Background Document for Meeting of
Advisory Committee for Reproductive Health Drugs
and
Drug Safety and Risk Management Advisory Committee

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of whether the benefit of calcitonin salmon for the treatment of postmenopausal osteoporosis outweighs the potential risk of cancer to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1 BACKGROUND

1.1 Objective of Meeting

This meeting is being convened to review and discuss the available data regarding the safety and efficacy of calcitonin salmon products for the treatment of osteoporosis. In light of the potential risk of cancer associated with calcitonin salmon use, FDA believes that it is important to revisit the risk/benefit assessment for calcitonin salmon products for the treatment of osteoporosis.

The Division of Epidemiology and the Division of Biometrics VII will present and review the data and status of the safety issues that have been identified. The Division of Reproductive and Urologic Products (DRUP) will present a review of the available calcitonin fracture efficacy data.

1.2 Issues for Committee Consideration

Committee Members will be asked to discuss whether the available data support the continued use of calcitonin salmon medications for the treatment of osteoporosis (i.e., that the benefits of use outweigh the risks). In addition, Committee Members will be asked to comment on whether fracture efficacy data should be required for approval of any future salmon calcitonin product.

1.3 Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by low bone mass and structural deterioration of bone tissue leading to bone fragility and increased risk of fracture. Based on NHANES III data[1], it is estimated that approximately 10 million people in the U.S. have osteoporosis and another 34 million have low bone mass (osteopenia). The goal of therapy is to reduce the risk of fracture. For postmenopausal osteoporosis, there are currently two approved indications:

1. Treatment of osteoporosis in postmenopausal women (or women at high risk of fracture, as with Forteo and Prolia)
2. Prevention of osteoporosis in postmenopausal women

Osteoporosis is predominantly diagnosed using bone mineral density (BMD) techniques based on the diagnostic criteria set forth by the World Health Organization (WHO) in 1994. However, it has long been recognized that BMD alone is not sufficient to accurately predict fracture risk which led to the development of a new risk assessment tool for prediction of osteoporotic fracture (FRAX). The FRAX algorithms, developed by the WHO in 2008, include clinical risk factors that predict an increased risk of fracture (age, sex, prior fragility fracture after age 50 years, history of corticosteroid use [the equivalent of ≥ 5 mg of prednisone for more than three months], parental history of hip fracture, rheumatoid arthritis,

secondary osteoporosis, current tobacco use, alcohol use of greater than 2 units daily, and low body mass index). Using the FRAX tool, fracture risk is reported as the 10 year risk of hip fracture and the 10-year risk of major osteoporotic fracture.

Currently, the National Osteoporosis Foundation recommends treatment be considered for patients who have had an osteoporotic fracture, patients with a BMD T-score of <-2.5 (2.5 standard deviations (SD) below the young adult mean), and patients over age 50 years with low bone mass (T-score -1.0 to -2.5) with 10-year risk probability of >3% for hip fracture or >20% for major osteoporotic fracture as obtained using the FRAX algorithm.

Products currently approved in the U.S. for treatment of postmenopausal osteoporosis are outlined in Table 1.

Table 1. Approved Products for the Treatment of Postmenopausal Osteoporosis

Class	Drug	Route	Dose
Bisphosphonates	Fosamax	oral	10 mg daily
		oral	70 mg weekly
	Fosamax Plus D	oral	70 mg/2800 IU weekly
		oral	70 mg/5600 IU weekly
	Binosto	oral	70 mg weekly
	Actonel	oral	5 mg daily
		oral	35 mg weekly
		oral	75 mg 2 days/month
		oral	150 mg monthly
	Actonel with Calcium	oral	35 mg once weekly 1250 mg days 2-7
	Atelvia	oral	35 mg once weekly
	Boniva	oral	2.5 mg daily
		oral	150 mg monthly
	Boniva	IV	3mg every 3 months
	Reclast	IV	5mg yearly
Calcitonin*	Miacalcin	SC	100 IU every other day
	Miacalcin	NS	200 IU daily
	Fortical	NS	200 IU daily
Estrogen Agonist/Antagonist	Evista	oral	60 mg daily
PTH analog	Forteo	SC	20 mcg daily
RANK ligand inhibitor	Prolia	SC	60 mg every 6 months
* Approval based on total body calcium, bone mineral content, or BMD, not fracture efficacy			

Since 1994, in order to gain approval for the treatment of postmenopausal osteoporosis (PMO) indication, a company must demonstrate that their drug significantly reduces the risk for morphometric vertebral fractures in postmenopausal osteoporotic women during 3 years of treatment.

