However, care should be exercised in patients receiving concurrent treatment with cardiac glycosides or calcium channel blocking agents. Dosages of these drugs may require adjustment in view of the fact that their effects may be modified by changes in cellular electrolyte concentrations.

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

4.6 Pregnancy and lactation

Calcitonin has not been studied in pregnant women. Calcitonin should be used during pregnancy only if treatment is considered absolutely essential by the physician.
It is not known if the substance is excreted in human milk. In animals, salmon calcitonin has been shown to decrease lactation and to be excreted in milk (see 5.3). Therefore, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequency categories:
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 disorder:
Very common: Nausea with or without vomiting is noted in approximately 10% of patients treated with calcitonin. The effect is more evident on initiation of therapy and tends to decrease or disappear with continued administration or a reduction in dose. An antiemetic may be administered, if required. Nausea/vomiting are less frequent when the injection is done in the evening and after meals.
Uncommon: diarrhoea

Vascular disorders:
Very common:
Skin flushes (facial or upper body). These are not allergic reactions but are due to a pharmacological effect, and are usually observed 10 to 20 minutes after administration.

General disorders and administration site conditions
Uncommon: local inflammatory reactions at the site of subcutaneous or intramuscular injection

Skin and subcutaneous tissue disorders
Uncommon: skin rash

Nervous system disorders:
Uncommon: metallic taste in the mouth; dizziness

Renal and urinary disorders:
Uncommon: diuresis

Metabolic and nutrition disorders:
Rare :In case of patients with high bone remodelling (Paget's disease and young patients) a transient decrease of calcemia may occur between the 4^{th} and the 6^{th} hour after administration, usually asymptomatic

Investigations:
Rare: Neutralising 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.

Immune system disorders:
Very rare: serious allergic-type reactions, such as bronchospasm, swelling of the tongue and throat, and in isolated cases, anaphylaxis.

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 I.U.) of injectable salmon calcitonin have been administered without adverse reactions, other than nausea and vomiting, and exacerbation of pharmacological effects.
Should symptoms of overdose appear, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

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

The pharmacological properties of the synthetic and recombinant peptides have been demonstrated to be qualitatively and quantitatively equivalent.

5.1 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. In pharmacological studies, calcitonin has been shown to have analgesic activity in animal models.

Calcitonin markedly reduces bone turnover in conditions with an increased rate of bone resorption such as Paget ‘s disease and acute bone loss due to sudden immobilisation.
The absence of mineralisation defect with calcitonin has been demonstrated by bone histomorphometric studies both in man and in animals.
Decreases in bone resorption as judged by a reduction in urinary hydroxyproline and deoxypyridinoline are observed following calcitonin treatment in both normal volunteers and patients with bone-related disorders, including Paget’s disease and osteoporosis.

The calcium-lowering effect of calcitonin is caused both by a decrease in the efflux of calcium from the bone to the ECF and inhibition of renal tubular reabsorption of calcium.

5.2 Pharmacokinetic properties

General characteristics of the active substance
Salmon calcitonin is rapidly absorbed and eliminated.
Peak plasma concentrations are attained within the first hour of administration.
Animal studies have shown that calcitonin is primarily metabolised via proteolysis in the kidney following parenteral administration. The metabolites lack the specific biological activity of calcitonin.
Bioavailability following subcutaneous and intramuscular injection in humans is high and similar for the two routes of administration (71% and 66%, respectively).
Calcitonin has short absorption and elimination half-lives of 10-15 minutes and 50-80 minutes, respectively. Salmon calcitonin is primarily and almost exclusively degraded in the kidneys, forming pharmacologically inactive fragments of the molecule. Therefore, the metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known.
Plasma protein binding is 30 to 40%.

Characteristics in patients
There is a relationship between the subcutaneous dose of calcitonin and peak plasma concentrations. Following parenteral administration of 100 I.U. calcitonin, peak plasma concentration lies between about 200 and 400 pg/ml. Higher blood levels may be associated with increased incidence of nausea and vomiting.

5.3 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. Calcitonin is secreted into the milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Instructions for use and handling <and disposal>

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

INJECTABLE HUMAN CALCITONIN

1. NAME OF THE MEDICINAL PRODUCT

{(Trade) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Company- specific.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (company specific).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calcitonin is indicated for:

- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
- Paget's disease
- Hypercalcemia of malignancy

4.2 Posology and method of administration

For subcutaneous, intramuscular or intravenous (product specific) use in individuals aged 18 years or more.

Human calcitonin may be administered at bedtime to reduce the incidence of nausea or vomiting which may occur, especially at the initiation of therapy.

