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Assessment report for calcitonin containing medicinal products

Procedure number: EMEA/H/A-31/1291

Referral under Article 31 of Directive 2001/83/EC

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 19 January 2011, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC. The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing calcitonin, and associated names should be maintained, varied, suspended or withdrawn.

The procedure described in Article 32 of Directive 2001/83/EC, was applicable.

2. Scientific discussion

2.1. Introduction

Calcitonin is a hypocalcaemic compound secreted from the thyroid[1], which was discovered almost 50 years ago. Its hypocalcaemic properties are mediated primarily through the inhibition of osteoclast-mediated bone resorption. However emerging evidence suggests a wider range of actions including inhibition of ion excretion in the kidney, inhibition of appetite, a role in embryo implantation and development and sperm function[2].

Calcitonin is a member of the calcitonin family of peptides, which also includes: amylin, α and β calcitonin gene-related peptides (α and β-CGRP), adrenomedullin, intermedin and the most recently discovered calcitonin receptor-stimulating peptide (CRSP).

Calcitonin is expressed in many species including fish, reptiles, mammals and birds. In mammals the major source of calcitonin are the parafollicular cells (C-cells) in the thyroid gland but it is also synthesized in a wide variety of other tissues, including the lung and intestinal tract. Non-mammalian calcitonin is derived from the ultimobranchial body and is generally more potent than calcitonin of thyroid origin[3]. Due to its higher potency, salmon calcitonin is the most commonly used form in clinical practice.

Parenteral formulations of calcitonin were first licensed in Europe in 1973. Since 1987 calcitonin has also been available as an intranasal formulation. Calcitonin is authorised in most European member states.

Injectable calcitonin is available as a solution for injection or infusion at 50, 100 or 200 International Units (IU)/ml. One IU corresponds to approximately 0.2µg of synthetic salmon calcitonin. The product can be administered intramuscularly, subcutaneously or intravenously. The intranasal formulation is available at 100 or 200 International Units (IU)/ml.

More recently a new oral formulation of calcitonin has been developed, which consists of the peptide hormone and 5-CNAC (8-(N-2-hydroxy-5-chloro-benzoyl)-amino-carpylic acid), a newly developed enhancer of gastrointestinal (GI) peptide absorption. This new oral formulation has not been submitted for approval in any of the EU member states.

[1] Copp DH, Cameron EC. Demonstration of a hypocalcemic factor (calcitonin) in commercial parathyroid extract. Science. 1961 Dec 22;134:2038.

[2] Purdue BW, Tilakaratne, Sexton PM. Molecular pharmacology of the calcitonin receptor. Receptors Channels 2002; 8, 243-255.

[3] H. D. Niall, H. T. Keutmann, D. H. Copp, and J. T. Potts, Jr. Amino acid sequence of salmon ultimobranchial calcitonin. Proc Natl Acad Sci U S A. 1969 October; 64(2): 771–778.

Concerns on the efficacy of certain indications were previously raised, which resulted in a referral under Article 12 of Directive 75/319/EC (corresponding to Article 31 of Directive 2001/83/EC) in 2000. After review of the available data, the CHMP (previously CPMP) adopted an opinion on 21 November 2002, on a favourable benefit/risk balance of injectable calcitonin in the following indications:

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

For intranasal calcitonin, the benefit risk balance was considered favourable only in:

- the treatment of established postmenopausal osteoporosis in order to reduce the risk of vertebral fractures. A reduction in hip fractures has not been demonstrated.

A Commission Decision for this previous referral procedure was issued on 12 June 2003.

Concerns of a possible association between calcitonin and prostate cancer have been raised and considered at different times. However, review of available data at the time by National Competent Authorities did not indicate a causal relationship. The issue was however kept under close monitoring.

In November 2010, preliminary safety findings relating to prostate cancer were observed during two clinical trials for the new oral formulation of calcitonin. On the basis of this new safety information the UK requested the opinion of the Committee for Medicinal Products for Human Use (CHMP), under Article 31 of Directive 2001/83/EC whether the marketing authorisations for medicinal products containing calcitonin should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the currently available short and long-term evidence of efficacy of calcitonin in the authorised indications (as per Commission Decision of 12 June 2003), and the information about the risk of cancer with calcitonin from pre-clinical studies, clinical trials, post-marketing spontaneous reports, pharmacoepidemiological studies and published literature. The CHMP also considered information provided by third parties during the referral procedure.

2.2. Non-clinical aspects

Information about the risk of cancer associated with calcitonin from pre-clinical studies was provided by the MAHs.

Two 104-week carcinogenicity studies with salmon calcitonin have been conducted in rats (Sprague Dawley) and mice (CD-1), which were injected with daily doses of calcitonin up to 10 IU/kg/day. In these studies an increase in the incidence of pituitary adenoma in male rats receiving the highest doses of calcitonin was found. A similar effect was noted in two 52-week subcutaneous chronic toxicity, which were conducted in rats (crl:CD BR).

However it was noted that rats, and in particular Sprague-Dawley rats, have a very high rate of spontaneous pituitary adenomas. This was also supported from the biopsies of the adenomas in these studies, which were characterised as non-functioning α-subunit secreting tumours that are known to occur spontaneously in rats[4]. Further evidence that this potential effect of calcitonin on the occurrence

[4]Jameson JL, Weiss J, Polak JM, Childs GV, Bloom SR, Steel JH, Capen CC, Prentice DE, Fetter AW, Langloss JM. Glycoprotein hormone alpha-subunitproducing pituitary adenomas in rats treated for one year with calcitonin Am J Pathol, 140 910; 75-84.

of pituitary adenomas is specific to rats was provided by binding studies, which demonstrated binding of ^{125}I- radio-labelled salmon calcitonin to extracts from rat pituitaries, but not human pituitaries.

An increase in pituitary adenomas was not observed in similar mice carcinogenicity studies, even though mice were subject to much higher doses in those studies (up to 800 IU/kg/day). However there were some findings from the 104-week carcinogenicity studies in mice that may possibly be relevant to the issue. Among the female mice that died unexpectedly before the study was completed, increased incidences of cystic ovaries and thickened uterine walls were macroscopically observed in mice receiving 800 IU/kg/day calcitonin. In terminal-sacrifice animals, increased incidences of distended gall bladder (800 IU/kg/day animals, 25% in males, 29% in females compared to 0% in placebo), cystic kidneys (250 and 800 IU/kg/day males, 67% and 65% respectively compared to 36% in placebo), thickened uterine walls (800 IU/kg/day, females only, 86% compared to 36% in placebo) and uterine masses (250 and 800 IU/kg/day, females only 36% for both groups compared to 0% in the placebo groups) were observed.

As mentioned above, a new oral formulation of calcitonin has recently been developed, which consists of the peptide hormone and 5-CNAC (8-(N-2-hydroxy-5-chloro-benzoyl)-amino-carpylic acid), a newly developed enhancer of GI peptide absorption. Information on the risk of cancer observed in the pre-clinical studies performed with the newly developed oral formulation has been provided.

2.3. Clinical efficacy

2.3.1. Efficacy of injectable calcitonin

Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures

The efficacy of calcitonin in this indication has been investigated in a number of randomised controlled studies which have shown that calcitonin reduces bone resorption and increases bone mass or bone mineral density. Some of the main studies supporting the efficacy of injectable salmon calcitonin in the prevention of acute bone loss due to sudden immobilization such as in patients with recent osteoporotic fractures are summarized below:

The study by Bordier *et al* [5] was a randomised, double-blind, placebo controlled study in a small number of patients with established osteoporotic vertebral compression fracture. Patients were treated with salmon calcitonin 50 IU/day (n=15) or placebo (n=17), and bone loss was assessed by measuring urinary calcium (Ca)/creatinine ratio. The results of this study are presented below.

Table 1: Fasting 2-hour urinary Calcium/Creatinine Ratio results as reported by Bordier *et al*

	Calcium/Creatinine ratio	
	Calcitonin	**Placebo**
Before treatment	0.534 ± 0.113	0.557± 0.052
Day 14	0.415 ± 0.082	0.739 ± 0.072
Day 28	0.463 ± 0.073	0.874 ± 0.133

5 Bordier P, Julien D, Caulin F. [Effect of calcitonin on bone pain and resorption parameters secondary to recent vertebral compression. Results of a double-blind study and an open study] Article in French. Rhumatologie 1986; 38: 215-21.

The Ca/creatinine ratio was increased from baseline in the placebo treated patients at days 14 and 28 of the trial, and this increase was statistically significant. Over the same period, the Ca/creatinine ratio decreased in patients treated with calcitonin but this was not statistically significant. The difference in the ratio between calcitonin and placebo was however significant. The authors concluded that in acutely immobilized osteoporotic patients, injectable salmon calcitonin is able to prevent increased bone resorption. It was concluded that some evidence has been provided by Bordier *et al* even though urinary calcium in the placebo treated patients decreased more (from 290 ± 18 to 200±16 mg/24 h) compared to the calcitonin group (from 267±19 to 240±22.7) at the end of the 4 weeks.

Tsakalakos *et al* [6] conducted an open randomised study in 40 elderly patients admitted to hospital with acute immobilisation due to recent (<3 days) hip fracture. All patients included in the study underwent surgery one week after admission and were randomised to no treatment or calcitonin 100IU/day for two weeks starting on admission. Patients with cardiac or renal insufficiency, hyperparathyroidism or other diseases affecting bone remodelling, and those receiving drugs affecting calcium homeostasis were excluded from the study. The results for the biochemical markers of bone resorption in this study are summarised below.

Table 2: Urinary calcium and hydroxyproline values in patients with acute immobilisation due to recent hip fracture as reported by Tsakalakos *et al*

	Control			Calcitonin (100 IU/day)		
Weeks	0	1	2	0	1	2
Calcium (mg/24h)	140.39 ±51.5	154.88 ±100.5	201.5 ±130.1	140.39 ±51.5	128.3 ±42.6	110.2 ±41.8
Hydroxyproline (mg/m2/24/h)	26.8 ±8.46	32.85 ±14.30	41.20 ± 21.44	26.8 ±8.46	27.5 ±6.16	18.52 ±2.07

At the end of week 2 urinary calcium had increased significantly ($p<0.01$) from baseline in patients not receiving any treatment. At the same time point calcitonin had significantly decreased urinary calcium compared to baseline ($p<0.01$). The difference between the two groups of patients was also significant ($p<0.01$). The differences in the results for urinary hydroxyproline were even more striking with the intergroup difference being significant both at week 1 ($p<0.01$) and week 2 ($p<0.001$). Although hydroxyproline is not considered to be a very specific marker for bone resorption, the authors of the study concluded that short term treatment of calcitonin can result in significant changes in biochemical markers of bone resorption caused by immobilisation resulting from hip fracture and therefore may prevent future bone loss in these patients.

The final study in support of this indication was by Resch *et al* [7], which investigated the long term effect of short term calcitonin treatment on forearm bone mineral content (BMC) and bone turnover. The study included 28 female patients with acute osteoporotic spine fractures who received either 100IU of calcitonin on alternate days for 6-8 weeks, or Hormone Replacement Therapy (HRT) over 12 months or unspecified analgesic treatment. Forearm BMC was measured by single photon

[6] Tsakalakos N, Magiasis B, Tsekoura M, et al. The effect of short-term calcitonin administration on biochemical bone markers in patients with acute immobilization following hip fracture. Osteoporos Int 1993; 3: 337-40.

[7] Resch H, Pietschmann P, Willvonseder R. Estimated long-term effect of calcitonin treatment in acute osteoporotic spine fractures. Calcif Tissue Int 1989; 45: 209-13.

absorptiometry (SPA) at baseline and at 6 and 12 months after treatment. The main results of the study are presented in the table below.

Table 3: Bone Mineral Content (BMC) and urinary hydroxyproline in patients with acute osteoporotic spine fracture as reported by Resch *et al*

Months	**0**	**6**	**12**	**p- value***
BMC*				
Control	30.5 ± 1.5	26.8±1.5	25.6±1.1	<0.025
Calcitonin	28.6 ± 1.5	31.3±1.1	32.1±2.0	<0.05
HRT	29.2 ± 1.0	29.6±1.5	31.1±1.5	<0.025
Urinary hydroxyproline (mg/24h)				
Control	3.3±0.5	2.8±0.5	2.3±0.5	<0.05
Calcitonin	3.1±0.5	2.0±0.2	1.8±0.2	<0.001
HRT	3.9±1.0	4.1±1.0	2.3±0.1	<0.025

*BMC is expressed in arbitrary units i.e. mass of bone mineral per unit length of bone * p-values at end of treatment

Although the authors concluded that short-term calcitonin treatment over 6-8 weeks is as effective as long term hormone replacement therapy in patients with acute osteoporotic spine fractures, this study did not provide any robust evidence of efficacy, as there is no information on the patients' treatment following discontinuation of calcitonin treatment and assessment of BMC.