1.4 Calcitonin Salmon Regulatory History

Calcitonin is a 32 amino acid peptide hormone produced by the parafollicular C-cells of the thyroid gland in mammals and by the ultimobranchial gland in birds and fish. Calcitonin is formed by the proteolytic cleavage of a larger pre-propeptide, a product of the CALC1 gene (CALCA) located on chromosome 11. The CALC1 gene belongs to a superfamily of related protein hormone precursors including islet amyloid precursor protein, calcitonin gene-related peptide, and the precursor of adrenomedullin. The calcitonin receptor, found primarily on osteoclasts, is a G protein-coupled receptor that is coupled by Gs to adenylyl cyclase and thereby to the generation of cAMP in target cells. Calcitonin plays an important role in mineral metabolism and bone homeostasis. When calcium levels are high, endogenous calcitonin is secreted and acts as a counter to parathyroid hormone by inhibiting bone resorption by the osteoclast, inhibiting uptake of calcium from the intestines, and reducing resorption of calcium from the kidneys. Calcitonin salmon was chosen for therapeutic use because it has better biological activity, longer half-life, better receptor affinity, and is less liable to degrade in serum than mammalian calcitonin. The 32 amino acid synthetic calcitonin salmon peptide hormone is produced by synthetic or recombinant technology and is 50% identical to the human calcitonin peptide.

Synthetic calcitonin salmon (Calcimar injection, lyophilized powder for injection, Sanofi-Aventis) was approved for the treatment of symptomatic Paget's disease of bone in January, 1975. A new formulation, a 200 IU/mL solution, was approved in April, 1978. Both formulations were approved for the treatment of hypercalcemic emergencies in March, 1980. Subsequently, an application for treatment of osteoporosis was submitted. The endpoints for the studies supporting approval for the treatment of postmenopausal osteoporosis indication were total body calcium assessed by neutron activation analysis and bone mineral content measured by single photon absorptiometry of the forearm. The data were presented before the Endocrinologic and Metabolic Advisory Committee on September 11, 1981. Following discussion the committee voted for approval based on data that "suggests calcitonin's effectiveness in increasing total body calcium in some patients for a period of up to 12 months". The Advisory Committee did not have great concern about an absence of demonstrated effect on bone density of the radius, a cortical bone site, because it was believed that the drug's predominant antiresorptive effect was on trabecular bone. However, committee members were concerned about the partial reversal of gains in total body calcium seen during the second year of treatment; the lack of data on fractures; and the uncertain validity of using total body calcium as a surrogate for fracture risk. Calcimar injection 100 IU daily was approved for treatment of postmenopausal osteoporosis on December 21, 1984. At the time of approval, the Applicant committed to conduct a Phase IV study to determine the effect of the drug on the incidence of vertebral fractures in postmenopausal osteoporosis.

A calcitonin salmon product produced by a different sponsor (Miacalcin injection, Novartis) was approved for the treatment of Paget's disease of bone, hypercalcemic emergencies, and postmenopausal osteoporosis on July 3, 1986. Based on chemistry and pharmacokinetic data, the applicant demonstrated that Miacalcin contained the same active ingredient as Calcimar.

In addition, the dosage form, route of administration, and conditions of use for Miacalcin injection were the same as Calcimar. For nonclinical and clinical evidence of safety and effectiveness, the applicant cross-referenced data in the Calcimar drug applications for which they had obtained the right to reference. At the time of approval, Novartis also committed to conduct a Phase IV study to determine the effect of the drug on the incidence of vertebral fractures in postmenopausal osteoporosis.