Prevention of acute bone loss:
The recommended dosage is 0,5 mg. daily or 0,25 mg. twice daily for 2 to 4 weeks, administered subcutaneously or intramuscularly. The dose may be reduced to 0,25 mg. daily at the start of remobilisation. The treatment should be maintained until patients are fully mobilized.

Paget's disease:
The dosage should be individually adapted to the patient's requirements. As a rule, it is recommended that treatment be initiated with a dose of 0.5 mg injected subcutaneously or intramuscularly once a day, for several weeks. Depending on the patient's response, this dosage may subsequently be raised to 0.5 mg twice a day or reduced for maintenance therapy, e.g. to 0.25 mg daily or to 0.5 mg 2-3 times a week.
As an aid in evaluating the efficacy of human calcitonin determination of serum alkaline phosphatase and urinary hydroxyproline excretion should be performed prior to initiation of therapy, during the first three months, and at intervals (approximately 3-6 months) if treatment needs to be continued. Adjustments in dose should be guided by clinical and radiological evidence, as well as changes in serum alkaline phosphatase and urinary hydroxyproline excretion.
The treatment should be continued for 6 months or more. If withdrawal of therapy is followed by a renewed exacerbation (marked by an increase in the biochemical parameters and recurrence of symptoms or radiological signs), the treatment should be resumed.

Hypercalcemia of malignancy:
For acute treatment 0.5 mg of human calcitonin is administered every 6 hours by slow intravenous injection, after previous rehydration.
Serum calcium should be measured every 6 hours. Twelve hours after serum calcium levels have returned to normal, treatment can be discontinued.
The therapeutic effect is usually obtained within the first 24 hours of treatment. In patients with incomplete results, increasing the dosage does not result in a further reduction of serum calcium. A new rise in serum calcium is observed a few days after treatment is discontinued.

Use in elderly, hepatic and renal impairment patients
Experience with the use of calcitonin in the elderly has shown no evidence of reduced tolerability or altered dosage requirements. The same applies to patients with altered hepatic function. The metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Calcitonin is also contraindicated in patients with hypocalcaemia.

4.4 Special warnings and special precautions for use

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 calcitonin. Such reactions should be differentiated from generalised or local flushing, which are common non-allergic effects of calcitonin (see 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Serum calcium levels may be transiently decreased to below normal levels following administration of calcitonin, notably upon initiation of therapy in patients with abnormally high rates of bone turnover. This effect is diminished as osteoclastic activity is reduced. However, care should be exercised in patients receiving concurrent treatment with cardiac glycosides or calcium channel blocking agents. Dosages of these drugs may require adjustment in view of the fact that their effects may be modified by changes in cellular electrolyte concentrations.

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

4.6 Pregnancy and lactation

Calcitonin has not been studied in pregnant women. There is no evidence from animal work that human calcitonin is free from either teratogenic potential or other adverse effects, on the embryo and/or the foetus. Calcitonin should be used during pregnancy only if treatment is considered absolutely essential by the physician.
It is not known if the substance is excreted in human milk. Therefore, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequency categories:
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 disorder:
Very common: Nausea with or without vomiting is noted in approximately 10% of patients treated with calcitonin. The effect is more evident on initiation of therapy and tends to decrease or disappear with continued administration or a reduction in dose. An antiemetic may be administered, if required. Nausea/vomiting are less frequent when the injection is done in the evening and after meals.
Uncommon: diarrhoea

Vascular disorders:
Very common:
Skin flushes (facial or upper body). These are not allergic reactions but are due to a pharmacological effect, and are usually observed 10 to 20 minutes after administration.

General disorders and administration site conditions
Uncommon: local inflammatory reactions at the site of subcutaneous or intramuscular injection

Skin and subcutaneous tissue disorders
Uncommon: skin rash

Nervous system disorders:
Uncommon: metallic taste in the mouth; dizziness

Renal and urinary disorders:
Uncommon: diuresis

Metabolic and nutrition disorders:
Rare :In case of patients with high bone remodelling (Paget's disease and young patients) a transient decrease of calcemia may occur between the 4^{th} and the 6^{th} hour after administration, usually asymptomatic

Immune system disorders:
Very rare: serious allergic-type reactions, such as bronchospasm, swelling of the tongue and throat, and in isolated cases, anaphylaxis.

Investigations:
The risk of developing neutralising antibodies, even in the case of long-term therapy, is low because the amino acid sequence is identical to that of endogenous human calcitonin.

