

**Rapporteur's  
Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**SALMON CALCITONIN**

**List of Product names and MAHs:**

Calsynar (Nasal spray and solution for injection)

MAH: Aventis Pharma

Calcitonin armour (Solution for injection)

MAH: Rorer Pharmaceuticals

Tonocalcin (Solution for injection)

MAH: Alfa Biotech, Alfa Wasserman

<b>Rapporteur:</b>	UK – Shirley Norton
<b>Start of the procedure (day 0):</b>	1 December 2008
<b>Date of this report:</b>	9 February 2009
<b>Deadline for Rapporteur's AR:</b>	9 February 2009
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<b>Finalisation procedure (day 90):</b>	<b>27 March 2009</b>

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	<ol style="list-style-type: none"> <li>1.Calsynar</li> <li>2.Calcitonin armour</li> <li>3.Tonocalcin</li> </ol>
INN (or common name) of the active substance(s):	Salmon Calcitonin
MAH:	<ol style="list-style-type: none"> <li>1.Sanofi Aventis Pharma</li> <li>2. Rorer Pharmaceuticals</li> <li>3. Alfa Biotech, Alfa Wasserman</li> </ol>
Currently approved Indication(s)	<p>Established post-menopausal osteoporosis to reduce the risk of vertebral fractures.</p> <p>Prevention of acute bone loss due to sudden immobilisation.</p> <p>Paget's disease</p> <p>Hypercalcaemia of malignancy.</p>
Pharmaco-therapeutic group (ATC Code):	Drugs affecting bone metabolism
Pharmaceutical form(s) and strength(s):	<p>Nasal Spray 200 IU/Spray</p> <p>Solution for Injection 50, 100, 400 IU/ml</p>
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## EXECUTIVE SUMMARY

Calcitonin is a synthetic polypeptide hormone of 32 amino-acids and belongs to the pharmacotherapeutic group of antiparathyroid hormones. Calcitonin of salmon origin has the same composition as human calcitonin.

Calcitonin's primary action is on the bone. The major effect of calcitonin is to inhibit bone resorption, principally through decreasing the numbers and the activity of osteoclasts. Additionally, it is thought to inhibit tubular reabsorption of calcium at the kidneys, leading to increased rates of loss in urine, having a principal role in the calcium homeostasis in conjunction with parathyroid hormone and 1,25 dihydroxyvitamin D [1,25-(OH)<sub>2</sub>D].

Calcitonin salmon (sCT) is used in the following indications:

- Via intranasal route: treatment of established post-menopausal osteoporosis to reduce the risk of vertebral fractures.
- Via parenteral route: indicated for prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, for Paget's disease and for hypercalcaemia of malignancy.

There is no approved paediatric posology for calcitonin containing products in the approved SmPC and use in children is not recommended.

In the literature, sCT has been used for the treatment of paediatric conditions associated with osteoporosis, including osteogenesis imperfecta and steroid induced osteoporosis in renal transplant and juvenile arthritis patients.

The data package submitted by one MAH under article 45 of the Paediatric Regulation comprises 1 preclinical juvenile animal study and 3 clinical studies conducted in children and adolescents, together with nonclinical and clinical overview reports. These were all published studies. The MAH also summarised the spontaneous suspected adverse event reports which have been received by the Company relating to use in children.

The MAH's view is that no change to the European SmPC texts is necessary as a consequence of the data presented.

Further 6 references have also been listed by a second MAH under article 45 of the Paediatric Regulation and have been included in the assessment. All of these references were published articles of clinical studies involving paediatric patients.

## RECOMMENDATION

Based on the review of the presented paediatric data on pharmacokinetics, safety and efficacy, the rapporteur considers that:

The presented data is insufficient to support a variation application to extend the use of salmon calcitonin to the paediatric population.

For consistency between salmon calcitonin containing products across the EU, it is recommended that the SmPC contains the following statement:

- 4.2 Posology and method of administration  
Use in children:

There is insufficient evidence to support the use of salmon calcitonin in conditions associated with paediatric osteoporosis. Use of salmon calcitonin in children 0 to 18 years is therefore not recommended.