Paget's disease

Twelve studies on Paget's disease of bone that were included in support of the initial authorisation for Miacalcic were submitted by Novartis. The efficacy of calcitonin in Paget's disease was evaluated in these very small trials (Table 4), which included some placebo controlled studies. Patients included in these studies were treated mostly with salmon calcitonin (but also with porcine calcitonin) with doses that varied between 50 and 200 IU/day (1 to 4 IU/kg per day). Treatment duration varied from 1 to 36 months, but was generally 3 to 18 months. Studies 1-4, 6-8 and 10 included a placebo arm.

The main endpoints from these studies were levels of serum alkaline phosphatase and urinary hydroxyproline, and also subjective clinical changes such as pain relief and increased mobility.

A summary of the biomarker results from these studies are summarised in the tables below:

Table 4: Effect of calcitonin on alkaline phosphatase and urinary hydroxyproline in patients with Paget's disease

Investigator (number of patients in study)	**Average serum alkaline phosphatase (U/l)**		**Average urinary hydroxyproline (mg/24 hours)**	
	Baseline	**Final**	**Baseline**	**Final**
Au (4)	517	279	298	200
Avioli (15)	770	730	290	239
Canary (4)	250	156	306	213
Canfield (8)	658	352	134	103
Gershberg (7)	495	522	124	89
Hamilton (9)	183	139	78	58
Hill (8)	427	322	251	123
Potts (24)	440	298	338	246
Prendergast (3)	337	247	101	31
Shai (9)	432	514	106	55
Wallach (21)	328	159	218	138
Wallach (23)	634	248	499	209
Overall (135)	**456 (183-770)**	**328 (139-**	**228 (78-499)**	**141 (31-246)**

Further details were provided only for the studies by Au and Avioli, which revealed a wide discrepancy in the baseline values for alkaline phosphatase and hydroxyproline. Importantly there were inconsistencies in the follow-up periods for the different patients included in the studies. Both studies followed a cross-over design, however the treatment periods were not pre-determined and varied between patients. The effect of calcitonin in these studies varied amongst patients, and in the case of the study by Avioli, after a year of treatment, alkaline phosphatase activity was still raised in 6 of the 14 evaluable patients. These patients were termed "treatment resistant" and the observed effect was attributed to neutralising calcitonin antibodies in these patients.

The following table presents the effects of Miacalcic ampoules on the clinical symptoms of Paget's disease in the studies included in the submission.

Table 5: Effect of calcitonin on clinical symptoms of Paget's disease

Clinical change	**Number of patients**		**% Improved**
	Evaluated	**Improved**	
Bone pain	76	58	76
Ambulation	46	39	85
Local heat	22	18	82
Headache	12	10	83
Hearing	29	4	13
Elevated cardiac output	6	4	67

The MAH also provided a summary of results of clinical symptoms and biochemical markers for 19 additional patients with Paget's disease, which were evaluated by a number of different investigators. These patients were treated with a variety of different doses of calcitonin. Of these patients, 13 received calcitonin 3 times a week, between 90 and 200 IU daily. The remaining 6 patients received 80-180 IU calcitonin daily intramuscularly or subcutaneously. Serum alkaline phosphatase was reduced

from an average initial value of 676 IU/l to an average of 377 IU/l i.e. a reduction of 44%. Urinary hydroxyproline was measured in four patients; it fell to an average of 60% of the initial value. Bone pain and throbbing pain was evaluated in 18 and 13 patients and was found to be improved in 16 and 11 patients respectively. However it is noted that this study was uncontrolled, which in combination with the small number of patients and the wide range of doses, precludes from determining any specific effect of calcitonin in this indication.

In addition, the MAH presented a brief overview of a number of published studies. However all these studies were open label and uncontrolled and were therefore not considered sufficient to provide evidence of efficacy.

Hypercalcaemia of malignancy

In addition to the published literature in relation to the use of injectable calcitonin for hypercalcaemia in malignancy, this indication is further supported by its established use in clinical practice.

2.3.2. Efficacy of intranasal calcitonin

Treatment of osteoporosis in order to reduce the risk of vertebral fractures

- **PROOF study**

The effect of calcitonin in the reduction of vertebral fractures in patients with osteoporosis has been investigated in a number of studies, including the pivotal Prevent Recurrence of Osteoporotic Fractures (PROOF) study (also known as study CT320). In this study, a total of 1,255 postmenopausal women with established osteoporosis were randomly assigned to receive salmon calcitonin nasal spray (100, 200, or 400 IU) or placebo daily. Of the participants in the study, 783 women completed 3 years of treatment, and 511 completed 5 years.

The primary efficacy endpoint was the risk of new vertebral fractures. Treatment with 200 IU calcitonin resulted in a 33% statistically significant reduction in the risk of developing a new vertebral fracture. The 100 IU and 400 IU calcitonin groups also showed decreases in new vertebral fractures of 15% and 16% respectively relative to placebo without however reaching statistical significance.

The main results from this study are summarised below:

Table 6: Vertebral fracture analysis from the PROOF study

	Placebo	100 IU/day	200IU/day	400 IU/day
All patients (n)	270	273	287	278
Patients with ≥ 1 new vertebral fracture				
	70 (25.9%)	59 (21.6%)	51 (17.8%)	61 (21.9%)
Relative risk	1.0	0.853	0.674	0.839
p-value vs placebo	-	0.370	**0.032**	0.316
Patients with ≥ 2 new vertebral fracture				
	33 (12.2%)	34 (12.5%)	24 (8.4%)	30 (10.8%)
Odds ratio	1.0	1.022	0.655	0.869
p-value vs placebo	-	1.000	0.162	0.688

	Placebo	100 IU/day	200IU/day	400 IU/day
Patients with 1-5 prevalent fractures (n)	203	201	207	206
Patients with ≥ 1 new vertebral fracture				
	60 (29.6%)	52 (25.9%)	40 (19.3%)	48 (23.3%)
Relative risk	1.0	0.94	0.64	0.78
p-value vs placebo	-	1.09	**0.029**	0.779
Patients with ≥ 2 new vertebral fracture				
	30 (14.8)	32 (15.9%)	18 (8.7)	23 (11.2)
Odds ratio	1	1.09	0.55	0.73

	Placebo	100 IU/day	200IU/day	400 IU/day
Three year valid comparators (n)	162	152	157	155
Patients with ≥ 1 new vertebral fracture				
	59 (36.4%)	49 (32.2%)	40 (25.5%)	42 (27.1)
Relative risk	1	0.91	0.66	0.71
p-value vs placebo	-	0.639	**0.044**	0.088

The evidence provided in support of the effect of calcitonin in reducing the risk of fracture is not convincing as it appears to be limited to only one of the doses tested during the relevant trials. Only patients treated with 200IU calcitonin/day demonstrated a statistical significant reduction in fractures compared to placebo. Even for this dose, statistical significance was not achieved when analysing patients with at least 2 new vertebral fractures.

In addition to the lack of a dose response, the results of this study are further limited by important methodological limitations (lack of adjustment for multiple testing and very high percentage of patients discontinuing the study). Even when overlooking these limitations, the overall clinical benefit of calcitonin in osteoporosis appears to be very modest, with an absolute reduction of approximately 6% and 1.7% in the patients with ≥1 and ≥2 new vertebral fracture respectively, compared to patients treated with placebo.

Secondary analyses were performed among participants with one to five prevalent vertebral fractures and among those who received the study drug for at least 3 years or who had a fracture during the first 3 years of treatment (3-year valid completer analysis). The 95% confidence interval (CI) for the reduction in the relative risk of developing a new fracture compared to placebo was provided only for the calcitonin 200IU/day.

Table 7: Reduction in the relative risk of developing a new vertebral fracture versus placebo in all patients, patients with 1-5 prevalent fractures and in 3-year valid completers treated with calcitonin 200IU/day

	Mean relative risk reduction (95% CI)
All patients	0.674 (0.470-0.967)
1-5 prevalent fractures	0.640 (0.429-0.955)
3 year valid completers	0.662 (0.443-0.989)

The upper limit of the 95% CI for the risk reduction for the various sub-groups of patients is very close to unity, raising further concerns about the clinical significance of the results. It should also be pointed out that the data presented did not control for the multiple dose testing (e.g. by applying the Bonferroni correction) as would be expected to ensure elimination of a false positive result. In the absences of such adjustment it is not certain that the results for the 200IU/day are indeed statistically significant.

- **Supportive data**

A brief summary of results from additional double-blind placebo controlled studies in patients with osteoporosis (mainly in relation to lumbar spine bone mineral density) was provided by Novartis. With the exception of study SMCO 522, the other studies were quite small with 8-21 patients included in each treatment group.

In Study SMCO 522, fracture analysis was limited to 114 patients treated with 50, 100 or 200IU of calcitonin and 40 patients treated with placebo. Very few patients experienced a fracture during this study: 2, 0 and 3 patients had a vertebral fracture in the 50, 100 and 200 IU calcitonin groups compared to 5 in the placebo group and this difference was statistically significant.

Study SMCO 514 was conducted over 2 years. Only 2 patients had fractures at baseline and only 3 experienced a new vertebral fracture during the study.

Studies CT211, SMCO 005 and SMCO 516 were conducted over 2, 1 and 1 years respectively.

A summary of the lumbar spine bone mineral density (LS-BMD) results from the calcitonin trials are summarised in the table below:

Table 8: Mean change (%) in lumbar spine bone mineral density (LS-BMD) results from the calcitonin trials and p-value vs placebo (in brackets)

	Placebo	Calcitonin (IU/day)				
Study		**50**	**100**	**200**	**200 e.o.d***	**400**
2 year endpoints						
CT320	+0.35	-	+1.13 (0.017)	+1.27 (0.013)	-	+1.24 (0.021)
SMCO 522	+0.20	+1.59, (0.044)	+1.36 (0.088)	+1.56 (0.046)	-	-
CT211	+0.617	-	-	-0.175 (ns)	-	+1.50 (ns)
SMCO 514	-1.85	-	-	+1.02 (0.004)	-0.77 (0.275)	-
1 year endpoints						
SMCO 005	+0.43	+1.24 (0.73)	+3.21 (0.24)	+5.26 (0.06)	-	-
SMCO 516	-0.4	-	+3.2 (0.04)	-	-	-

*e.o.d: every other day, bone mineral density was determined by dual X-ray absorptiometry in the first 3 studies and by dual photon absorptiometry in the other 4 studies

The data presented by the MAH on bone mineral density suggest that calcitonin has a positive effect, which however appears to be minimal, despite being statistical significant.

2.3.3. Discussion and Conclusions on efficacy

The indications currently authorised as per the outcome of the previous referral procedure that was concluded in 2003, were reviewed in the current procedure.

In addition to the published literature in relation to the use of injectable calcitonin for hypercalcaemia in malignancy, this indication is further supported by its established use in clinical practice.

With regards to the use of injectable calcitonin in acute bone loss prevention, the evidence of efficacy is based on published literature. The CHMP accepted that some evidence of efficacy in this indication has been provided, mainly by the study by Tsakalakos *et al*.

For Paget's disease, the evidence of efficacy is based on published literature of a number of small studies, where the treatment duration was in most cases between 3-18 months. Based on these data, the CHMP confirmed the benefits of injectable calcitonin in the short term treatment of the Paget's disease.

The indication of fracture prevention in osteoporosis, is supported by results from a reasonably sized, placebo controlled double blind study known as the PROOF (Prevent Recurrence of Osteoporotic Fractures) study. This pivotal study showed that only one of the investigated doses - 200IU calcitonin/day was associated with a statistical significant effect, although for this dose, statistical

significance was not achieved when analysing patients with at least 2 new vertebral fractures. In addition to the lack of a dose response, the results of this study are further limited by important methodological limitations (lack of adjustment for multiple testing and very high percentage of patients discontinuing the study). Even when overlooking these limitations, the overall clinical benefit of calcitonin in osteoporosis appears to be very modest, with an absolute reduction of approximately 6% and 1.7% in the patients with ≥1 and ≥2 new vertebral fracture respectively compared to patients treated with placebo.

2.4. Clinical safety

The MAHs were requested to provide information about the risk of cancer associated with calcitonin from, clinical trials, post-marketing spontaneous reports, pharmacoepidemiological studies and published literature articles.

2.4.1. Clinical studies

A meta-analysis of 17 randomised, controlled double blind studies conducted with intranasal calcitonin was submitted by Novartis. Additional information from the individual calcitonin trials were also provided, including data from the pivotal trial CT320 (the PROOF study). From these trials, information with regards to the carcinogenic potential of calcitonin has been provided.