The two separate postmarketing fracture studies for the calcitonin salmon injection products were not conducted. For the Miacalcin product, the company decided to rely on the postmarketing study conducted with Calcimar and to concentrate its efforts on development of a new calcitonin formulation, a nasal spray. Enrollment in the postmarketing fracture study for Calcimar injection was slow, reaching approximately 50% of the planned enrollment after 4 years. Results of an interim analysis appeared unfavorable for Calcimar therapy compared to placebo and the data were presented before the Endocrinologic and Metabolic Advisory Committee on July 24, 1991. At the meeting's conclusion, the committee agreed unanimously that there was evidence that calcitonin salmon reduces bone loss at least over a 2-year period, but no evidence that it reduces fractures. The committee voted against removing the postmenopausal osteoporosis indication and recommended that a new fracture study with improved design be conducted. Further discussion of this study is included in the calcitonin efficacy review.

An application for marketing approval of Miacalcin nasal spray (synthetic calcitonin salmon) was submitted in 1992. Bioavailability of Miacalcin nasal spray is approximately 3% of the injectable synthetic calcitonin salmon product. Three double-blind, placebo-controlled studies with bone mineral content or bone mineral density as the primary endpoint were submitted in support of the application. During the review period, a new osteoporosis guidance document was released. The guidance document "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", outlined the need for fracture data in support of product approval. The application was presented before the Endocrinologic and Metabolic Advisory Committee on November 18, 1994. The submitted application did not contain fracture data but a fracture efficacy trial (trial CT320) was ongoing. The committee concluded that the BMD changes were "sufficient to establish clinically important efficacy of nasal calcitonin", although it was observed that BMD changes were relatively small. The available fracture data were considered limited and inconclusive. Most members of the committee were in favor of approval of Miacalcin nasal spray for treatment of established postmenopausal osteoporosis. Miacalcin nasal spray was approved for treatment of postmenopausal osteoporosis August 17, 1995. At the time of approval, Novartis committed to complete the ongoing fracture trial. Data from trial CT320 were submitted for labeling in 1999 and was found not approvable, based on the ambiguous results of the statistical analyses of the fracture data. Further discussion of trial CT320 (also known as the PROOF trial) is included in the calcitonin efficacy review.

An application for marketing approval of Fortical nasal spray (recombinant calcitonin salmon, Upsher-Smith) for treatment of postmenopausal osteoporosis was submitted in 2003. The Applicant relied on the FDA's prior findings of safety and effectiveness of Miacalcin

nasal spray, referred to as a 505(b)(2) application. The Applicant provided evidence of pharmacokinetic and pharmacodynamic equivalence of their recombinant calcitonin salmon to the marketed synthetic calcitonin salmon. Fortical nasal spray was approved for treatment of postmenopausal osteoporosis on August 12, 2005. A postmarketing fracture study was not required.

Calcimar was withdrawn from the US market by the Applicant in 1999 (lyophilized powder) and 2007 (solution). Currently, the approved calcitonin salmon products in the US market include Miacalcin injection, Miacalcin nasal spray, Fortical nasal spray, and related generic products. Current product labeling for Miacalcin injection, Miacalcin nasal spray, and Fortical nasal spray can be found in Appendix A: Product Labeling.

FDA conducted a review of the drug utilization data for calcitonin-containing products in the outpatient retail pharmacy setting from year 2006 through year 2011. National sales of osteoporosis products decreased by 38% from 62 million packages sold in year 2007 to 38.8 million packages sold in year 2011. In year 2011, sales of calcitonin-containing products accounted for approximately 4.5% of the osteoporosis market and approximately 1.7 million packages were distributed nationwide, a decrease of 48% from 3.3 million packages noted in year 2006. Data in year 2011 indicated that approximately 91% of calcitonin-containing product sales were distributed as calcitonin nasal spray products and 9% of total sales were distributed as calcitonin vials (injectable products). Annual sales of calcitonin nasal spray decreased by 50% from 3.1 million bottles sold in year 2006 to 1.6 million bottles sold in year 2011. Annual sales of calcitonin vials remained steady and ranged from 152,000 vials to approximately 160,000 vials for the review period. In year 2011, the largest proportion of calcitonin-containing products sales (48%) were distributed to outpatient retail pharmacy settings. Non-retail settings accounted for 33% of sales, primarily to long term care settings, and 19% of sales were to mail-order/specialty pharmacies.