## I. INTRODUCTION

On 6 October 2008, the MAH submitted 4 completed paediatric studies for calcitonin, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

Short critical expert nonclinical and clinical overviews have also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for medicinal products with the active substance salmon calcitonin and that there is no consequential regulatory action.

In addition a list of 6 references was submitted from a different MAH for calcitonin, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

## II. SCIENTIFIC DISCUSSION

### II.1 Information on the pharmaceutical formulation used in the clinical studies

Salmon calcitonin is currently globally marketed in parenteral formulations (50, 100, 400 IU/mL) for subcutaneous or intramuscular injection and for dilution as an intravenous infusion and in intranasal formulations (100 and 200 IU/spray). Different pharmaceutical forms have been used in the submitted clinical studies with dose adjustments by the clinical researchers, as there are not currently individual paediatric formulations available.

### II.2 Non-clinical aspects

#### 1. Introduction

All non-clinical studies performed and reported by the first MAH on calcitonin salmon were included in the original submissions to National Competent Authorities together with the non-clinical expert reports. A literature review conducted by the MAH based on several databases (Medline, Embase and Caplus) showed one article involving juvenile animals, which was considered relevant for the paediatric use of calcitonin.

The MAH submitted the following published article:

De Vernejoul MC, Pointillart A, Bourdeau A, Morieux C, Modrowski D, Miravet L , Caulin F.  
**Effect of calcitonin administration on young pig trabecular bone remodeling.**  
Bone 1990;11:29-33

#### Assessor's Comment

The MAH has not provided detailed information regarding the methods used for the review of literature.

#### 2. Non Clinical overview

The provided report is a very useful summary of the available data. In respect of the paediatric population the report concludes that:

*“In conclusion, the review of the recent literature did not provide any new relevant information for the paediatric target population.”*

### 3. Non clinical study

#### ➤ Description

Study of bone remodelling in 10-week-old pigs treated for 60 days with different continuous or intermittent treatment schedules of porcine calcitonin.

#### ➤ Methods

##### Study design

38 10-week-old pigs randomly divided into 5 groups. The choice of the investigated spaces and age was based on the fact that bone remodelling is rapid in growing pigs and in 2 months, 3 remodelling periods can be observed.

Groups	A	C1	C2	C3	C4
Number of pigs	10	8	8	8	4
Dose and route of administration	No treatment (=control)	4 IU/kg, IM	4 IU/kg, IM	4 IU/kg, IM	Minipumps SC
Treatment schedule	-	1 injection every day	1 injection/day with one day out of every fourth day	1 injection/day with 5 consecutive days out of 20 days	Continuous
Cumulative dose	-	9292±246 IU	2426±210 IU	2039±190 IU	7545±271 IU

IM: Intramuscularly; SC: subcutaneously

#### ➤ Results

The results were evaluated by histomorphometry after double tetracycline labelling on iliac trabecular bone. The measurements did not show any significant changes between the treatments for bone volume, trabecular thickness, osteoclastic surfaces, osteoclast number and interstitial bone thickness (an indirect estimate of the amount of resorbed bone). Reversal and resorption surfaces were decreased in groups C2, C3 and C4. The extent of osteoblast and mineralizing surfaces was increased in groups C2, C3 and C4. Mineral apposition rate was not modified in any group. Bone formation rate was increased in groups C2 and C4. Wall thickness (assessment of the amount of bone formed) was not modified by treatment.

Plasma calcium, plasma phosphate, alkaline phosphatase, plasma parathyroid hormone and 25-dihydroxyvitamin D (25-OHD) levels were unchanged by the different calcitonin schedules. By contrast, plasma 1,25 dihydroxyvitamin D [1,25-(OH)<sub>2</sub>D] levels were markedly increased in group C2 and C4 as compared to controls.