Clinical trials with calcitonin have also been conducted by Sanofi-Aventis (2 trials) and Alfa Wasserman (20 trials). These trials were however very small (number of patients in the trials ranged between 4 and 40) and the majority of these were uncontrolled open label studies. In addition, the duration of these trials was very short, up to 3 months, including 5 single dose studies in healthy volunteers. The other MAHs stated that they had not conducted clinical trials with calcitonin.

Injectable studies

No randomised, double blind trials were conducted with the injectable formulations by Novartis, which did not allow a valid estimation of the incidence of malignancies to be made. However 4 cases of prostate cancer were identified, two cases each in two patients receiving injectable Miacalcic or placebo.

Intranasal studies

The following section includes the results of a pivotal trial CT 320, with Miacalcic nasal spray and a meta-analysis of 17 randomised, controlled double blind studies (including CT 320) for intranasal calcitonin that was submitted by Novartis.

- **Cancer cases in study CT320**

Novartis provided the narratives of all cases in which a neoplasm event was reported during study CT320. There were 80 patients treated with calcitonin that experienced 83 adverse events relating to malignancy during this trial.

Sixteen placebo treated patients also experienced events suggestive of malignancy.

A summary of the reported events by treatment group and reported time to onset is presented in the table below:

Table 9: Summary of characteristic of event of malignancy reported during study CT 320

Calcitonin 100 IU/day		
Reported events (n=27)		
	Basal cell carcinoma	12 (44.4%)
	Squamous cell carcinoma	1 (3.7)
	Skin cancer	1 (3.7)
	Breast cancer	6 (22.2)
	Pancreatic	2 (7.4)
	Acute myeloid leukaemia	1 (3.7)
	Vocal cord cancer	1 (3.7)
	Colon cancer	2 (7.4)
	Uterine cancer	1 (3.7)
Time to onset (months)		
	0-3	1 (3.7)
	3-6	1 (3.7)
	6-12	7 (25.9)
	12-24	2 (7.7)
	>24	16 (59)
Calcitonin 200 IU/day		
Reported events (n=25)		
	Basal cell carcinoma	7 (28)
	Skin cancer	2 (8)
	Colon adenocarcinoma	1 (4)
	Breast cancer	3 (12)
	Endometrial	1 (4)
	Lymphoma of spine	1 (4)
	Abdominal adenocarcinoma	1 (4)
	Pancreatic cancer	2 (8)
	Ovarian cancer	1 (4)
	Mesothelioma	1 (4)
	Lung cancer	1 (4)
	Squamous cell carcinoma	3 (12)
	Bowen's carcinoma	1 (4)
Time to onset (months)		
	0-3	2 (8)

	3-6	2 (8)
	6-12	3 (12)
	12-24	6 (24)
	>24	12 (48)
Calcitonin 400 IU/day		
Reported events (n=31)		
	Basal cell carcinoma	9 (29)
	Squamous cell carcinoma	1 (3)
	Breast cancer	6 (19.3)
	Colon cancer	3 (9.7)
	Non-Hodgkins lymphoma	2 (6.5)
	Melanoma	1 (3)
	Abdominal cancer	1 (3)
	Ovarian cancer	2 (6.5)
	Stomach cancer	1 (3)
	Lung cancer	3 (9.7)
	Metastatic brain cancer	1 (3)
	Pancreatic cancer	1 (3)
Time to onset (months)		
	0-3	4 (12.1)
	3-6	2 (6.1)
	6-12	4 (12.1)
	12-24	7 (21.1)
	>24	16 (48.5)
Placebo		
Reported events (n=16)		
	Basal cell carcinoma	3 (18.7)
	Brain tumour	1 (6.2)
	Benign breast tumour	1 (6.2)
	Breast cancer	2 (12.5)
	Breast cancer recurrent	1 (6.2)
	Carcinoid type tumour	1 (6.2)
	Chronic lymphocytic leukaemia	1 (6.2)
	Leiomyosarcoma	1 (6.2)
	Lung cancer	1 (6.2)
	Pancreatic cancer	1 (6.2)

	Multiple myeloma	1 (6.2)
	Oesophageal cancer	1 (6.2)
	Ovarian cancer	1 (6.2)
Time to onset (months)		
	0-3	3 (18.7)
	3-6	0 (0)
	6-12	0 (0)
	12-24	3 (18.7)
	>24	10 (62.5)

Possible confounders were reported on a number of cases for all treatment groups. Most commonly these included previous history of cancer or smoking, which was reported in 5/25 (or 20% of patients) from the calcitonin 100IU/day, 9/24 (or 37.5%) in the calcitonin 200 IU/day, 13/33 (or 39.4%) from the calcitonin 400IU/day and in 8/16 (50%) in the placebo group.

For the reported cases of malignancy, the narratives provided did not reveal a significant imbalance of confounders between the calcitonin and the placebo treated patients, and an increased incidence of malignancy events were observed in the calcitonin-treated patients. Time to onset of events was also evenly matched across the different treatment arms.

Two supportive documents analysing the cases of basal cell carcinoma and breast cancer observed during this trial were also provided. According to these documents a total of 26 cases of primary basal cell carcinoma (23 in the calcitonin treatment arms and 3 in the placebo arm), and 16 cases of primary breast cancer (14 in the calcitonin and 2 in the placebo arm) were observed during trial CT320.

Basal cell carcinoma

The overall relative risk of being diagnosed with basal cell carcinoma for women treated with calcitonin compared to placebo was 2.5 (95%CI: 1.2-5.1), while the relative risk in the three calcitonin arms compared to placebo were: 3.4 (9%% CI: 1.4-8.0); 1.9 (95% CI: 0.7-5.1) and 2.3 (95% CI: 0.9-5.9) for the calcitonin 100IU, 200 IU and 400 IU groups respectively.

Novartis also explored the effect of the cumulative dose in the incidence of these cases. Patients were split in quartiles with respect to the total calcitonin dose received and incidence rates of basal cell carcinoma were calculated.

Table 10 : Incidence rates per 100,000 person years, of basal cell carcinoma (BCC) and relative risks by quartiles of cumulative dose intake of calcitonin during trial CT320.

Cumulative dose range ($IU \times 10^2$)	Number of patients	Person-years	Cases of BCC	Incidence rate	RR (95% CI)
<1119	233	269.93	12	4445.6	1
1120-1876	234	892.42	6	672.3	0.15 (0.06-041)
1881-3682	235	944.33	5	529.5	0.12 (0.04-0.34)
3684-7604	234	1064.82	0	0	-

Even though this analysis would appear to suggest that calcitonin is not causally associated with basal cell carcinoma, there are many limitations in this analysis which prevent any meaningful conclusions to be drawn. This is also highlighted in the guidelines for osteoporosis by the National Institute for Health and Clinical Excellence (NICE), which reference this study noting the " ..very high level of missing data, with 58% missing in the 200 IU calcitonin group and 59% missing in the placebo group at 5 years". Furthermore, the highest examined dose in this analysis (760,400 IU of calcitonin) correlates to 5.2 years exposure to 400IU/day which exceeds the duration of the trial. The validity of these results is therefore highly questionable.

A similar analysis with respect to total duration of treatment showed that the incidence rates for these cases was highest in the quartile with the lowest duration of treatment, however for the same reasons as with the dose analysis, it is not possible to make any conclusions regarding the effect of treatment duration on the incidence of basal cell carcinoma.

Breast cancer

The overall relative risk of developing breast cancer in this study in patients treated with placebo compared to placebo was 2.3 (95%CI: 0.51-9.96). The relative risk in the three arms compared to placebo were: 3.0 (95%CI: 0.61-14.88); 1.4 (95% CI: 0.24-8.47); and 2.4 (95% CI: 0.47-12.46) for the calcitonin 100IU, 200 IU and 400 IU groups respectively.

A similar analysis to the basal cell carcinoma cases was performed for cases of breast cancer. This analysis also suggested an inverse correlation between the risk of developing breast cancer and the cumulative dose and duration of treatment with calcitonin. As with the basal cell carcinoma analysis, no conclusions on the risk of breast cancer can be derived from this analysis.

- **Meta-analysis of intranasal Miacalcic trials**

A meta-analysis of 17 randomised, controlled, double blind studies with intranasal calcitonin for all types of malignancy was submitted. All the studies were placebo controlled except one study, in which the patients were treated with calcitonin or an unspecified "control".

In the meta-analysis provided by Novartis, patients were exposed only to the intranasal formulation of calcitonin since no randomized, controlled, double-blind clinical trials were available for Miacalcic injectable formulations.

A summary of the included studies with patient exposures and cases of cancer reported is provided in the table below.

Table 11: Summary of studies included in the meta-analysis of calcitonin trials

Study	Number of patients Calcitonin / placebo**	Exposure (years) Calcitonin / placebo	Reported cancer cases Calcitonin / placebo (n / %)**
2402	149/147	64.7/60.1	-
CT 211	31 /15	57.1 /25.4	3 (9.7) /3 (20)
CT 310	211/68	354.2/113.8	4 (1.4) /1 (1.5)
CT 311	244/79	374.3/133.2	8 (2.9)/4 (5.0)
CT 312	201/102	321.3/160.6	**11 ((5.5) / 3 (2.9)**
CT320	944/311	3260.4/1050.3	**81 (8.6) / 16 (5.1)**
MIA 16	32/30	0/0	**1 (3.13) / 0 (0)**
SMCO005	32/10	23.9/8.2	**1 (3.1) / 0 (0)**
pSMCO503	26/26	48.5/46.4	**-**
SMCO504	29/29	44.3/48.8	**1 (3.4) / 0 (0)**
*SMCO506**	*147/141*	*373.0/372.3*	***3 (2.0) / 1 (0.7)***
SMCO511	60/60	189.6/183.5	**2 (3.3) / 0 (0)**
SMCO514	71/46	135.9 /85.9	**2 (2.8) / 0 (0)**
SMCO517	168/83	290.6/145.8	**-**
SMCO520	65/32	107.0/55.0	**-**
SMCO522	156/52	256.5/86.2	**4 (2.6) / 0 (0)**
SMCO524	100 /33	185.0/62.0	**1(1) / 0 (0)**

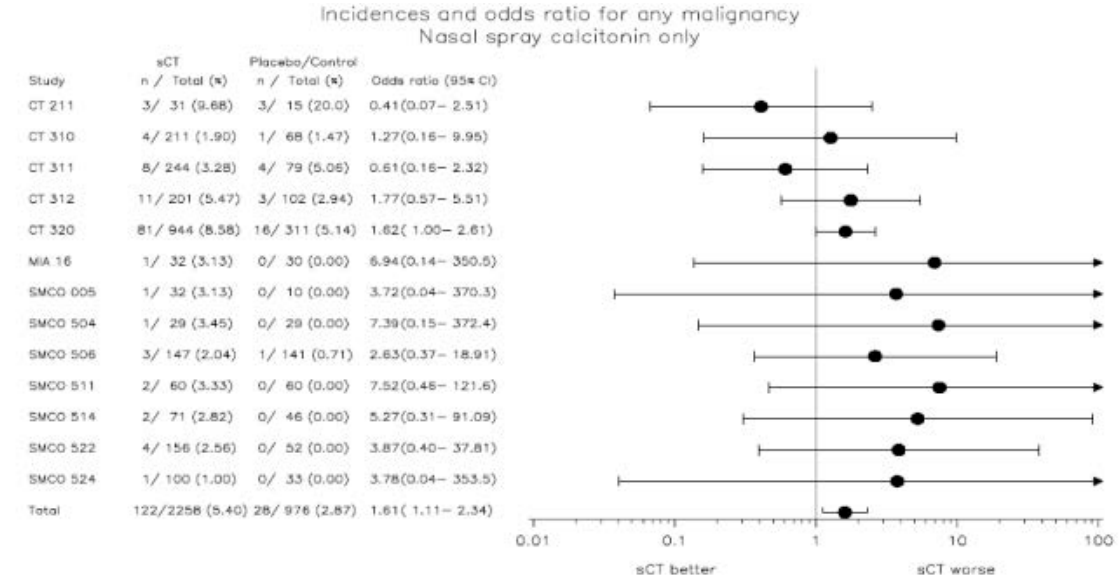
* The comparator in this study was an unspecified “control” rather than placebo

** Numbers corrected in accordance with the latest submissions

A breakdown of events reported in the largest study CT 320 conducted with intra-nasal calcitonin can be found in Table 9 above, which revealed that a wide range of tumours had been observed in this trial.

A forest plot with the OR for each individual trial was also provided by Novartis:

Figure 1: Forest plot for incidence of events of malignancy in the calcitonin clinical trials[8]



Odds ratio (sCT vs Placebo/Control) obtained by Peto method.
Arrows represent estimates outside of axis range.
Odds ratio estimate in Total row only includes studies with at least one event in either treatment group.