4.9 Overdose

Nausea, vomiting, flushing and dizziness are known to be dose dependent when calcitonin is administered parenterally. However, no cases of overdosage have been reported.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiparathyroid hormone, ATC code: H05BA03 (calcitonin, human synthetic).

5.1 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, human calcitonin decreases bone resorption. In pharmacological studies, calcitonin has been shown to have analgesic activity in animal models.

Calcitonin markedly reduces bone turnover in conditions with an increased rate of bone resorption such as Paget ‘s disease disease and acute bone loss due to sudden immobilisation.
The absence of mineralisation defect with calcitonin has been demonstrated by bone histomorphometric studies both in man and in animals.
Decreases in bone resorption as judged by a reduction in urinary hydroxyproline and deoxypyridinoline are observed following calcitonin treatment in both normal volunteers and patients with bone-related disorders, including Paget’s disease and osteoporosis.

The calcium-lowering effect of calcitonin is caused both by a decrease in the efflux of calcium from the bone to the ECF and inhibition of renal tubular reabsorption of calcium.

5.2 Pharmacokinetic properties

Following single intramuscular and subcutaneous doses of synthetic human calcitonin, systemic uptake of exogenous calcitonin is rapid; mean peak serum levels are attained within 20 minutes after both routes. Peak serum concentrations average 4 ng/ml after i.m. and 3-5 ng/ml after subcutaneous injection of 0.5 mg doses. The i.m. and s.c. doses (0.5 mg) are bioequivalent in terms of serum AUCs. Peak concentrations and AUC values of exogenous calcitonin in serum increases proportionally with subcutaneous doses of 0.25 mg and 0.50 mg of synthetic human calcitonin. Exogenous calcitonin is rapidly eliminated from the circulation, mean apparent half-lives being 1.1 hours after i.m. and 1.1 - 1.4 hours after subcutaneous. administration.
Under steady-state conditions, a mean metabolic clearance of about 600 ml/min was maintained during constant intravenous infusion of human calcitonin. After single intravenous injection, a mean value of 720 ml/min was observed. The apparent volume of distribution averages 11.4 l, which corresponds to 0.15 l/kg, calculated for a body weight of 75 kg.
Following single intravenous injection of synthetic human I-calcitonin, 95% of the dose is excreted in the 48-hour urine; 2.4% of the dose is accounted for by unchanged I-calcitonin and the rest by iodinated degradation products.
Human calcitonin is primarily and almost exclusively degraded in the kidneys, forming pharmacologically inactive fragments of the molecule. Therefore, the metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known.

5.3 Preclinical safety data

Human calcitonin is not directly mutagenic in bacterial or eukaryotic systems *in vitro* or in mammalian tests *in vivo*. It did give positive results in bacterial mutagenicity tests in the presence of a metabolic activating system. These findings are most probably a consequence of the oxidation of amino acids released by hydrolysis or a reflection of an alteration of bacterial growth by hydrolysis products and are not considered an indication of human calcitonin mutagenicity.
No long-term carcinogenicity studies have been conducted with human calcitonin.
Animal reproduction studies have not been performed with human calcitonin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Instructions for use and handling <and disposal>

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

INJECTABLE ELCATONIN

1. NAME OF THE MEDICINAL PRODUCT

{(Trade) name of product <strength> <pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Elcatonin is an analog of eel calcitonin

Company- specific.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Elcatonin is indicated for:

- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
- Paget's disease
- Hypercalcemia of malignancy

4.2 Posology and method of administration

For intramuscular or intravenous (product specific) use in individuals aged 18 years or more.

Elcatonin may be administered at bedtime to reduce the incidence of nausea or vomiting which may occur, especially at the initiation of therapy.

Prevention of acute bone loss:
The recommended dosage is 40 I.U. daily for 2 to 4 weeks, administered intramuscularly. The dose may be reduced to 40 I.U. every other day at the start of remobilisation. The treatment should be maintained until patients are fully mobilized.

Paget's disease:
The recommended dosage is 40 IU per day administered intramuscularly, however, a minimum dosage regimen of 40 IU three times a week has achieved clinical and biochemical improvement. Dosage is to be adjusted to the individual patient's needs. The effect of calcitonin may be monitored by measurement of suitable markers of bone remodeling such as serum alkaline phosphatase or urinary hydroxyproline or deoxypyridinoline. The duration of treatment depends on the indication for treatment and the patient´s response, but should be a minimum of 3 months. The dose may be reduced after the condition of the patient has improved.

Hypercalcemia of malignancy:
The recommended starting dose is 40 IU every 6 to 8 hours by intramuscular injection. In addition, elcatonin could be administered by intravenous injection after previous rehydration.