Outpatient retail prescription data show that in year 2011, approximately 795,000 prescriptions were dispensed and 205,000 patients received prescriptions for calcitonin-containing products from outpatient retail pharmacies. From year 2006 to year 2011, the overall number of dispensed prescriptions and patients receiving dispensed prescriptions for calcitonin-containing products decreased by 54% (of prescriptions) and 51% (of patients), respectively. Nearly 100% of prescriptions were dispensed for calcitonin nasal spray, primarily to female patients (92% of nasal calcitonin prescriptions) during the total review period. Based on office-based physician survey data, “Osteoporosis” (ICD-9 733.0) was the most common diagnosis for calcitonin nasal spray, 64% of drug use mentions during the review period (see Table 2). The complete drug utilization review can be found in Appendix B: Drug Utilization Review.

Table 2: Nationally Estimated Number of Patients Who Received a Prescription for Calcitonin-Containing Products by Product Formulation in U.S. Outpatient Retail Pharmacies, 2006-2011

	2006		2007		2008		2009		2010		2011		Total Y2006-2011	
	Patient Count N	Share %	Patient Count N	Share %	Patient Count N	Share %	Patient Count N	Share %	Patient Count N	Share %	Patient Count N	Share %	Patient Count N	Share %
Grand total	423,405	100.0%	383,254	100.0%	307,036	100.0%	261,727	100.0%	242,506	100.0%	205,524	100.0%	1,037,642	100.0%
Nasal	421,452	99.5%	381,306	99.5%	305,443	99.5%	260,395	99.5%	241,345	99.5%	204,580	99.5%	1,031,875	99.4%
Fortical	167,863	39.8%	210,964	55.3%	200,563	65.7%	180,310	69.2%	143,737	59.6%	101,771	49.7%	595,746	57.7%
Miacalcin Nasal & gen	300,982	60.2%	199,765	44.7%	128,615	34.3%	109,888	30.8%	115,553	40.4%	115,627	50.3%	612,222	42.3%
Injectable	2,919	0.5%	2,949	0.5%	2,465	0.5%	1,833	0.5%	1,567	0.5%	1,271	0.5%	10,268	0.6%

Source: IMS Total Patient Tracker. Year 2006-2011 Data Extracted January 2013 File: TPT 2012-1682 Calcitonin by year 1-7-13

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories.

For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Currently, there are multiple calcitonin salmon products in development, including several oral calcitonin products. A fracture study has been conducted with one of these products. Further discussion of this trial (study 2303) is included in the calcitonin efficacy review. Data from studies of an oral calcitonin salmon product revealed an imbalance in prostate cancer between active drug-treated subjects and placebo-treated subjects. This finding led to further evaluations by FDA and other regulatory agencies including the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concerning a potential risk of cancer associated with use of calcitonin. Further discussions of this meta-analysis are included in the calcitonin safety review.

The status of the reviews for other regulatory agencies is as follows:

- In a press release on July 20, 2012, The European Medicines Agency's CHMP recommended that after taking into account the limited efficacy of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the benefits of calcitonin-containing medicines did not outweigh their risks in this indication. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation be withdrawn. The injectable formulation should be used only for:
  - Prevention of acute bone loss due to sudden immobilization, with treatment recommended for two weeks with a maximum duration of four weeks
  - Paget's disease in patients who do not respond to alternative treatments or for whom such treatments are not suitable, with treatment normally limited to three months
  - Hypercalcemia caused by cancer

  A formal decision by the European Commission regarding the adoption of the CHMP's recommendations remains pending at the time of this review.