The Odds Ratio (OR) for the incidence of cancer in these trials in patients treated with calcitonin was 1.61 (1.11-2.34) (see figure 1). When including the trials in which no cases of malignancy had been reported the estimated OR is 2.12 (Mantel Haenzel method). The higher incidence of events of malignancy in the calcitonin treated arms of the study compared to placebo is statistically significant. The increase in absolute risk of cancer for patients treated with calcitonin compared with placebo in the intra-nasal trials was 2.36%.

Most of the malignancy cases were reported in study CT 320, with 81/944 cases observed in the arms treated with salmon calcitonin (out of which 57 cases were basal cell carcinomas plus 5 additional non-melanoma skin cancer cases) vs. 16/311 cases (out of which 15 cases were BCCs plus 1 additional non-melanoma skin cancer case) in the placebo arm. It is important to note that the results of study CT320, which due to duration and size was probably the most reliable of the conducted studies to determine differences between placebo and calcitonin, also point towards a higher incidence of events of malignancy even though the results do not reach statistical significance.

The association between calcitonin and placebo is further supported by secondary analyses including trials with no events, the large study CT320 or all cases of basal cell carcinoma, as summarised in the table below:

Table 12: Summary of secondary analyses for incidence of malignancy in the intra-nasal calcitonin trials[9]

	Number of patients (Calcitonin / placebo)	Cases / Incidence (Calcitonin / placebo)	Peto OR (95% CI)
Including trials with no events	2666/1264	122 (4.58)/ 28 (2.22)	**1.61(1.11-2.34)**
Excluding Study CT 320	1314/665	41 (3.12) / 12 (1.80)	1.60 (0.88-2.90)
Excluding cases of BCC*	2258/976	84 (3.72) /23 (2.36)	1.42 (0.92-2.19)

*BCC: Basal cell carcinoma ** Numbers corrected in accordance with the latest submissions

[8] Corrected in accordance with the latest submission
[9] Numbers corrected in accordance with the latest submission

It is worth pointing out that the cases of basal cell carcinoma do not have a significant effect on the overall results, and the reported risk when excluding these cases is higher in patients treated with calcitonin. Overall, the sensitivity analysis performed by Novartis provides further evidence of a possible association, especially as the exclusion of the non-events trials appears to be valid and results in an increased risk of malignancy with calcitonin.

A meta-analysis on the risk of cancer was performed for the intra-nasal trials, for each dose of calcitonin against placebo. This analysis suggested a similar level of risk for all calcitonin doses compared to placebo, as illustrated by the results summarised in the table below.

Table 13: Odds ratio for the risk of cancer by calcitonin dose compared to placebo in the intra-nasal calcitonin trials

Calcitonin dose	100 IU	200 IU	400 IU
OR (95% CI)	1.52 (0.87,2.65)	1.55 (0.94,2.55)	1.44 (0.87,2.37)

Heterogeneity test for the intranasal calcitonin trials meta-analysis

To assess heterogeneity between these trials, Cochran's Q test and I^2 statistic were used for all malignancy events and for individual Preferred Terms (PT). The high p-values of the Q-test and low I^2 (0.8289 and 0 respectively for all cases of malignancy) are suggestive of low heterogeneity across the studies. The only event for which there appears to be some heterogeneity is for malignant melanoma (I^2=57%, p-value for Q test =0.095). The information provided by the MAH confirms the validity of the meta-analysis as there does not appear to be significant heterogeneity across the studies included in the analysis.

Duration of intra-nasal calcitonin trials

Twelve of the conducted trials with intra-nasal calcitonin were 2 years in duration (CT211, CT310, CT 311, CT 312, MIA 16, SMCO 503, SMCO 504, SMCO 514, SMCO 517, SMCO 520, SMCO 522, SMCO 524. Only 2 studies were of shorter duration (study 2402 was 6 months and study SMCO 005 one year). Two further studies were conducted over 3 years (study SMCO 506 & study SMCO 511) and one study (CT 320) was 5 years in duration. The duration of most of the studies was comparable. Malignancy events were not reported in the study with an observation period of 6 months, which is therefore expected to have a negligible effect on the results.

Stratification of results by study duration, age groups and cumulative dose of calcitonin

According to the MAH, it was not feasible to recover patient-level data for time on treatment or cumulative dose (particularly for patients who did not report a malignancy), since electronic data were unavailable for most of the nasal calcitonin studies, several of which were conducted over 20 years ago.

However the MAH presented the distribution of malignancy cases according to age, time to onset and dose administered during the trials. These results are summarised in the following table.

Table 14: Distribution of malignancy cases during the intra-nasal calcitonin trials according to patient's age, time to onset and administered dose

	Calcitonin	Placebo
Age (years)		
<60	30 (22.7%)	7 (21.8%)
60-70	53 (40.1%)	16 (50%)
>70	49 (37.1%)	9 (28.1%)
Unknown	0	1 (3.1%)
Time to onset (years)*		
< 1	34	7
1-2	22	4
>2	43	10
Unknown	2	1
Dose (International Units)		
50	6 (18.7%)	-
100	32 (24.2)	-
200	47 (35.6%)	-
400	47 (35.6%)	-

**Information on time to onset was not available for all the cases*

The MAH also provided a summary of time to events per calcitonin dose which are summarised in Table 15. No clear relationship, between time to onset and calcitonin dose was observed.

Table 15: Summary of time to events of malignancy by calcitonin dose in the intra-nasal calcitonin trials

Calcitonin dose	**25 IU**	**50 IU**	**100 IU**	***200 IU**	***400 IU**
Time to event (months)					
Mean	21.8	9.6	25.9	17.7	23.9
Median	25.6	11.0	23.7	13.7	18.0

** Time to onset was not available in five cases (2 in the 200 IU and 3 in the 400 IU groups)*

The CHMP considered that the analysis provided with regards to age, time to onset and dose does not provide any significant information on the possible association of calcitonin with cancer.

Demographics of trial participants

Summary tables of the demographics of the participants in 14 of the 17 intranasal calcitonin trials have been provided. The data provided by the MAH on the demographics of the different treatment arms of the calcitonin trials did not include pre-existing history of cancer, but appeared to be adequately balanced for other major risk factors such as age, smoking and alcohol consumption, and therefore it is unlikely that the observed increased risk of cancer could be attributed to inadequate randomisation of the patients in these trials.

Breakdown of all events of malignancy observed in the trials

The MAH presented the number of cases of neoplasm (both benign and neoplasm), death and death due to malignancy for all the intra-nasal calcitonin trials per treatment group and per trial.

Table 16: Cases of neoplasms, deaths and deaths due to malignancy in the calcitonin intra-nasal trials

		Calcitonin (N=2284)			
	Placebo (N=969)	**50 IU (N=239)**	**100 IU (N=622)**	**200 IU (N=754)**	**400 IU (N=669)**
Neoplasm					
Malignant	30	6	32	46	46
Benign	4	0	2	1	0
Total	34	6	34	47	46
Death					
All cause	24*	3	7	31	20*
Cancer	0	1	2	2	3

** The fatal cases for the placebo and calcitonin 400IU groups, contain one case each in which the patients had also been receiving nandrolone*

It should be noted that 4 of the malignant cases in the calcitonin 200 IU and 4 in the 400 IU groups occurred in the open label extension phase of two trials. In addition, 4 fatal cases were also reported in the open label phase of these studies (1 in the 100 IU group and 3 in the 200 IU group).

On the other hand, 5 malignant cases in the open label phase of these studies were reported for the placebo group. In the MAH's response these cases have been accounted for in the placebo group, but as it is not possible to determine the treatment that these patients received in the extension phase of the study, these cases have not been included in the table above.

Similarly, 4 additional fatal cases were observed in the open label phase of these two studies in the placebo group (one of which was related to cancer), which have also been omitted from Table 16, as it is not possible to determine their exposure in the open label phase.

Of significance is the clear imbalance in the cancer mortality between the two treatment arms of the trials. One cancer death occurred in the placebo treated patients but this occurred during the open label extension phase of a double-blind trial. On the other hand, there were 8 cases in the calcitonin group, in most of which there appears to be pre-existing relevant medical history. However rather than confounding these cases, this observation would appear to be supportive of the notion that calcitonin can promote tumour growth, as has been suggested in the published literature.

An analysis of cancer mortality and all-cause mortality for the different arms of the trials

The MAH also provided tabulated summaries of all the fatal cancer cases which are summarised below. In this summary there appear to be 9 malignancy cases from the double blind controlled studies, all in patients treated with calcitonin. In two cases the dose of calcitonin was recorded as not known, even though from the trial by trial breakdown of fatal cases, it appears that both patients had received 400 IU/day.

Table 17: Summary of fatal cases related to cancer from the calcitonin intra-nasal calcitonin trials

Event	Age/Sex	Dose	Time to onset	Comments
Lung neoplasm malignant	NA/M	200 IU	730 days	Hx of interstitial lung disease and RA
Progressive lymphoma	74/F	NA	540 days	Hx of lymphoma and RA
Bronchogenic carcinoma/ liver adenocarcinoma	70/M	NA	540 days	Hx of COPD, RA
Lymphoma of spine	74/F	200 IU	Unknown	Hx of thoracic spinal tumour excision
Mesothelioma	71/F	200 IU	930 days	Hx of breast cancer
Leukaemia	U/F	400 IU	28 days	Pre-existing leukaemia
Breast cancer metastasis	48/F	50 IU	765 days	Tumorectomy of breast cancer, one year prior to inclusion in study
Colon carcinoma	49/F	100 IU	NA	-
Adenocarcinoma of billiary tract	49/F	100 IU	NA	-

NA: Not available, RA: Rheumatoid Arthritis

An estimate of the absolute risk of the incidence of cancer in patients treated with calcitonin

Following a review by the MAH, the absolute risk for calcitonin (sCT) and placebo was calculated to be 122/2666=4.58%, and 28/1264=2.22%, respectively. The attributable difference is 4.58%-2.22%=2.36%.

Additional data from the new oral calcitonin formulation

Three recently conducted double-blind, multi-centre, placebo-controlled studies with the newly developed oral formulation of salmon calcitonin were also taken into consideration during this referral. Two of these were osteoarthritis studies (C2301 and C2302), where patients received 0.8mg twice daily. The third one was study A2303, a phase III study, conducted in post-menopausal women with osteoporosis.

- **Cancer cases in study C2301**

The recently conducted clinical study was the first of two osteoarthritis studies, where patients received 0.8mg of the newly developed oral formulation of salmon calcitonin twice daily over 24 months. Preliminary analysis of the safety data demonstrated an imbalance in the number of patients with treatment emergent adverse events in the System Organ Class (SOC) 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' of 4.6% in the active group (recombinant sCT/5-CNAC) compared to 2.7% in the placebo group (relative risk RR 1.68 [95% CI 0.92, 3.09]).

The most frequently reported preferred term in this SOC was prostate cancer (4 cases out of 169 males in the active group vs. zero out of 201 males in the placebo group) and basal cell carcinoma (3/169 in the active group vs 0/201 in the placebo group). As a result of this, the MAH conducted a detailed post-hoc prostate cancer screening programme, which will be discussed separately.

Events of malignancy or of unspecified tumours (but excluding benign tumours) reported in this trial are summarised in the Table below:

Table 18: Adverse events of malignant or unspecified tumours from study C2301

Preferred term (PT)	**Calcitonin (N=585) n (%)**	**Placebo (N=584) n (%)**
Breast cancer	2 (0.3)	2 (0.3)
Prostate cancer	4 (0.7)	0
Basal cell carcinoma	3 (0.5)	0
Neoplasm skin	2 (0.3)	1 (0.2)
Skin cancer	0	2 (0.3)
Uterine cancer	2 (0.3)	0
Bile duct cancer	1 (0.2)	0
Breast neoplasm	1 (0.2)	0
Cervix carcinoma	1 (0.2)	0
Lung neoplasm	0	1 (0.2)
Lung neoplasm malignant	1 (0.2)	0
Malignant melanoma	1 (0.2)	0
Neoplasm	1 (0.2)	0
Ovarian cancer	1 (0.2)	0
Rectal cancer	1 (0.2)	0
Squamous cell carcinoma	1 (0.2)	0
Thyroid neoplasm	1 (0.2)	0
Total	**23 (3.9)**	**6 (1.0)**

The figures provided indicate that the estimated relative risk (RR) and 95% CI for patients receiving calcitonin in relation to placebo for these terms is 3.8 (1.56-9.32).

- **Cancer cases in study C2302**

Details of all cases reporting malignancy from study C2302 was also provided, including calculation of relative and absolute risks for the incidence of cancer in these trials.

Table 19: Absolute and relative risks for the incidence of cancer in the oral calcitonin trial C2302

	Calcitonin		**Placebo**		**RR (95% CI)**
Study	**n/N**	**Risk (95% CI)**	**n/N**	**Risk (95% CI)**	
C2302	21/520	4.0 (2.35-5.73)	14/508	2.8 (1.33-4.18)	1.47 (0.75-2.85)

- **Cancer cases in study A2303**

A2303 was a double-blind, multi-centre, placebo-controlled phase III study with the new oral calcitonin formulation, conducted in post-menopausal women with osteoporosis and completed in December 2011. The treatment period was 36 months.