If the response is not satisfactory after one or two days, the dose may be increased to a maximum of 80 IU every 6 to 8 hours.

Use in elderly, hepatic and renal impairment patients
Experience with the use of calcitonin in the elderly has shown no evidence of reduced tolerability or altered dosage requirements. The same applies to patients with altered hepatic function. The metabolic clearance is much lower in patients with end-stage renal failure than in healthy subjects. However, the clinical relevance of this finding is not known (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Calcitonin is also contraindicated in patients with hypocalcaemia.

4.4 Special warnings and special precautions for use

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 calcitonin. Such reactions should be differentiated from generalised or local flushing, which are common non-allergic effects of calcitonin (see 4.8). Skin testing should be conducted in patients with suspected sensitivity to calcitonin prior to their treatment with elcatonin.

4.5 Interaction with other medicinal products and other forms of interaction

Serum calcium levels may be transiently decreased to below normal levels following administration of elcatonin, notably upon initiation of therapy in patients with abnormally high rates of bone turnover. This effect is diminished as osteoclastic activity is reduced. However, care should be exercised in patients receiving concurrent treatment with cardiac glycosides or calcium channel blocking agents. Dosages of these drugs may require adjustment in view of the fact that their effects may be modified by changes in cellular electrolyte concentrations.

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

4.6 Pregnancy and lactation

Elcatonin has not been studied in pregnant women. Elcatonin should be used during pregnancy only if treatment is considered absolutely essential by the physician.
It is not known if the substance is excreted in human milk. Therefore, breast-feeding is not recommended during treatment.

4.7 Effects on ability to drive and use machines

No data exist on the effects of injectable elcatonin on the ability to drive and use machines. Injectable elcatonin may cause transient dizzines (see 4.8. Undesirable effects) which may impair the reaction of the patient. Patients must therefore be warned that transient dizzines may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

The undesirable effects observed during treatment with elcatonin are similar to those reported after administration of salmon calcitonin.

Frequency categories:
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 disorder:

Very common: Nausea with or without vomiting is noted in approximately 10% of patients treated with calcitonin. The effect is more evident on initiation of therapy and tends to decrease or disappear with continued administration or a reduction in dose. An antiemetic may be administered, if required. Nausea/vomiting are less frequent when the injection is done in the evening and after meals.
Uncommon: diarrhoea

Vascular disorders:
Very common:
Skin flushes (facial or upper body). These are not allergic reactions but are due to a pharmacological effect, and are usually observed 10 to 20 minutes after administration.

General disorders and administration site conditions
Uncommon: local inflammatory reactions at the site of subcutaneous or intramuscular injection

Skin and subcutaneous tissue disorders
Uncommon: skin rash

Nervous system disorders:
Uncommon: metallic taste in the mouth; dizziness

Renal and urinary disorders:
Uncommon: diuresis

Metabolic and nutrition disorders:
Rare :In case of patients with high bone remodelling (Paget's disease and young patients) a transient decrease of calcemia may occur between the 4^{th} and the 6^{th} hour after administration, usually asymptomatic

Investigations:
Rare: Neutralising 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.

Immune system disorders:
Very rare: serious allergic-type reactions, such as bronchospasm, swelling of the tongue and throat, and in isolated cases, anaphylaxis.

4.9 Overdose

Nausea, vomiting, flushing and dizziness are known to be dose dependent when calcitonin is administered parenterally. Should symptoms of overdose appear, treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiparathyroid hormone, ATC code: H05B A04 (elcatonin).

The pharmacological properties of the synthetic and recombinant peptides have been demonstrated to be qualitatively and quantitatively equivalent.

5.1 Pharmacodynamic properties

Calcitoinin is a calciotropic hormone, which inhibits bone resorption by a direct action on osteoclasts. By inhibiting osteoclast activity via its specific receptors, calcitoinin decreases bone resorption.
In pharmacological studies, calcitonin has been shown to have analgesic activity in animal models.

Calcitoinin markedly reduces bone turnover in conditions with an increased rate of bone resorption such as Paget ‘s disease and acute bone loss due to sudden immobilisation.
The absence of mineralisation defect with calcitonin has been demonstrated by bone histomorphometric studies both in man and in animals.
Decreases in bone resorption as judged by a reduction in urinary hydroxyproline and deoxypyridinoline are observed following calcitoinin treatment in both normal volunteers and patients with bone-related disorders, including Paget’s disease and osteoporosis.