- In a press release dated July 31, 2012, Health Canada informed Canadians that it is assessing the possibility of an increased risk of cancer with long-term use of the drug calcitonin.

2 Salmon Calcitonin: Safety

2.1 Overview of the Safety Issue

Calcitonin salmon has been marketed in the United States since 1975. Few safety concerns have been raised in the postmarketing period. Recently, however, a concern regarding calcitonin salmon and prostate cancer was raised. The findings that form the basis of this concern are from two trials utilizing a new oral formulation of calcitonin salmon. The imbalance of prostate cancer noted in these trials led to a more extensive evaluation of calcitonin salmon use and malignancy. This safety review will focus on data reported to the relevant Investigational New Drug Applications, the FDA Adverse Event Reporting System and the available epidemiologic evidence.

2.2 The Initial Safety Signal

Several oral calcitonin products are under development. One product SMC021, containing recombinant calcitonin salmon with 5-CNAC {8-(5-Chloro-2-hydroxybenzoylamino) octanoic acid disodium salt monohydrate} as a gastrointestinal absorption enhancer, is in the late stages of development for treatment of osteoarthritis and for treatment of postmenopausal osteoporosis. Two phase 3 randomized, controlled trials, C2301 and C2302, were conducted in a total of 1430 female and 776 male subjects age 51 – 80 years with knee osteoarthritis. These were 2-year studies in which subjects were randomized 1:1 to receive SMC021 0.8 mg twice daily or placebo twice daily. The third study C2303 was a 36-month trial conducted in 4665 women age 50 – 86 years who had been diagnosed with postmenopausal osteoporosis. Subjects in this trial were randomized 1:1 to receive either SMC021 0.8 mg oral calcitonin or placebo once daily.

In November 2010, the sponsor informed FDA's Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Division of Reproductive and Urologic Products (DRUP) of a new safety finding noted by the Data Safety Monitoring Committee (DSMC) of an imbalance of prostate cancer in the two osteoarthritis studies. At the time the finding was noted, Study C2301 was complete and study C2302 was ongoing. Initial results of study C2301 showed a numerical imbalance in prostate cancer: 4 cases with SCM021 compared to none with placebo. The 2 cases of prostate cancer in study C2302 were unblinded, revealing that both had been on SMC021 as well. Thus, there were a total of 6 cases of prostate cancer with SMC021, and none with placebo. The DSMC recommended that all men participating in the studies be notified and screened for the occurrence of prostate cancer.

Investigators then attempted to re-contact all 776 male subjects, and obtained consent from 91% to undergo screening for prostate cancer. In this group, they retrospectively analyzed PSA levels in stored serum samples from study baseline and months 1, 6, 12 and 24 (or early termination visit), as well as at an additional follow-up visit. About 17% of the men were

found to have had at least one elevated PSA; all of these men were followed up and most were referred to a urologist. This process ultimately resulted in diagnoses of prostate cancer in an additional 8 SMC021 and 10 placebo subjects from study C2301, and an additional 6 subjects in each treatment group from study C2302. This brought the total number diagnosed with prostate cancer to 36, and the original 6 vs. 0 imbalance became 20/365 (5.4%) men treated with calcitonin salmon CNAC vs. 16/405 (4.0%) men treated with placebo.

Table 3: Studies C2302 and C2302 combined: Male subjects diagnosed with prostate cancer

	SMC021 N=368* n (%)	**Placebo** N=405* n (%)	**Total** N=773* n (%)
Diagnosed clinically (during study)	6 (1.6)	0	6 (0.8)
Diagnosed by screening (post hoc)	14 (3.8)	16 (4.0)	30 (3.9)
Total prostate Ca	20 (5.4)	16 (4.0)	36 (4.7)
* N = male subjects who received drug (safety population)			

The DRUP urology team reviewed the available data in order to determine the relative prognostic significance of cancers associated with SMC021 vs. placebo, and that of cancers detected clinically vs. those found at screening. Clinical and pathologic stage data were inadequate to assess these cancers, however PSA data were available in all cases and Gleason scores in most (34/36 for Gleason sum, 29/36 for primary pattern).