A list of all events of malignancy in this trial as presented in the provided case narratives are summarised in the table below.

Table 20: Events of malignancy reported in patients in trial A2303

Preferred term	Calcitonin (N=2334)	Placebo (N=2331)
Breast cancer	19	14
Basal cell carcinoma	16	8
Ovarian cancer	3	-
Uterine cancer	3	1
Rectal cancer	3	3
Lung neoplasm malignant	3	5
Skin cancer	3	2
Chronic lymphocytic leukaemia	3	1
Thyroid cancer	2	1
Malignant melanoma	2	2
Squamous cell carcinoma	2	-
Multiple myeloma	2	-
Lymphoma	2	1
Bladder cancer	-	3
Vulvar cancer	-	2
Uterine carcinoma in situ	1	-
Lung cancer metastatic	1	-
Bronchial carcinoma	1	-
Nasal sinus carcinoma	1	-
Renal cell carcinoma	1	-
Adult T-cell leukaemia	1	-
Cervix carcinoma stage 0	1	-
Cervix carcinoma	1	-
Ovarian cancer metastatic	1	1
Endometrial cancer	1	-
Colon cancer	1	1
B-cell lymphoma	1	-
Adrenal carcinoma	1	-

Mastectomy	1	1
Metastasis	1	1
Neoplasm malignant	1	-
Renal cancer	-	1
Carcinoma in situ	-	1
Chronic leukaemia	-	1
Carcinoid tumour of the GI tract	-	1
Carcinoid tumour of the stomach	-	1
Carcinoid tumour pulmonary	-	1
Lung adenocarcinoma stage IV	-	1
Cervix carcinoma stage III	-	1
Adrenocortical carcinoma	-	1
Mucoepidermoid carcinoma	-	1
Gastro-oesophageal cancer	-	1
Rectosigmoid cancer	-	1
Metastases to the lymph nodes	-	1
Pancreatic carcinoma	-	1
Pancreatic carcinoma metastatic	-	1
Breast cancer metastatic	-	1
Total	79 (3.38%)	63 (2.7%)

Table 21: Absolute and relative risks for the incidence of cancer in the oral calcitonin trials A2303

	Calcitonin		**Placebo**		**RR (95% CI)**
Study	**n/N**	**Risk (95% CI)**	**n/N**	**Risk (95% CI)**	
A2303	89/2334	3.8 (3.04-4.59)	87/2331	3.7 (2.96-4.50)	1.02 (0.76-1.36)

- **Meta-analysis of cancer cases of the oral calcitonin clinical trials**

A meta-analysis of the three recently conducted phase III studies using the newly developed oral formulation of salmon calcitonin was also provided.

A summary of the study characteristics is given in the Table below:

Table 22: Characteristics of oral sCT phase III studies

Study	Indication	Dose	Duration	Sample size
A2303	Osteoporosis(OP)	0.8 mg once daily	3 years	SMC021: 2334 Placebo: 2331
C2301	Osteoarthritis (OA)	0.8 mg twice daily	2 years	SMC021: 585 Placebo: 584
C2302	Osteoarthritis (OA)	0.8 mg twice daily	2 years	SMC021: 520 Placebo: 508

The two osteoarthritis (OA) trials were of almost identical design, same target exposure (2 years, twice daily) and similar sample size including both male and female patients. The single osteoporosis (OP) trial had a different target exposure (3 years, once daily), a larger sample size and included only women.

From the data on the oral calcitonin trials presented above, the estimated incidence of cancer in all three oral calcitonin trials is 3.8% for calcitonin and 3.1% for placebo. Therefore the attributable difference is 0.7%. The incidence rate ratio (i.e. exposure time adjusted risk ratio) of malignancy events in the 3 recent calcitonin trials was calculated (Table 23).

Rate ratios were calculated by Poisson regression with the time to first malignancy event or last dosing (whichever was first) in the denominator. Sex was included as a covariate to account for potential differences due to sex-specific types of malignancies. Analysis was conducted using the fixed effects model, but no information on heterogeneity or weighting of the individual studies was provided. The results of the meta-analysis are presented in the following table:

Table 23: Meta-analysis of the malignancy event incidence rates per 100 patient years exposure (until event or censorship) in the oral calcitonin clinical trials

	Incidence Rate (95%CI)		Incidence rate ratio (95% CI)
Study	**Calcitonin**	**Placebo**	
A2303	1.7 (1.37,2.07)	1.5 (1.24,1.88)	1.10 (0.820,1.48)
C2301	2.5 (1.65,3.81)	0.6 (0.27,1.35)	4.13 (1.67,10.19)
C2302	2.7 (1.75,4.13)	1.7 (0.99,2.83)	1.61 (0.818,3.163)
Combined	2.0 (1.62,2.45)	1.5 (1.20,1.87)	1.33 (1.035, 1.72)

A relatively large number of patients dropped out in all studies, and these were higher in the calcitonin group compared to placebo. This was primarily due to very early drop outs in the calcitonin group caused by intolerability to “events typical for oral calcitonin (gastrointestinal events, hot flushes, erythema etc)”. However after reviewing the case narratives provided for the malignancy cases, there were very few instances in both treatment arms where the patient was only briefly exposed to treatment before the diagnosis of malignancy. It therefore appears unlikely that this would have a significant effect on the reported incidence rates.

It is also important to note that in this analysis a number of additional prostate cancer cases, which were identified following the post-hoc screening programme, were included in study C2302 (but not

C2301). In addition, male participants in trial C2302 were discontinued prematurely from the study following the prostate cancer signal in trial C2301.

The reported lower risk in trial A2303 compared to the other 2 trials could possibly be explained by the lower calcitonin dose used in that trial (0.8mg once daily compared to twice daily in the two osteoarthritis trials).

- **Time analysis of incidence of cancer in the oral and intranasal calcitonin trials**

A time to event summary for the intranasal and oral calcitonin trials was provided, which did not reveal any significant differences between the two treatment arms of the trials or the calcitonin formulations.

Table 24: Summary of time to events of malignancy by formulation and treatment in the calcitonin trials

	Intra-nasal		Oral	
	Calcitonin	**Placebo**	**Calcitonin**	**Placebo**
Time to onset (months)				
Mean	21.8	22.4	17.1	17.3
Median	16.8	16.8	16.2	16.9

Finally, the MAH provided a breakdown of the incidence of first malignancy by 6-month treatment windows for both the intra-nasal and oral calcitonin trials.

Table 25: Time analysis of incidence of cancer in the calcitonin trials

	Calcitonin / Placebo							
Months	**0**	**6**	**12**	**18**	**24**	**36**	**48**	**60**
Intra-nasal trials								
N	2634/1234	2377/1105	2077/902	1885/826	1770/784	742/334	495/154	383/128
Events	-	22/9	25/2	14/2	10/2	24/4	7/1	15/5
%	-	0.9/0.8	1.2/0.2	0.7/0.2	0.6/0.3	3.2/1.2	1.4/0.6	3.9/3.9
Oral trials								
N	3439/3423	2876/3092	2664/2887	2507/2757	2094/2290	427/404	-/-	-/-
Events		20/17	21/22	30/20	21/18	38/30	-/-	-/-
%	-	0.7/0.5	0.8/0.8	1.2/0.7	1.0/0.8	8.9/7.4	-/-	-/-
All trials								
N	6073/4657	5253/4197	4741/3789	4392/3583	3864/3074	1169/738	495/154	383/128
Events	-	42/26	46/24	44/22	31/20	62/34	7/1	15/5
%	-	0.8/06	1.0/0.6	1.0/0.6	0.8/0.7	5.3/4.6	1.4/0.6	3.9/3.9

The breakdown of events per 6-month time frames appears to suggest an increased risk of cancer for calcitonin treated patients after 12 months compared with placebo. However, the number of patients in the trials after 2 years drops considerably, which could have an effect on the ability to detect any differences after 2 years of treatment. Nevertheless, even at those later time points, calcitonin-treated

patients are still at a higher risk compared with placebo treated patients. The increase in the risk is more evident in the intra-nasal trials. As it has been discussed previously, the post-hoc prostate cancer screening and discontinuation of patients from the oral calcitonin trials following the emergence of a safety signal from the first oral calcitonin trial could have possibly masked any imbalance between the two treatment arms in these trials.

- **Cases of prostate cancer**

Due to the initial results from the completed study C2301 indicating a numerical imbalance of prostate cancer cases (4 cases out of 169 males in the calcitonin group vs. zero out of 201 males in the placebo group), the Data Monitoring Committee (DMC) of this study on 19 October 2010, recommended a prostate cancer screening program to be implemented in both C2301 and C2302 studies. This signal was further investigated by analysing retrospectively information on Prostate Specific Antigen (PSA) levels for all male patients included in the trial.

The MAH analysed the baseline characteristics of the male participants including testing PSA levels at baseline, various time points and at the end of study. Patients with elevated PSA levels were referred to an urologist for further examination and are presented in the table below:

Table 26: The number of samples analysed per time point in study C2301

	C2301 (n)			Placebo (n)		
	All	**Normal***	**Above***	**All**	**Normal***	**Above***
Month 00	155	139	16	187**	172	15
Month 06	133	118	15	170	155	14
Month 12	129	114	15	160	145	14
Month 24	120	109	11	156	142	13
R3* **	151	138	13	188	172	15
Completers** **	118	108	10	154	141	13

** "Normal" refers to the subjects with normal baseline total-PSA and "Above" refers to the subjects with baseline total-PSA above the normal range for their age group as defined below:*

<40 years Normal Range (ng/mL)<1.4, 40-49 years <2.0, 50-59 years <3.1, 60-69 years <4.1, ≥70 years <4.4

***One patient did not have a baseline sample available in the freezer.*

****R3 corresponds to the previously unscheduled PSA prostate cancer screening visit. The R3 visit took place 28-42 months (mean 33 months) after study start.*

*****Completers: Patients that have all samples available form baseline to R3.*

Total and serum free PSA values were also obtained and compared for the different time points in the study between placebo and calcitonin treated patients. This included further sub-analysis for patients with normal baseline PSA values and for patients with increased baseline values. Analysis of the statistical significance of these findings was not performed, however there does not appear to be major differences between placebo and calcitonin treated patients in this analysis.

Table 27: Shift between normal and increased PSA values at baseline and post-baseline during study C2301

	Post-baseline	
	Normal (%)	**Increased**
Calcitonin (n=155)		
Baseline normal: 139 (89.7%)	127 (91.4)	12 (8.6)
Baseline increased: 16 (10.3%)	0 (0)	16 (100)
Placebo (n=187)		
Baseline normal: 172 (92.0%)	153 (88.9%)	19 (11.0%)
Baseline increased: 15 (8.0%)	1 (6.7%)	14 (93.3%)

During this prostate cancer screening programme, the MAH identified 18 cases of prostate cancer (in addition to the 4 initial cases mentioned in Table 18), of which 8 were in patients treated with calcitonin and 10 in placebo treated patients. The mean age was very similar between placebo (68.5 years) and calcitonin (68.0) treated patients in this study. Only 5 of the patients diagnosed with prostate cancer had normal values of PSA at baseline.

Two additional cases of prostate cancer were initially observed in the second osteoarthritis study C2302. In this study, 200 males were randomized to oral calcitonin and 204 males to placebo.

In addition to the prostate cancer screening programme, all remaining male patients in this second study were required to exit the study earlier than the scheduled 24 month.

From study C2302, 12 cases of prostate cancer were identified (in addition to the 2 previously identified cases), 6 in each of the two treatment arms of the trial. The mean age was very similar between placebo (68.5 years) and calcitonin treated patients (68.0 years) in the first study, and slightly higher for calcitonin treated patients in the second study (70.9 years for the calcitonin-treated patients compared to 65.6 for the placebo treated patients). Only 3 of the patients diagnosed with prostate cancer had normal values of PSA at baseline.

The prostate cancer screening programme whilst identifying additional cases of prostate cancer cannot be used as evidence that calcitonin is not associated with prostate cancer. Considering the elderly population included in these trials identification of additional prostate cancer cases is not surprising as it is known that prostate cancer can remain undetected for long periods of time. The PSA analysis provided is overall of limited value and simply demonstrates that calcitonin has no significant effect on PSA values. However, it is known that factors other than prostate cancer, such as benign prostate enlargement, inflammation or infection can also influence PSA values.

It is important to consider that the incidence of prostate cancer cases during the trials only in calcitonin treated patients could possibly be explained by treatment related cancer progression resulting in symptomatic manifestation of the disease and further investigations leading to the diagnosis. A role for calcitonin in prostate cancer progression has been suggested in a number of published literature studies (discussed further in this report).