The calcium-lowering effect of calcitoinin is caused both by a decrease in the efflux of calcium from the bone to the ECF and inhibition of renal tubular reabsorption of calcium.

5.2 Pharmacokinetic properties

General characteristics of the active substance
Elcatonin is rapidly absorbed and eliminated.
Peak plasma concentrations are attained within the first hour of administration.
Animal studies have shown that elcatonin is primarily metabolised via proteolysis in the kidney following parenteral administration. The metabolites lack the specific biological activity of elcatonin.
Bioavailability following intramuscular injection in humans is high and similar to other calcitonins
Elcatonin has short absorption and elimination half-lives of approx 4 hours. Entire elcatonin and its metabolites are excreted by the renal excretion (73%) and the biliar excretion 7%.

5.3 Preclinical safety data

Conventional long-term toxicity, reproduction and mutagenicity, studies have been performed in laboratory animals. Elcatonin is devoid of embryotoxic, teratogenic and mutagenic potential.

Elcatonin does not cross the placental barrier.

In lactating animals given calcitonin, suppression of milk production has been observed. Calcitonin is secreted into the milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Instructions for use and handling <and disposal>

7. MARKETING AUTHORISATION HOLDER

{Name and address}

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

INTRANASAL SALMON CALCITONIN

1. Name of the medicinal product

Company-specific.

2. Qualitative and quantitative composition

Company-specific.
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 I.U. 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).

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 examinations 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.

The excipient benzalkonium chloride is an irritant and may cause irritation of the nasal mucosa (company-specific).

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

No drug interactions with intranasal salmon calcitonin have been reported.

4.6. Use during 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 pruritis

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 I.U.) 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 I.U. as a single dose and up to 800 I.U. 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 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 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 I.U. 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 I.U. 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 I.U. 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 I.U. 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. Daily intranasal administration of high doses of a calcitonin formulation containing 0.01% benzalkonium chloride for 26 weeks was well tolerated by monkeys.
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

6.2. INCOMPATIBILITIES

6.3. SHELF LIFE

6.4. SPECIAL PRECAUTIONS FOR STORAGE

6.5. NATURE AND CONTENT OF CONTAINER

6.6. INSTRUCTIONS FOR USE/HANDLING

7. Marketing authorisation holder

8. Marketing authorisation number

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text

INTRANASAL ELCATONIN

1. Name of the medicinal product

Company-specific.

2. Qualitative and quantitative composition

Elcatonin is an analog of eel calcitonin
Company-specific.
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 80 I.U. 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).

Use in elderly patients, in hepatic impairment and in renal insufficiency
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 examinations 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 elcatonin have been reported.

4.6. Use during 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 however shown no embryotoxic and teratogenic potential. It appears that elcatonin does not cross the placental barrier in animals.
It is not known whether elcatonin is excreted into human breast milk. Therefore, breast-feeding is not recommended during treatment.

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

The undesirable effects observed during treatment with elcatonin are similar to dose reported after administration of salmon calcitonin
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 pruritis
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. However, no cases of overdosage have been reported. If symptoms of overdose appear, treatment is to be symptomatic.

5. Pharmacological properties

Pharmacotherapeutic group: antiparathyroid hormone, ATC code: H05BA04 (elcatonin).

5.1. 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, elcatonin 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 using intranasal salmon calcitonin in postmenopausal women (PROOF study), administration of 200IU 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 I.U. 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 I.U. group. A reduction in hip fractures has not been demonstrated.

The recommended dosage of elcatonin for the treatment of established post-menopausal osteoporosis is 80 I.U. once a day. Higher dosages were not more effective.

5.2. Pharmacokinetic properties

Pharmacokinetic parameters of intranasally administered elcatonin 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 40 I.U. dose relative to parenteral administration is between 45 and 53 %. Intranasal calcitonin is absorbed rapidly through the nasal mucosa and peak plasma concentrations are attained within the first hour of administration. 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 elcatonin since these are not directly predictive of the therapeutic response. Hence, calcitonin activity is to be evaluated by using clinical parameters of efficacy.

5.3. Preclinical safety data

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

Elcatonin is devoid of embryotoxic, teratogenic and mutagenic potential. Daily intranasal administration of high doses of elcatonin formulation containing 2% of ammonium glycyrrhizinate for 12 weeks was well tolerated by .rats and dogs.

Elcatonin 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

6.2. Incompatibilities

6.3. Shelf life

6.4. Special precautions for storage

6.5. Nature and content of container

6.6. Instructions for use/handling

7. Marketing authorisation holder

8. Marketing authorisation number

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text