The prostate cancer incidence in these two trials, including results of post hoc screening, was high. However, screening prior to enrollment did not include PSA or rectal exams, and most of the cases identified (32 out of 36) were from Denmark, where PSA screening for prostate cancer is not routine. Most subjects ultimately diagnosed with prostate cancer had elevated baseline PSA (> 4 ng/mL) that would have been detected prior to randomization if the studies had been conducted in the U.S., where routine PSA screening is common, and with more extensive screening at enrollment.

During the studies, mean PSA levels increased slightly in both treatment cohorts. There were no statistically significant differences in changes from baseline between SMC021 and placebo, either for all subjects or for the 36 subjects ultimately diagnosed with prostate cancer.

Among subjects with cancer, there was a slight trend toward higher Gleason sums for subjects who had received SMC021 relative to placebo (6.9 vs., 6.4, p=0.27). There was no difference in Gleason scores of men diagnosed clinically during the trials compared to those identified through subsequent screening.

A literature review was also conducted. The published work on calcitonin is abundant. Calcitonin is present in neuroendocrine cells of many organs including lung and prostate. It is frequently secreted by both neuroendocrine tumors and a broad spectrum of malignancies including prostate cancer. Alternative splicing of the gene coding for calcitonin produces a related peptide of 37 amino acids, called calcitonin gene-related peptide (CGRP). CGRP is

one of the most abundant peptides produced in both peripheral and central neurons. It is a potent vasodilator and can function in the transmission of pain. Calcitonin and CGRP are secreted by many neuroendocrine tumors *in vitro*; however, no clinical syndrome has been associated with the secretion of calcitonin or CGRP in men with prostate cancer.

In situ hybridization combined with immunohistochemistry has shown that the calcitonin receptor is expressed on prostatic neuroendocrine cells, including calcitonin-producing and non-calcitonin producing cells, suggesting an autocrine and paracrine regulatory role.

In prostate tissue, the concentration of calcitonin and the number of neuroendocrine cells expressing calcitonin protein was highly variable but similar in healthy men (n = 12) and men with prostate cancer (n = 11) but reduced in men with benign prostate hyperplasia (n = 19).[2] In another study that evaluated prostate tissue, the expression of calcitonin and calcitonin receptor mRNAs were localized to the basal epithelium of benign and low grade prostate cancer tissues.[3] The location changed to the luminal epithelium in men with moderate to high-grade prostate cancer and the abundance and number of cells expressing both mRNAs appeared to increase with the severity of the Gleason score. Elevated serum calcitonin levels have not been reported in patients with adenocarcinoma of the prostate, however, it has been observed in some patients (9 out of 16 in one series) with small cell carcinoma, a rare subtype of prostate cancer.[4] In contrast, serum CGRP levels are significantly elevated in patients with high grade or high stage prostate cancer.[5] *In vitro* studies have shown an increase in expression of both calcitonin and its G protein-coupled receptor in advanced prostate cancer.[6]

The only evidence that calcitonin may promote prostate cancer metastasis is based on human prostate cancer cell lines studied *in vitro* that demonstrated reduced cell-cell adhesion through the disassembly of tight and adherens junctions and activation of beta-catenin signaling. In a series of *in vitro* experiments using human prostate cancer cell lines, Shah and colleagues have suggested that the calcitonin autocrine axis may play a role in the metastatic potential of the prostate cancer. Neuroendocrine differentiation in prostatic carcinoma has been related to regulation of proliferation and metastatic potential and correlated with prognosis. In cell culture, calcitonin stimulates expression of a splice variant of CD44, a transmembrane glycoprotein, in prostate cancer cell lines that could promote loss of cell adhesion.[7] More than 80% of prostate carcinomas initially respond to androgen ablation, but most relapse, due to the heterogeneous presence of androgen-dependent and independent clones. The pathways of cellular proliferation and apoptosis are inexorably linked to minimize the occurrence of neoplasia, and dysfunction of apoptosis is proposed as a pathogenic process in malignant tumors. Androgen-dependent prostatic cancer cells undergo apoptosis after androgen deprivation, but not androgen-independent ones due to a defect in the initiation step. Calcitonin has been shown to modulate the apoptotic response of prostate cancer cells by inducing resistance to etoposide-induced apoptosis *in vitro.*[8, 9] Almost all of the published studies on calcitonin and prostate cancer come out of one laboratory. The publications of Dr. Shah's laboratory over the past twenty years are summarized below. However, it is important to note that these studies are based on the actions of human calcitonin. Therefore, the relevance of these data to the clinical use of calcitonin salmon therapy is unknown.