- **Mortality analysis of the oral calcitonin trials**

The MAH did not provide any analysis for the risk of death in the oral calcitonin trials. The number of deaths in each of the oral calcitonin trials was presented, which did not reveal any significant differences between calcitonin and placebo treated patients. But of relevance in the analysis of the association of calcitonin with cancer was the fact that 7 of the deaths in the calcitonin group (or 37.5% of the fatal cases) were due to malignancy, compared to 2 cancer deaths in the placebo group (or 10.5%).

- **Data submitted by a third party**

Data were also submitted by a third party with another oral calcitonin product for the treatment of post-menopausal women with osteoporosis. The data submitted were from two studies, one phase 3 and one phase 2 trials in which patients were treated with oral salmon calcitonin (n=349), intranasal calcitonin (n=182) or placebo (n=147) for over 1 year. There were 4 events of malignancy in the oral calcitonin arm of the trial (1.1% of patients), compared to 3 events in the placebo treated patients (2.0%). No events of malignancy were reported in the intra-nasal calcitonin treated group. Due to the short duration of the trials and also the relatively small number of patients that were included in these studies, the lack of a safety signal of cancer in these trials is not considered adequate to refute the evidence provided by the longer and larger trials conducted by Novartis.

2.4.2. Post-marketing spontaneous reports

Data from the Sanofi-Aventis pharmacovigilance database (Table 28) and the Novartis Global Safety Database (NGSD, Table 29) were analysed to identify all cases mapping to the Neoplasms benign, malignant and unspecified SOC The results of these searches are summarised below:

Table 28: Cases of Neoplasms benign, malignant and unspecified SOC from The Sanofi-Aventis pharmacovigilance database (data lock point of 31st March 2011)

Age / gender	Reported term	Time to onset (months)
58/F	Neoplasm	17
61/F	Carcinoma	11
62/M	Pulmonary carcinoma	7
53/F	Breast neoplasm malignant	5

Table 29: Most commonly reported types of malignancies reported in patients receiving calcitonin in the Novartis Global Safety Database

Type of cancer	Spontaneous reports		Solicited reports		Total
	HCP	NHCP	HCP	NHCP	
Basal cell carcinoma	0	1	19	4	24
Breast cancer	5	3	22	14	44
Colon cancer	0	0	7	6	13
Lung neoplasm malignant	2	2	6	8	18
Lymphoma	0	1	3	4	9
Malignant melanoma	0	2	4	1	7
Neoplasm malignant	0	5	13	10	29
Pancreatic carcinoma	1	1	5	5	12
Prostate cancer	1	0	3	4	8
Squamous cell carcinoma	0	0	8	2	10
Thyroid neoplasm	2	4	1	0	7

HCP: Health care professional, NHCP: Non-health care professional

These include spontaneous reports and also solicited cases, most of which were from clinical trials according to the MAH.

The CHMP acknowledged the difficulty in establishing causality based solely on spontaneous reports especially for an adverse event such as cancer. The difficulties in this case are further exacerbated by the fact that majority of the cases are very sparsely documented and that the target population is at an increased risk for cancer (due to advanced age). The value of these reports in establishing a possible association between calcitonin and cancer is therefore limited, and more weight should be placed on the other sources of information available.

2.4.3. Published literature

A brief overview of the literature studies concerning prostate cancer progression and calcitonin is presented in this section.

The presence of neuroendocrine cells, which secrete neuropeptides including calcitonin, in the prostate is well established[10]. In addition the presence of high binding affinity sites for calcitonin in plasma membrane fractions of human prostate tissue and the prostate cancer cell line LNCaP has been demonstrated using radioactive salmon calcitonin[11].

[10] di Sant' Agnese PA. Neuroendocrine differentiation in carcinoma of the prostate: diagnostic, prognostic and therapeutic implications. Cancer (Suppl 1). 1992; 70:254-268.

Shah GV, Noble MJ, Austenfeld M, Weigel J, Deftos LJ, Mebust WK. Presence of calcitonin-like immunoreactivity (iCT) in human prostate gland: evidence for iCT secretion by cultured prostate cells. Prostate. 1992;21(2):87-97.

[11] Shah GV, Rayford W, Noble MJ, Austenfeld M, Weigel J, Vamos S, Mebust WK. Calcitonin stimulates growth of human prostate cancer cells through receptor-mediated increase in cyclic adenosine 3',5'-monophosphates and cytoplasmic Ca2+ transients. Endocrinology. 1994 Feb;134(2):596-602.

A role for calcitonin in the growth and migration of prostate cancer cells has been suggested following a study which used 3 different prostate cancer cell lines[12]. This study demonstrated an increase in the proliferation and chemotaxis (the directed movement towards a certain chemical) of the LNCaP cell line, but a decrease in the proliferation of the remaining two cell lines (DU-145 and PC-3).

The levels of calcitonin in normal, hyperplastic and neoplastic tissue have been compared in a small study[13]. Calcitonin was detected in all prostate tissue specimens (from 42 patients). Levels of calcitonin in carcinoma tissue were found to be intermediate between normal and hyperplastic prostate tissue. The only significant difference was the reduction in the levels of calcitonin in the hyperplastic tissue compared to normal or cancerous tissue. *In-situ* hybridization histochemistry showed that expression of calcitonin and calcitonin receptor mRNA was confined in the basal epithelium of benign and low grade prostate cancer specimens[14]. In contrast, calcitonin and calcitonin receptor mRNA were detected throughout the luminal epithelium of moderate and high-grade prostate specimens.

The invasiveness of prostate cancer cell lines was shown to be positively influenced by calcitonin, even though this was demonstrated in only two of the four cell lines tested[15]. The most convincing result was in the PC-3M cell line. Calcitonin increased the levels of MMP-9 (metalloproteinase 9) in PC-3M cells. The ability of MMPs 2 and 9 to degrade gelatine was also increased in response to calcitonin. However, there was no clear dose response relationship, as the lowest concentration of calcitonin used (10 nM) suppressed the gelatinolytic activity of both MMP-2 and MMP-9 and peaked at 50 and 1000nM. These events were suggested to be mediated by Protein Kinase A (PKA), as inhibition or over-expression of PKA attenuated calcitonin induced invasiveness.

Expression of a functional calcitonin receptor has also been demonstrated in a human endothelial cell line[16]. Endothelial cell network formation assays, endothelial cell proliferation assays, cell invasion assays and *in vitro* tube morphogenesis on Matrigel suggested a role for calcitonin in angiogenesis. Angiogenesis in mice implanted with PC-3M cells over-expressing calcitonin was greater than those receiving PC-3M cells transfected with an empty vector plasmid or a plasmid expressing inactive ribozyme. The authors suggested that the angiogenic properties of calcitonin could significantly influence tumour growth by regulating intra-tumoural vascularization.

Over-expression and silencing of calcitonin in PC-3M, PC-3 and LNCaP cells was also used to investigate the role of calcitonin in tumour metastasis[17]. Implantation of calcitonin over-expressing PC-3M cells in nude mice, increased sizes of both primary and metastatic tumours in most distant organs, except mesentery and liver. Conversely, knock-down of calcitonin expression abolished tumourigenicity

[12] Ritchie CK, Thomas KG, Andrews LR, Tindall DJ, Fitzpatrick LA. The effects of growth factors associated with osteoblasts on prostate carcinoma proliferation and chemotaxis: implications for the development of metastatic disease. Endocrinology. 1997 Mar; 138(3):1145-50.

[13] Abrahamsson PA, Dizeyi N, Alm P, di Sant'Agnese PA, Deftos LJ, Aumüller G. Calcitonin and calcitonin gene-related peptide in the human prostate gland. Prostate. 2000 Aug 1;44(3):181-6.

14 Chien J, Ren Y, Qing Wang Y, Bordelon W, Thompson E, Davis R, Rayford W, Shah G. Calcitonin is a prostate epithelium-derived growth stimulatory peptide. Mol Cell Endocrinol. 2001 Jul 5;181(1-2):69-79

[15] Sabbisetti VS, Chirugupati S, Thomas S, Vaidya KS, Reardon D, Chiriva-Internati M, Iczkowski KA, Shah GV. Calcitonin increases invasiveness of prostate cancer cells: role for cyclic AMP-dependent protein kinase A in calcitonin action. Int J Cancer. 2005 Nov 20;117(4):551-60.

[16] Chigurupati S, Kulkarni T, Thomas S, Shah G. Calcitonin stimulates multiple stages of angiogenesis by directly acting on endothelial cells. Cancer Res. 2005 Sep 15;65(18):8519-29.

[17] Shah GV, Thomas S, Muralidharan A, Liu Y, Hermonat PL, Williams J, Chaudhary J. Calcitonin promotes in vivo metastasis of prostate cancer cells by altering cell signaling, adhesion, and inflammatory pathways. Endocr Relat Cancer. 2008 Dec;15(4):953-64.

and metastatic activity of PC-3M cells, as the primary tumour mass declined by 89% compared with wild type PC-3M cells and only a few colonies of metastatic cells were seen in the lymph nodes. Adenoviral vectors were also used to silence calcitonin expression and investigate the effect in tumour progression.

Adenoviral preparations silencing calcitonin (rAAV-CT) or encoding the empty vector (rAAV-C) were injected intra-tumourally in nude mice (which lack the thymus gland and therefore have a severely compromised immune system) and LPB-Tag transgenic mice, (which develop spontaneous prostate cancer around 30 days post-natal). Tumour mass was reduced by 80% in the nude mice and by 60% in the LPB-Tag mice, injected with the silencing vector compared to the control vector.

Evidence from published literature studies both *in vitro* and *in vivo* suggests an association between prostate cancer progression and calcitonin. However there are several limitations in these studies that need to be considered. Human and not salmon calcitonin has been used in all the experiments in these studies. Salmon and human calcitonin share only a 50% amino acid sequence homolog and have different secondary structures. Furthermore, salmon calcitonin is considered a much more potent hypocalcaemic agent than the human form. It is not possible to determine whether the suggested acceleration in tumour growth with human calcitonin would also apply to salmon calcitonin.

Generalization of the results is further limited by the fact that different cell lines responded differently to calcitonin, implying cell-line specificity. Despite the fact that the androgen-dependent LNCaP cell line appeared to be responsive to calcitonin in migration and proliferation experiments, subsequent experiments were performed mainly with the androgen independent PC-3M cell-line.

The *in vivo* data also suggest that calcitonin is involved in tumour progression. However, the physiological relevance of these experiments is debatable, as they were conducted in genetically manipulated mice with severely compromised immune system (nude mice), or in mice which naturally develop prostate cancer (LPB-Tag). In addition, calcitonin was administered either through cells over-expressing calcitonin or an adenoviral vector system and therefore it is not possible to correlate the levels of calcitonin in these experiments with normal therapeutic doses.

Despite these limitations, these studies provide a possible mechanism which can explain the increased risk of cancer which has been observed in the calcitonin clinical trials.

2.4.4. Discussion and Conclusions on safety

During this procedure the CHMP reviewed the available evidence on the risk of cancer with the use of calcitonin.

The results of the biggest of the trials conducted with intra-nasal calcitonin , study CT320 (also known as the PROOF study), provides some evidence of an increased risk of cancer in the calcitonin arm compared with placebo even though the reported results fail to reach statistical significance (relative risk, 95%CI: 1.47 (0.91-2.36)).

Further evidence of a possible association between calcitonin and the risk of cancer is provided by a meta-analysis of 17 randomised, controlled, double blind studies with intranasal calcitonin performed by one of the MAHs. The Odds Ratio (OR) for the incidence of cancer in these trials in patients treated with calcitonin was 1.61 (1.11-2.34). When including trials in which no cases of malignancy had been reported the estimated OR is 2.12. The increase in absolute risk of cancer for patients treated with calcitonin compared with placebo in the intra-nasal trials was 2.36%. The most commonly reported malignancies in these trials were basal cell carcinoma and breast cancer.

In addition, the mortality analysis revealed that only patients treated with calcitonin died from cancer during these trials, which suggests that calcitonin accelerates tumour growth.

Further evidence of a positive association between calcitonin and cancer was provided from the analysis of recently conducted trials with the new oral calcitonin formulation. Two of these were osteoarthritis studies (C2301 and C2302), where patients received 0.8mg twice daily. The third one was study A2303, a phase III study with the new oral calcitonin formulation, conducted in post-menopausal women with osteoporosis.