#### ➤ Conclusions

In conclusion, 2 month calcitonin treatment did not decrease the amount of bone resorbed in growing pigs. Continuous calcitonin infusion and intermittent calcitonin administration induced an increase in the extent of active bone formation which might be in part dependent on an increased production of 1,25-(OH)<sub>2</sub>D.

#### ➤ Discussion on non clinical aspects

The authors of this article comment that the failure to decrease bone resorption in these animal models was, perhaps, unexpected as the effect of calcitonin on osteoclasts is well documented. Among the reasons that are implicated are insufficient duration of the experiment or lack of sensitivity to the methods used for bone measurements. The production of calcitonin antibodies was excluded as homologous calcitonin was used.

### Assessor's Comment

This is a very old study that fails to demonstrate the known anti-resorptive effect of calcitonin. The choice of the juvenile animal model was for design reasons of the experiment. The selection of the dosing regimes was not analysed and that could be another reason of the lack of effect. The assessor is of the opinion that the data provided from this study do not provide any new relevant information for the paediatric population.

## II.3 Clinical aspects

### 1. Introduction

The MAH identified in the literature research 3 studies (study E, study F, study G as listed below) performed with calcitonin in the treatment or prevention of osteoporosis in children. Additionally 4 papers were provided to support the rationale for the indication of paediatric interest.

The MAH submitted the following 7 published articles:

- A. Stallings VA. **Calcium and bone health in children: a review.** Am J Ther. 1997;4(7-8):259-73
- B. Von Scheven E. **Pediatric bone density and fracture.** Curr Osteopor Rep. 2007;5(3):128-34
- C. Kalifa G, and Ferey S. [**Loss in bone mineral density in children**]. Encyclopédie Médico - Chirurgicale 2003;31-150-A-10
- D. Monier-Faugere MC, Mawad H, Friedler RM et al. **High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation.** J Am Soc Nephrol 2000;11:1093-9
- E. El-Husseini AA, El-Agroudy AE, El-Sayed MF et al. **Treatment of osteopenia and osteoporosis in renal transplant children and adolescents.** Pediatr Transplant 2004;8(4):357-51
- F. Siamopoulou A, Challa A, Kapoglou P et al. **Effects of intranasal salmon calcitonin in juvenile idiopathic arthritis: an observational study.** Calcif Tissue Int. 2001;69(1):25-30
- G. Mallet E, Lefort J and Caulin F. **Prevention of trabecular bone loss in children's femoral fracture: effects of treatment with calcitonin.** Clinical Science. Medical Research Society Meeting at the London Hospital and Medical College 1986;70 (suppl 13):82

### **Assessor's Comment**

The MAH has not provided detailed information regarding the methods used for the review of literature in a systematic way. There is an extended bibliography on paediatric osteoporosis as the issue remains highly controversial. The MAH's comment that "...peak bone mass obtained during childhood and adolescent growth, is one of the major determinants for the risk of developing osteoporosis and fracture in adulthood. Any condition that interferes with normal bone mineral accrual during childhood has the potential to reduce peak bone mass and subsequently increase future risk for fracture" is still debatable as no clear evidence exists to support the long term implications of paediatric osteoporosis.

## **2. Clinical overview**

The provided report is a very useful summary of the available data. In respect of the paediatric population the report concludes that:

*"Although calcitonin salmon pharmaceutical forms, solution for injection and solution for nasal spray, is suitable for a paediatric use, the clinical efficacy in children has not been sufficiently documented. Data on the treatment of osteoporosis in children with calcitonin are very limited. However they seem to show a beneficial effect in patients at high risk to develop severe osteoporosis or worsen existing osteoporosis due to their condition or their treatment. Furthermore, no risk for the treatment of osteoporosis with calcitonin has been identified in the paediatric population.*

*...(the MAH) is of the opinion that the available data do not allow to change the currently approved labelling."*

## **3. Clinical studies**

### ***TREATMENT OF OSTEOPENIA AND OSTEOPOROSIS IN RENAL TRANSPLANT CHILDREN AND ADOLESCENTS.***

***El-Husseini et al, 2004***

#### **➤ Methods**

- **Objective**

Investigate the efficacy and safety of different treatment options on bone loss in young renal transplant recipients.