In the first of these trials (study C2301), a statistically significant increased risk of cancer was reported in patients treated with calcitonin compared with placebo (incidence rate ratio 4.13 (1.67-10.19)). The most commonly reported malignancy in this study was prostate cancer. As a result, an intensive post-hoc prostate cancer screening programme was implemented for all male participants in the two osteoarthritis trials. The increased risk of cancer with calcitonin in the other two trials with the new oral formulation, was not statistically significant incidence rate ratio of 1.61 (0.81-3.16) and 1.10 (0.82-1.48) for studies C2302 and A2303 respectively. Possible explanations for these discrepant results include the lower dose in the osteoporosis trial, and the premature discontinuation of male patients and an intensive prostate cancer screening programme in the second osteoarthritis trial, which identified additional cases and may have masked possible imbalances of cancer cases across the different treatment arms in these trials. However, in all trials there was a higher incidence of malignancies reported in calcitonin treated patients compared to placebo. In addition, the meta-analysis of the trials with the new formulation showed a statistical significant increase in the incidence rate ratio for patients treated with calcitonin, 1.33 (1.035-1.72), similar to the increase observed during the intranasal trials. Importantly, cancer mortality was again considerably higher in calcitonin treated patients in these trials compared to placebo; 7 cases (37.5%) compared to 2 (10.5%).

With regards to prostate cancer, information provided on prostate specific antigen (PSA) levels from all male patients in the first two osteoarthritis studies C2301 and C2302 showed that calcitonin does not have an effect on PSA levels. However the PSA analysis alone is of limited value as it is known that factors other than prostate cancer can influence PSA values and cannot explain the higher incidence of prostate cancer in patients treated with calcitonin. A number of published studies using prostate cancer cell lines and animal models have also suggested a role for calcitonin in prostate cancer progression. Although these studies in isolation were considered so far insufficient to establish a causal association due to some important limitations and the lack of any robust evidence of risk in humans, they assume a new significance in light of the more recent data from the calcitonin clinical trials.

Data from the Sanofi-Aventis pharmacovigilance database and the Novartis Global Safety Database were also analysed to identify all cases mapping to the Neoplasms benign, malignant and unspecified system organ class (SOC). Bearing in mind that the majority of the cases are very sparsely documented, establishing causality for an adverse event such as cancer based solely on spontaneous reports is not feasible.

The consistency of the results in the oral and intranasal trials suggests that the reported events are causally associated with calcitonin. The majority of the cancer cases reported in the calcitonin trials occurred after 12 months of treatment. A possible explanation, for the relatively short time of onset is that calcitonin promotes tumour progression rather than oncogenesis, as has also been suggested in the published literature addressing the role of calcitonin in prostate cancer. However despite the likelihood that calcitonin is involved in cancer promotion the exact mechanism that could explain the increased occurrence of malignancies in calcitonin treated patients has not been fully elucidated.

The diminishing use of calcitonin over the last years suggest that there is limited scope to further investigate the association by means of epidemiological studies, which in any case would be difficult to conduct and adequately control for all possible confounders for cancer.

Overall there appears to be sufficient and consistent evidence from the intranasal and oral calcitonin trials, that calcitonin is associated with an increased risk of cancer. This is most likely due to tumour growth acceleration, which has also been suggested in the published literature.

2.5. Overall benefit/risk assessment

Benefit/risk balance of calcitonin in the treatment of osteoporosis in order to reduce the risk of vertebral fractures

The limited efficacy data in this indication need to be balanced against an increased risk of cancer as demonstrated in the analysis of calcitonin trials. The consistency of the evidence across clinical trial data, provide strong evidence of a causal association. Even though there is some uncertainty surrounding the true magnitude of this risk which appears to be different across the different trials the relative risk is consistently higher in patients treated with calcitonin compared with placebo.

Considering the limited evidence of efficacy, the risk of cancer associated with the use of calcitonin, and the long term duration of treatment required for this indication, the benefit risk balance for the intranasal formulation of calcitonin for the treatment of osteoporosis in order to reduce the risk of vertebral fractures, which is the only indication for this pharmaceutical form, is considered to be negative.

Benefit/risk balance of calcitonin in Paget's disease

As discussed previously the efficacy of calcitonin in the treatment of Paget's disease is limited and is partially validated by its well-known use and its pharmacological plausibility.

In view of the safety concerns the CHMP was of the view that it was necessary to restrict the target population for this indication. Considering the availability of alternative treatments in this indication, the CHMP agreed that the use of calcitonin in Paget's disease should be limited to 3 months, and only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment. In exceptional circumstances eg. in patients with impending pathologic fracture, the CHMP agreed that the treatment duration may be extended up to a recommended maximum of 6 months. It was also agreed that periodic re-treatment may be considered in these patients taking into account the potential benefits and the association of cancer with long term calcitonin use.

Benefit/risk balance of calcitonin in the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures

Only limited evidence of efficacy in this indication is available. However, the short-term nature of the intended use of calcitonin in these patients is expected to minimise the potential risk of cancer, and therefore the benefit/risk balance is considered to be positive, but the treatment duration should be limited. Treatment duration is recommended to be 2 weeks and not exceeding 4 weeks in any case.

Benefit/risk balance of calcitonin in hypercalcaemia of malignancy

Efficacy of calcitonin for this indication is supported by established use of calcitonin in clinical practice. Considering the nature of the indication in the setting of advanced cancer, the benefit/risk balance in this indication is considered still to be positive.

2.6. Changes to the product information

The CHMP recommended that amendments be introduced in the Summary of Product Characteristics (SmPC) of the injectable formulation of calcitonin-containing products changes, affecting the following sections: 4.1, 4.2, 4.4 and 4.8.

Similar amendments should be introduced to sections 1, 2, 3, and 4 of the Package Leaflet (For detailed changes see enclosure 10). One of the MAHs proposed to conduct a healthcare professional survey using an online questionnaire. The CHMP considered that that such a survey would be of interest to assess the effectiveness of the changes to the product information.

2.7. Re-examination procedure

Following the adoption of the CHMP opinion and recommendations during the July 2012 CHMP meeting, a re-examination request was received on 8 August 2012 from one of the MAH Therapicon, who was involved in the referral procedure. The re-examination of the CHMP opinion was related to the benefit-risk balance of the intranasal formulation of calcitonin in the *indication "treatment of osteoporosis in order to reduce the risk of vertebral fractures".*

The MAH also expressed disagreement on some procedural aspects of the referral procedure. However it is noted that the CHMP is a scientific committee and that while it operates within the legal framework, it cannot discuss the specific merits of procedural and legal aspects of administrative procedures laid down in the legislation. As a result, procedural and legal considerations are outside the remit of the CHMP, and therefore the re-examination of the CHMP opinion of the referral procedure under Article 31 of Directive 2001/83/EC focused only on the scientific grounds for re-examination.

Detailed grounds for re-examination submitted by the MAH

The scientific points of disagreement presented in the MAHs detailed grounds included non-clinical and efficacy aspects, pharmacovigilance, overall benefit (risk assessment), formulation and statistical issues.

- Non-clinical aspects

The MAH Therapicon presented additional published literature studies to support their view that the high levels of CT receptor (CTR) are associated with growth suppression, and also to show that cell types other than prostate cell lines have been investigated to determine if the impact of CT binding to its receptor is consistent with suppression of cell proliferation.

Evidence was also provided from published studies performed in transgenic rodents, which constitutively over express CT achieving blood levels 10-20 fold higher than nasal CT have not reported any increased observations for cancer.

The MAH Therapicon also argues that the chronic carcinogenicity studies demonstrate that there is no evidence for multi-site tumour promotion of calcitonin based on the rodent chronic toxicity (one-year duration) and carcinogenicity (two-year duration) studies, as stated in the non-clinical section above.

- Efficacy aspects

The MAH claims that the CHMP assessment report criticises on several points, the PROOF study, which is the pivotal study demonstrating efficacy of intranasal sCT for the treatment of postmenopausal osteoporosis. It is also argued that although the improvement in bone mineral density (BMD) following administration of calcitonin is more modest than observed with other agents, recent understanding of bone biology recognizes that BMD accounts for only a small fraction of the fracture efficacy for anti-resorptive drugs.

- Pharmacovigilance

The MAH argues that a review of all available pharmacovigilance data has not been taken into account during the assessment. Data from global safety databases such as WHO Vigibase™ system, and information from Health Canada and the US have revealed little or no AEs relating to malignancies reported with the use of calcitonin-containing medicines.

- Overall benefit: risk assessment

The MAH emphasises that the primary prospectively defined endpoint for the PROOF study - the efficacy of 200 IU calcitonin daily for the prevention of vertebral fracture, has been demonstrated.

While the MAH acknowledges that spontaneous (post-marketing) reports (from the Sanofi-Aventis and Novartis safety databases) are of limited value, it is argued that the report obtained from the WHO Vigibase™ reviewed for adverse drug events in the —Neoplasms SOC reported between 1976 and 2012 for all calcitonin-containing products, contained approximately 43 reports of ADRs consistent with cancer.

When considered as a whole, the MAH argues that the presented data are inconsistent with a hypothesis of calcitonin as a tumour accelerator or promoter.

- Formulation issues

Benzalkonium chloride (BAK) is included in the approved Miacalcic product as a preservative for the sCT peptide at a concentration of approx. 0.01% (w/w). The daily exposure of BAK upon intranasal administration of a therapeutic dose of sCT is 9 micrograms. The MAH argues that the presence of BAK in the nasal spray product may add to or cause some adverse effects seen with that product.

- Statistical issues

The MAH believes there are substantial methodological and logical flaws, such that an inappropriate conclusion was reached. In addition to these issues, the absence of causality and other sources of potential bias are also raised.

CHMP conclusion on grounds for re-examination

- Efficacy aspects

As mentioned previously and also by the MAH, the efficacy of the intranasal calcitonin-containing medicinal products to reduce the risk of vertebral fractures in postmenopausal women is based on the results of a randomized placebo control study referred to as the PROOF (Prevent Recurrence of Osteoporotic Fractures) study. A total of 1,255 women with established osteoporosis were randomly assigned to receive salmon calcitonin nasal spray (100, 200, or 400 IU) or placebo daily, and the primary end-point was the risk of new vertebral fractures in 200IU group compared to placebo.

Treatment with 200 IU intranasal calcitonin significantly reduced the risk of new vertebral fractures by 33% compared to placebo [200 IU: 51 of 287, placebo: 70 of 270, relative risk (RR) = 0.67, 95% confidence interval (CI): 0.47– to 0.97, P=0.032]. The 100 IU and 400 IU calcitonin groups showed decreases in new vertebral fractures of 15% and 16% respectively relative to placebo although without reaching statistical significance. A reduction in the relative risk of developing a new vertebral fracture versus placebo in patients with 1-5 prevalent fractures and in 3-year valid completers, both secondary analyses, was also provided showing statistically significant reductions in the two highest doses tested vs placebo.

As previously highlighted there are limitations in the PROOF study, i.e. statistical significance was not achieved (for calcitonin 200UI) when analysing patients with at least 2 new fractures, lack of a dose-response relationship, lack of adjustment for multiple testing and very high percentage of treatment discontinuations. Despite that, and in line with the MAH's claim, these study results have been accepted over 40 years as being valid to support the efficacy of intranasal calcitonin in the prevention of vertebral fractures in postmenopausal women with osteoporosis and was considered sufficient to conclude on a positive benefit/risk balance during the previous referral.

However, the CHMP is of the view that the magnitude of the effect is modest, with an absolute reduction of approximately 6% and 1.7% in the patients with ≥1 and ≥2 new vertebral fracture respectively compared to placebo. It is also noted that the effect is limited to vertebral fractures and not always supported by other relevant secondary endpoints. Nevertheless, considering that no new efficacy studies were presented which modify the previous outcome on efficacy the conclusion remains that calcitonin-containing medicinal products can be effective in the treatment of postmenopausal osteoporosis.

Even though the MAH acknowledges that the demonstrated effect of intranasal sCT on BMD is modest, it is argued that even modest increases in BMD can result in a significant decrease in fractures, according to advances in the understanding of bone biology. However the CHMP considered that BMD, is still regarded to be an important surrogate marker, which was shown to have a modest but statistically significant increase in comparison with placebo.

- Safety aspects

Non-clinical aspects

An association between prostate cancer progression and cancer has been suggested in the brief overview of the published literature studies presented earlier on in this assessment report. The MAH Therapicon has submitted a summary of published literature that provides evidence to the contrary. Ritchie, et al. (1997)[18], reported that hCT decreased proliferation of PC-3 and DU-145 cell lines and Segawa, et al. (2001)[19] also reported that DU-145 cells treated with CT had decreased levels of ERK[20] activity (which has been shown to be closely related with the suppression of cell proliferation) and cell growth.

However the CHMP is of the view that it is not possible to reach a conclusion about the association between CT and cancer progression from the results of the published non-clinical in vitro studies. Data suggest that there is some relation for prostate cancer but it is not possible to generalise these results.

The physiological relevance of the *in vivo* experiments that suggest CT is involved in tumour progression is debatable as they were conducted in genetically manipulated mice, and CT was administered through cells overexpressing CT or by an adenoviral vector system. Therefore it is not possible to correlate the levels of CT in these experiments with the therapeutic doses.