- **Study design**

Prospective randomized placebo-controlled study

- **Study population /Sample size**

From a cohort of patients who underwent renal transplantation at age 17 years or less and had confirmed osteopenia (T-score = -1 and -2.5) or osteoporosis (T-score ≤ -2.5) measured by DEXA, 60 patients were blindly randomized into 4 groups, consisting 15 patients each. There were no statistically significant differences between all groups regarding age, sex, duration of chronic renal failure, post transplant periods.

- Treatments

These treatment groups were:

- 1) Control group
- 2) Oral alfacalcidol group (0.25 µg/day)
- 3) Oral alendronate (5 mg/day),
- 4) Nasal spray calcitonin (200 IU/day).

All patients received calcium (500 mg) daily supplementation as well as corticosteroid and cyclosporine A, as part of their immunosuppressive regimen. No differences were detected between the groups with respect to the mean cumulative steroid dose at baseline and after treatment.

- Outcomes/endpoints

Parameters of bone turnover, calcium metabolism and DEXA were measured before and after 12 months of treatment duration. Lumbar spine (LS) and total body (TB) BMD (T-score) using between-groups comparisons. Serum creatinine, calcium, phosphorus, albumin, alkaline phosphatase and intact PTH were measured. To assess bone turnover, serum osteocalcin as a marker of bone formation and urine deoxypyridinoline as a marker of bone resorption were measured.

- Statistical Methods

The results were presented as means with s.d. for normally distributed data or medians with percentiles for non-normal distributions. Normally distributed continuous variables were compared using t-tests. Categorical variables were compared using chi-square tests. Changes over time were analysed with ANOVA for repeated measures with post hoc t-tests. All statistical tests were two-sided, with a p-value less than 0.05 taken to indicate statistical significance.

## ➤ Results

- Efficacy results

Biochemistry: There were no statistically significant differences between the groups in any of the parameters measured pre and post treatment.

DEXA: despite the BMD in the whole body and at the lumbar spine being comparable in all groups at baseline, after 12 months of treatment the control group showed significant bone loss, while the treatment groups showed significant improvement. Further adjustments (two-way ANOVA) with repeated measures showed that patients who received alfacalcidol had a better improvement of BMD.

- Safety results

After 1 year treatment all patients had a functional graft. The following adverse events were reported:

Group 1 control – one subject had a traumatic humerus fracture

Group 3 treated with alendronate - one subject with transient hypocalcaemia

Group 4 treated with calcitonin - one subject with transient hypocalcaemia

**Assessor's Comment**

The sample size is relatively small but renal transplant patients represent a limited cohort.

The T-score, which represents the standardized deviation from the healthy adult mean, should be reserved for patients who have ceased growing, while the age- and gender-matched Z-score is currently preferred for paediatric patients.

According to the authors' conclusion, the study confirmed the value of alfacalcidol and antiresorptive agents in the treatment of established bone loss in young renal transplant recipients, even after the period of most rapid bone loss has already occurred.

This study emphasises on within group comparison, before and after treatment. However it appears that the comparison between the groups showed a statistically significant difference, but this information is not clearly provided in the paper. All treatments were well tolerated and safe. Fracture of a long bone associated with osteoporosis was only seen in the placebo group.

***EFFECT OF INTRANASAL SALMON CALCITONIN IN JUVENILE IDIOPATHIC ARTHRITIS: AN OBSERVATIONAL STUDY.***

*Siamopoulou et al, 2001*

**➤ Methods**

- Objective  
Review changes in bone mineral density and biochemical markers of bone turnover in children with severe JIA during a 3 year therapy with intranasally administered salmon calcitonin and oral calcium.
- Study design  
Observational prospective study with controls for the bone biochemical markers
- Study population /Sample size  
10 children with severe JIA treated with prednisolone (before or during the study) + NSAID, MTX, gold injections +/- cyclosporine A, who had no vertebral fractures, were included in the study. 20 health age and gender matching children were used as controls of the bone biochemical markers.
- Treatments  
Intranasal salmon calcitonin (100IU/day 2months on and 2 months off for 1 year and 200IU/day for 2 years) and oral calcium (500mg/day).
- Outcomes/endpoints  
BMD and BMD<sub>vol</sub> are measured annually with dual photon absorptiometer at the lumbar spine. Biochemical markers included serum 25OHD<sub>3</sub>, 24,25(OH)<sub>2</sub>D<sub>3</sub>, 1,25(OH)<sub>2</sub>D<sub>3</sub>, intact PTH, osteocalcin, Ca and alkaline phosphatase. 24hour urine Ca, hydroxyproline and pyridinolines were also measured.
- Statistical Methods  
There is no mentioning of the statistic analysis used and mean values are used.

## ➤ Results

- Efficacy results

Bone Density: the mean values of BMD demonstrated a small rise during treatment (BMD 7.2-9.5%/year, BMD<sub>vol</sub> 2.0-6.0%/year), however the individual values only showed increase in 5 out of 10 patients, remained unchanged and in one case there was deterioration.

Biochemistry: The mean values of the bone resorption markers showed a significant decrease after the first year of treatment but in the following 2 years they showed no major changes with the exception of hydroxyproline. The bone formation markers showed no significant changes.

- Safety results

No adverse reactions are mentioned and the authors state that the treatment was well tolerated.

### Assessor's Comment

The sample size is very small and the design of the study limits the significance of the findings.

The BMD end point is measured with dual photon absorptiometer at the lumbar spine that does not allow comparison with newer studies that use DEXA.

The dose selection and the pattern of the intermittent administration are not justified. It is noted that in the first year while the dose is relatively small, the most significant changes in the bone turnover are observed. Biochemical markers also plateaued after the first year.

According to the authors' conclusion, the results of this study indicate that calcitonin is effective to a satisfactory degree. Additional symptomatic improvement of pain and mobility is also documented

In the assessor's opinion, this is a very limited study to offer robust evidence on the efficacy of calcitonin in paediatric rheumatoid patients.

## ***PREVENTION OF TRABECULAR BONE LOSS IN CHILDREN'S FEMORAL FRACTURE; EFFECTS OF TREATMENT WITH CALCITONIN.***

*Mallet et al, 1985*

## ➤ Methods

- Objective

Prevention of osteoporosis in patients during prolonged immobilization due to femoral fracture.

- Study design

Prospective randomized study

- Study population /Sample size

19 children aged mean 3 years immobilized for at least 7 weeks after a femoral fracture were divided into 2 groups, treatment and control.

- Treatments

Calcitonin 100 UI/1.73 m<sup>2</sup> subcutaneous for 4 weeks

- Outcomes/endpoints

Serum Ca, P, alkaline phosphatase, intact PTH, 24OHD and 24 urinary excretion of Ca, P, hydroxyproline/creatinine were assessed. X-rays with a 4 graded scale of mineralization for metaphyse were taken and blindly reviewed simultaneously by 2 radiologists.

- Statistical Methods

No statistical methods are mentioned.

➤ **Results**

- Efficacy results  
Biochemical markers showed no statistical significant change between the groups. The radiological modifications showed signs of significant demineralization in the control group, compared to the patients under calcitonin treatment.
- Safety results  
No safety data are presented

**Assessor's Comment**

Osteoporosis due to post fracture immobilization is a problem almost exclusively in adults. Transient demineralization has been noted in adolescents with femur fractures but there is no evidence justifying the need of treatment. However in patients with neurodevelopment diseases and reduced weight bearing, poor bone quality is an issue currently under extensive investigation.

This study is described as an abstract with very limited information to validate the results. The sample size is very small and the age of the patients is very young to justify intervention to prevent osteoporosis. The use of X rays as measure of BMD is, with current standards, more than insufficient. Finally the biochemical markers could only provide inconclusive data, after a major fracture and the rapid healing callus formation in patients in this age group.