The MAH justifies the absence of clinical relevance of the pituitary adenomas observed in rats during carcinogenicity studies arguing that Sprague-Dawley rats in particular, have a high rate of spontaneous pituitary adenomas. The CHMP agrees that this is indeed supported by the biopsies of these adenomas, which were characterised as non-functioning α-subunit secreting tumours that are known to occur spontaneously in rats, and by a binding study which demonstrates that salmon calcitonin binds to extract from rat but not human pituitaries. Additionally, pituitary adenomas were not found in a similar

[18] Ritchie CK, Thomas KG, Andrews LR, Tindall DJ, Fitzpatrick LA. Effects of the calciotrophic peptides calcitonin and parathyroid hormone on prostate cancer growth and chemotaxis. Prostate. 1997, 30:183–187.
[19] Segawa N, et al. Phosphorylation of Mitogen-activated Protein Kinase is Inhibited by Calcitonin in DU145 Prostate Cancer Cells. Cancer Res. 2001, 61:6060-6063.
[20] Extracellular signal-regulated kinase

carcinogenicity study performed in mice, even though mice were treated with higher doses than rats. Therefore, the effect could be considered to be species-specific. The CHMP considers that the most relevant non-clinical studies are the chronic carcinogenicity assays in rats and mice, which are not conclusive with regard to the carcinogenic potential of calcitonin.

The CHMP also consulted a group of experts to gain their view on whether there could be a possible mechanism for which calcitonin may be related to cancer progression. There was a clear consensus among the experts that from the data currently available a possible mechanism has not been established, neither for any specific cancer type nor for an unspecific tumour promoting effect.

Statistical issues (meta-analysis)

The MAH also raised some points on the methodological flaws of the meta-analysis of the 17 intranasal calcitonin studies and provided a re-analysis of data.

The MAH argues that the studies included in the meta-analysis lacked a defined PICO (population, intervention, comparison and outcome) statement. The CHMP notes that any meta-analysis driven by a safety signal will always be, per definition, conducted post-hoc, the objective of such an analysis being to quantitatively rule out a potential harm to patients. For this purpose the methodology used was judged to be sufficient by the CHMP.

The MAH also questions the validity of the evidence of the available clinical trials that substantiated the efficacy of the product, arguing that the evidence is not valid for safety because of confounding factors. While this argument might be valid for observational studies, the CHMP is of the view that the potential bias in randomised clinical trials is likely to be less, as the randomisation procedure should provide sufficiently well balanced groups. Even so, the CHMP concluded that there is evidence of an increased risk of cancer among the exposed, with some degree of consistency – especially among the larger studies.

The MAH considers that the exclusion of four studies from the meta-analysis in which no cancer cases were observed, lacks basis. While it is recognised by the CHMP that the inclusion or exclusion of single trials will adjust the overall odds ratio (OR) in different directions, it is acknowledged that it is reasonable to conduct a list of sensitivity analyses to assess the robustness of the results. The differences are not considered to be sufficiently convincing to alter the previous CHMP conclusion regarding an increased risk of cancer with calcitonin-containing medicinal products.

The MAH questions the results of the meta-analysis because of the use of fixed-effects models in the presence of heterogeneity. The CHMP considers that while this argument might be valid for the meta-analysis conducted on the studies with the oral formulations, it cannot be supported in the analysis with all intranasal trials where no clear heterogeneity is observed. Moreover, beyond any discussion of whether the statistical significance is achieved in some cases or not, there is an evident, consistent and clear trend of an increased risk of cancer. In this setting, the statistical significance is superseded by clinical relevance.

It is also pointed out by the MAH that the point estimate OR is used, which is more likely to provide a significant result then the corresponding RR. However the CHMP was of the view that regardless of whether OR or RR are used, the signal is apparent, which can even be partly assessed by even looking at crude rates. The inconsistency in the summary statistics given is recognised by the CHMP but the impact on the overall interpretation must be regarded as marginal or non-existing.

The CHMP also consulted a group of experts to gain their view on whether the results of the meta-analysis could be considered reliable. All the experts were of the view that the meta-analysis did have shortcomings and some flaws, partly due to the quality of the data. However the view of the majority

of experts was that the results across different analytical approaches of the available data were such that a safety signal related to cancer could not be dismissed at this stage.

The MAH also discusses the lack of causality based on the Bradford-Hill criteria, which have been taken into account and assessed. However none of the arguments presented refute the conclusion derived from the results of the intranasal (and oral) studies, which suggests that that there is an increased risk of cancer associated with the use of calcitonin.

Pharmacovigilance

The MAH discussed the low number of post-marketing spontaneous cases of cancer reported with calcitonin. The CHMP noted that the low reporting is not unexpected in this particular situation where the event under scrutiny (i.e malignancies), is not uncommon in the target population that otherwise receive a number of concomitant medications, where the risk increases with time making it very unlikely for physicians to establish a possible relation. Another factor that could explain low reporting rate is the fact that calcitonin have been authorised for nearly 40 years. Therefore, the scarce number of cases of cancer in patients who are or have been treated with calcitonin that are found in global safety databases cannot lead to any conclusions, mainly when balanced against data coming from clinical trials.

In the presence of a safety risk identified by analysing the most relevant and robust evidence available, i.e. meta-analysing well designed and conducted randomised controlled clinical trials with calcitonin medicinal products, the value of the spontaneous reporting is questionable, and cannot revert a conclusion based on the randomised controlled clinical trials.

Formulation issues

The MAH argues that the use of BAK as a preservative in intranasal formulations has revealed increasing concern that exposure of nasal epithelia to BAK may lead to induction of pathologic or histological changes by causing increased swelling of nasal epithelium.

The CHMP notes that some of the studies reported have been conducted with BAK at very high concentrations in non-clinical assays, much higher than those allowed in intranasal/ocular formulations, and at exposures higher than those expected to be systematically available following these routes of administration when used as a preservative in those formulations. But so far, no association with cancer related events has been reported, neither local nor systemic.

Since this association has not formally been studied, a potential contribution is questionable. It is also noted that no discussion has been presented by the MAH on some critical findings to support this hypothesis, i.e. the systemic exposure to BAK at the doses used in intranasal formulations is expected to be low, and no tumorigenic association has been found so far with other solutions in which BAK is commonly used. Furthermore the studies with oral calcitonin formulations that are free-BAK formulations also raised this safety concern. Notably, BAK is a preservative commonly used in a number of intranasal and ophthalmic formulations for which no association has been suggested.

Given that the oral formulations are BAK free formulations, the CHMP considers this hypothesis to be highly questionable and does not provide an explanation for the concern.

In summary the MAH has not provided convincing evidence/arguments in support of a potential contributor effect of BAK.

- Overall benefit-risk assessment

As mentioned before, it is agreed that the PROOF study shows a modest efficacy of calcitonin in the reduction of the risk of vertebral fractures. However, the new evidence related to the risk of cancer impacts the safety profile of calcitonin-containing medicines.

From the meta-analysis of the intranasal calcitonin studies, the data point towards an increase in the risk of cancer in patients treated with intranasal calcitonin compared to placebo. As expected, the risk of cancer increases when excluding the four studies with no events. These data are also supported by the meta-analysis of the 3 studies (C2301, C2302 and A2303) performed with the oral formulations.

Recognising the potential limitations of the clinical trials included in the analysis, the observed increased risk of cancer needs to be balanced against the modest benefit of calcitonin.

Overall conclusion of the re-examination procedure

The scope of the re-examination was the benefit/risk of intranasal formulation of calcitonin-containing medicinal products in the indication of "treatment of osteoporosis in order to reduce the risk of vertebral fractures".

Based on the totality of the data available on the safety and the efficacy of intranasal calcitonin-containing medicinal products and having noted the opinion of the Ad-Hoc Expert meeting, the CHMP confirmed its initial conclusion that the limited efficacy in this indication needs to be balanced against evidence from clinical trials for an increased risk of cancer with long-term use of calcitonin.

Considering the limited evidence of efficacy, the risk of cancer with the use of calcitonin, and the long term duration of treatment required for this indication, the benefit risk balance for the intranasal formulation of calcitonin for the treatment of osteoporosis in order to reduce the risk of vertebral fractures, which is the only indication for this pharmaceutical form, is considered to be negative.

The Committee therefore concluded the benefit-risk balance of calcitonin-containing intranasal formulation indicated for the treatment of osteoporosis is no longer positive under normal conditions of use and recommends the suspension of the corresponding marketing authorisations.

For the lifting of the suspension the MAH(s) should provide new randomised controlled data that will be able to robustly demonstrate that the benefits of calcitonin-containing medicines outweigh their risks in patients with osteoporosis taking into account the increased risk of cancer and cancer mortality associated with long term use of calcitonin.

2.8. Communication plan

As part of this referral procedure the CHMP agreed the wording of a Direct healthcare professional communication (DHPC) designed to inform hospital chief pharmacists, rheumatologists, orthopaedic surgeons, oncologists and general practitioners of the increased risk of malignancies with the long term use of calcitonin compared with placebo treated patients and on the fact that:

- The intranasal formulation of calcitonin should no longer be used for the treatment of established post-menopausal osteoporosis in order to reduce the risk of vertebral fractures since the risks associated with calcitonin outweigh the benefits in this indication, and therefore the marketing authorisation of the nasal spray formulation will be withdrawn from the market.
- Calcitonin will only be available as a solution for injection and infusion, and should only be used for:
    - prevention of acute bone loss due to sudden immobilisation, with a recommended treatment period of two weeks and a maximum treatment period of four weeks;

- Paget's disease, restricted to patients who do not respond to alternative treatments or for whom such treatments are not suitable, and with treatment normally limited to three months (longer treatment and periodic retreatment may be considered taking into account the benefits and risks);
- hypercalcaemia caused by cancer.

Treatment with calcitonin should be limited to the shortest possible time using the smallest effective dose.

As per the initial CHMP opinion this communication was to be sent by 31 August 2012 to all relevant healthcare professionals. This communication is to be sent to all relevant healthcare professionals at the latest within 1 month of the Commission decision, where it has not already been sent.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the Committee was of the opinion that:

For the injectable calcitonin-containing medicinal products

- The Committee considered all the available data on the efficacy and safety of calcitonin-containing medicines in particular new data in relation to the risk of cancer.
- The Committee considered all the available data on the efficacy and safety of calcitonin-containing medicines in particular new data in relation to the risk of cancer.
- The Committee is of the opinion that data from clinical studies provide evidence for an increased risk of cancer with long-term use of calcitonin.
- The Committee therefore considered the benefit-risk balance of injectable calcitonin-containing products under normal conditions of use in each of the authorised indication and concluded that:
    - for the treatment of Paget's disease the benefit-risk balance remains positive provided that the duration of use is restricted to 3 months and only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment. The duration of treatment may be extended to a maximum of 6 months under exceptional circumstances and periodic re-treatment may be considered.
    - for the prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, the benefit-risk balance remains positive provided that the duration of use is restricted to 2 weeks, not exceeding 4 weeks in any case.
    - for the treatment of hypercalcaemia of malignancy the benefit-risk balance remains positive provided that the treatment duration is limited to the shortest possible time using the minimum effective dose
- The Committee considered that in order to maintain a positive benefit-risk for the above indications additional changes to the product information (section 4.2 Posology and method of administration, section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects) in relation to the risk of cancer should be included.

Therefore, the Committee recommended the variation of the marketing authorisations for calcitonin containing medicinal products (injectable formulations) in accordance with changes to the product information as set out in Annex III of the CHMP Opinion.

Grounds for the suspension of the marketing authorisation for the intranasal calcitonin-containing medicinal products

- The Committee considered all the available data on the efficacy and safety of calcitonin-containing medicines in particular new data in relation to the risk of cancer.
- The Committee is of the opinion that data from clinical studies provide evidence for an increased risk of cancer with long-term use of calcitonin.
- The Committee in light of the previous review and in the absence of new efficacy data, considered that the intranasal calcitonin-containing medicines can be effective in the treatment of established postmenopausal osteoporosis in order to reduce the risk of vertebral fractures. However the evidence of efficacy of intranasal calcitonin-containing medicines in this indication remains limited.
- The Committee also took in to account that in patients with osteoporosis, intranasal calcitonin treatment is to be administered on a long-term basis.
- In view of the new safety concerns in relation to the risk of cancer in long-term use and the limited efficacy of calcitonin in the treatment of osteoporosis, the Committee is of the opinion that pursuant to Article 116 of Directive 2001/83/EC the benefit-risk balance of the intranasal formulations of calcitonin-containing medicinal products is not positive under normal conditions of use.

Therefore the Committee recommended the suspension of the Marketing Authorisations for the intranasal formulation of calcitonin.

The conditions for the lifting of the suspension of the Marketing Authorisations are set out in Annex IV of the Opinion.