In the assessor's opinion, this is a very poor quality study that fails to address the real issue of immobilization osteoporosis in children.

**4. Discussion on clinical aspects**

In the submitted studies, the key problem of paediatric osteoporosis is reviewed, in renal transplant patients, in rheumatoid patients and in fracture patients. Steroid induced reduction of bone density is a well recognised problem that needs further research into establishing safe and effective methods of prevention and treatment. However the efficacy data from these studies reviewed here are not robust and only partly confirm the expected from adults effect of calcitonin in the growing skeleton. Osteoporosis after fracture is rarely an issue in the paediatric population unless is combined with other underlying conditions that effect bone quality. In terms of safety, no major issues were noted with the use of calcitonin in these studies. However the number of patients was overall very small.

## 5. Postmarketing safety surveillance

The MAH also summarised the spontaneous suspected adverse event reports which have been received by the Company relating to use in children (Data from MAH's global pharmacovigilance database). 7 spontaneous case-safety reports in children treated with calcitonin were identified. All reports were non-serious, with only one serious case of weakness due to nausea and vomiting requiring hospitalization. Gastrointestinal reactions (e.g. nausea and vomiting), skin flushes, local inflammatory reactions at the site of injection were the non-serious reactions reported in children with calcitonin use.

The MAH conclude that the events reported in children in association with calcitonin use have been recognized in adults as common undesirable effects of calcitonin, and they are included in the current product labelling information for this patient population.

### Assessor's Comment

The MAH did not provide more details of these reports. However no new serious adverse reaction is noted in the paediatric population.

## II.4 Additional references

The following list of studies was submitted as under article 45 of the Paediatric Regulation by another MAH. These published studies were included in the assessment and they are summarized below.

### **GENERALIZED AND FOCAL DYSTONIC SYNDROMES: POSSIBLE THERAPY WITH SALMON CALCITONIN**

Patti et al, 1985

The authors report the effects of repeated administration of salmon calcitonin to patients affected by idiopathic torsion dystonia (ITD) and writer's cramp syndrome (WCS).

Among the subjects studied, 6 were patients  $\leq 18$  years diagnosed with ITD (n=5) and WCS (n=1). They were treated with 20 or 40 micrograms daily of salmon calcitonin intramuscularly for 30 days. The outcome measure was evaluation of dystonic symptoms 2 hour after the first injection and at day 15 and day 30 of the treatment.

Improve rating score was observed for all patients at day15 and 30. The authors conclude that these results support the suggestion that calcitonin may act at central level influencing the extrapyramidal motor system.

### Assessor's Comment

This study is limited to a very small number of patients, has design limitations and does not prove efficacy.

## COMPARISON OF PLASMA AND SYNOVIAL CONCENTRATIONS OF SYNTHETIC SALMON CALCITONIN AFTER SINGLE INTRAVENOUS DOSE

Sinigaglia et al, 1992

The plasma and synovial fluid concentrations of synthetic salmon calcitonin in 10 patients with knee joint effusions have been compared after a single i.v. dose of 200 IU calcitonin.

10 patients with moderate active knee synovitis (knee-effusions of miscellaneous origins) aged  $\geq 18$  years were studied. Plasma and synovial fluid concentrations of calcitonin were measured using a specific RIA before and 30 and 60 min after administration.

Plasma calcitonin concentrations 60 min after administration were significantly lower than at 30 min, while the synovial fluid concentration remained relatively constant. The results show that synthetic salmon calcitonin penetrates into the articular cavity after a single i.v. dose of 200 IU and that a steady concentration persists there over 60 min.

### Assessor's Comment

The study was done in adult patients with active rheumatologic disease. The inflamed synovium has different trans-synovial exchange and penetration by molecules. The information provided by this study is not considered relevant to paediatric use of calcitonin

## THERAPY OF OSTEOGENESIS IMPERFECTA WITH SYNTHETIC SALMON CALCITONIN

Castells et al, 1979

The aim of the study is to evaluate the long-term use of synthetic salmon calcitonin in the management of osteogenesis imperfecta (OI).

Forty-eight children, ranging in age from 6 months to 15 years, and two young adults, received synthetic salmon calcitonin subcutaneously 2 MRC (Medical Research Council) units/kg three days a week and a daily oral calcium supplement of 230 to 345 mg for up to 48 months. Biochemical markers were assessed before and regularly during treatment, including PTH and antibodies to synthetic calcitonin. Radiographic bone density was determined by the method of radiographic photodensitometry (absorptiometry) and mineral concentration (MC) of the patients treated was compared with that of 308 normal subjects (age range 0 to 20 years).

The annual fracture rate was decreased during calcitonin therapy as compared to the period preceding therapy (3.2 fractures/year before therapy, 0.6 fractures/year during therapy). There was an increase in the ability of the patient to stand and move and in the subjective feeling of strength in the lower extremities. There was no increase in serum PTH and there were no significant changes in plasma alkaline phosphatase and urinary excretion of hydroxyproline. Serum antibodies to synthetic calcitonin rose slightly in 30% of the patients. Statistical analysis of radiographic bone density was performed in 38 patients. Treated patients did not gain MC as rapidly as age-matched children. Only in children under 5 years the rate of bone mineral deposition exceeded the norm. The tendency for MC to catch up was greatest during the 1<sup>st</sup> year of treatment but the mean rate of increase was not sustained during the full course of therapy.

In terms of safety, most patients tolerated treatment well. After the 1<sup>st</sup> injection, 25% of the patients experienced flushing in the hands and the feet and 20% had nausea. These symptoms usually resolved after the next injections. In 3 patients nausea and vomiting persisted and therapy was discontinued. 2 patients had urticarial reactions and also discontinued therapy. Some patients complained of aching bone pain during treatment and radiographic evidence of stress fractures (in the tibia or femur) was occasionally observed. In some patients, pain was thought to be related to degenerative changes in the hips and knees. Hypocalcemia, hypophosphatemia or hypomagnesemia were not observed in these patients.

**Assessor's Comment**

This is a very interesting study to evaluate the effects of calcitonin on fracture rate and bone density in patients with OI. However there are several limitations. The method of assessing MC is not used currently, limiting comparison with more recent studies. Improved bone density was only seen in very young children and only during the 1<sup>st</sup> year of treatment. A control group of patients with OI was not available and findings were reviewed against normal children. Antibody formation is a known problem and was confirmed in this study. The adverse events noted in this study are well known in the use of calcitonin. The authors do not provided numbers for patients who experienced pain and stress fractures. The findings of this study do not add robust efficacy data on the use of calcitonin in paediatric OI patients.

**EFFECTS OF SYNTHETIC SALMON CALCITONIN THERAPY IN CHILDREN WITH OSTEOGENESIS IMPERFECTA.**

Rebelo et al, 1989

In this study bone fracture rate and linear growth were evaluated in children with osteogenesis imperfecta (OI), treated with synthetic salmon calcitonin.

A total of four children (aged 9 months to 3 years) with OI were treated with synthetic salmon calcitonin (2 IU/kg subcutaneously on 3 days each week) for 18-24 months. The children also received daily oral calcium 250-500mg.

The annual fracture rate declined in 3 patients. There was no advancement or retardation of bone age, in relation to height age, except in one patient, which showed slight bone age retardation. There was no significant inflexion of linear growth during treatment in any patient, with a transient improvement of height velocity documented in 2 patients.

Persisting vomiting in one patient and transient diarrhoea in another patient were observed. One case of transient hypomagnesaemia was noted.

**Assessor's Comment**

The data produced by this study are limited to a small number of patients and do not indicate efficacy. The reported adverse events are known to be associated with the use of calcitonin. The findings of this study do not add robust efficacy data on the use of calcitonin in paediatric OI patients.

**EFFECT OF LONG-TERM CALCITONIN THERAPY BY INJECTION AND NASAL SPRAY ON THE INCIDENCE OF FRACTURES IN OSTEOGENESIS IMPERFECTA.**

Nishi et al, 1992

This study was undertaken to evaluate the clinical response to long-term calcitonin therapy in patients with osteogenesis imperfecta (OI) and to compare the effect of injection or intranasal administration on the incidence of fractures.

10 patients, aged 1 month to 14 years with OI were studied. The duration of the treatment with calcitonin varied from 22 months to 76 months. The treatment regimes were as follow:

Before April 1987	Porcine calcitonin	SC	Twice a week	3 MRC units/kg
After May 1987	Salmon calcitonin	Nasal spray of an aerosolized water solution	Twice a week	50 IU (BW<20kgr) 100 IU (BW>20kgr)
Since Nov 1989	Salmon calcitonin	Intranasally	Twice a week for 2 weeks on and 2 weeks off	As before

The authors report that fracture rate decreased in all 10 patients and that the effect of calcitonin therapy did not change when the route of administration or the dosing schedule changed. No significant change in bone age, in comparison with chronological age, was observed. Hypercalciuria was noted in 5 patients but no other biochemical abnormality was observed during treatment.

No side effects were observed during intranasal administration, whereas nausea and vomiting were seen in 3 of 6 patients who received injections.

#### **Assessor's Comment**

The data produced by this study are limited to a small number of patients and do not indicate efficacy. In the statistical analysis provided it is noted that patients were excluded in the mean calculation of the annual fracture rate, without clear justification. The findings of this study do not add robust efficacy data on the use of calcitonin in paediatric OI patients.

### **VITAMIN D METABOLISM IN OSTEOGENESIS IMPERFECTA DURING CALCITONIN THERAPY**

Nishi et al, 1984

The effect of exogenous calcitonin on vitamin D metabolism and the clinical response were studied in patients with osteogenesis imperfecta.. Six patients, aged 1 month to 15 years with OI, receiving adequate amounts of Ca, P, magnesium and vitamin D, were treated with porcine sc or intramuscularly in a dose of 3MRC units/kg twice a week. The duration of therapy varied among the cases from 6 months to 24 months. Plasma concentrations of 25-hydroxyvitamin D (25-OHD) and 1,25-dihydroxyvitamin D [1,25-(OH)<sub>2</sub>D] along with other bone biochemical markers.

The fracture rate decrease in all 6 patients. In the 1<sup>st</sup> month of therapy, urinary excretion of Ca and hydroxyproline was increased in 4 patients and 2 patients respectively; thereafter these parameters remained normal. Other serum and urinal parameters have remained unchanged.

The mean pre-treatment value of plasma 1,25-(OH)<sub>2</sub>D was significantly higher than the mean value of age-matched control subjects (P less than .05). High or normal plasma levels of 1,25-(OH)<sub>2</sub>D before calcitonin therapy were decreased after 1 month of therapy and remained normal thereafter in all six patients. Plasma 25-OHD concentrations, which were normal before calcitonin injection, remained normal during calcitonin administration. These findings suggest that there may be acute and chronic effects of calcitonin on vitamin D metabolism in OI. However this acute effect of calcitonin on 1,25-(OH)<sub>2</sub>D is different from the results of some experimental animal studies.

**Assessor's Comment**

The data produced by this study are limited to a small number of patients with no control group of OI patients to adequately compare the findings.

**III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION****➤ Overall conclusion**

The presented data are considered to be insufficient to support a variation application to extend the use of salmon calcitonin to the paediatric population.

**➤ Recommendation**

It is recommended that the SmPC contains the following statement:

4.2 Posology and method of administration

Use in children:

There is insufficient evidence to support the use of salmon calcitonin in conditions associated with paediatric osteoporosis. Use of salmon calcitonin in children 0 to 18 years is therefore not recommended.

**IV. ADDITIONAL CLARIFICATIONS REQUESTED**

No additional data have been requested