- Extracts of both benign and malignant human prostatic tissue are positive for calcitonin immunoreactivity[10]
- Calcitonin-like immunoreactive material is secreted by primary prostate cells in culture[9]
- Prostatic cell lines (LNCaP) in culture express calcitonin receptors[5,11]
- Calcitonin stimulates expression of a splice variant of CD44 in prostate cancer cell lines (LNCaP, PC-3 and metastasis-derived PC-3M cell lines) grown in culture and in nude mice[12,13]
- The over expression of calcitonin leads to a more aggressive phenotype (increased cell invasion through secretion of gelatinases and urokinase-type plasminogen activator) in prostate cancer cell lines grown in culture.[14,15,16,17]
- Calcitonin induces chemoresistance to etoposide in PC-3M cells grown *in vitro* via calcitonin receptor-induced activation of Akt-surviving pathway
- Activation of calcitonin-calcitonin receptor axis induces epithelial-mesenchymal transition in some human prostate cell lines as characterized by cadherin switch and the expression of the mesenchymal marker, vimentin.[18]

In summary, calcitonin, a neuroendocrine peptide, and its receptor are localized in the basal epithelium of benign prostate but can be found in the secretory epithelium of malignant prostates. Calcitonin increases tumorigenicity and invasiveness of multiple prostate cancer cell lines *in culture* via cyclic AMP-dependent protein kinase-mediated actions. These actions include increased secretion of matrix metalloproteinases and urokinase-type plasminogen activator and an increase in prostate cancer cell invasion. Activation of calcitonin-calcitonin receptor autocrine loop in prostate cancer cell lines leads to the loss of cell-cell adhesion, destabilization of tight and adherens junctions, and internalization of key integral membrane proteins *in vitro*. In addition, the activation of calcitonin-calcitonin receptor axis induced epithelial-mesenchymal transition of prostate cancer cells as characterized by cadherin switch and the expression of the mesenchymal marker, vimentin. The activated calcitonin receptor phosphorylated glycogen synthase kinase-3, a key regulator of cytosolic beta-catenin degradation within the WNT signaling pathway. This resulted in the accumulation of intracellular beta-catenin, its translocation in the nucleus, and transactivation of beta-catenin-responsive genes. These results identify actions of calcitonin-calcitonin receptor axis on prostate cancer cells that lead to the destabilization of cell-cell junctions, epithelial-to-mesenchymal transition, and activation of WNT/beta-catenin signaling in human prostate cell lines. Their results also suggest that cyclic AMP-dependent protein kinase plays a key role in calcitonin receptor-induced destabilization of cell-cell junctions and activation of WNT-beta-catenin signaling. These *in vitro* findings suggest that autocrine and paracrine functions of the neuroendocrine peptides, in this case human calcitonin, may play a role in the tumorigenicity of prostate cancer, particularly androgen-independent cell lines. There is currently no evidence that calcitonin will 1) induce prostate cancer in benign epithelium or 2) cause a latent cancer to become more aggressive. Moreover, prostate neoplasms were not evident in rodents treated with calcitonin salmon for two years and there is no clinical evidence in the literature to support any of these *in vitro* findings.

After assessment of all data, it was concluded that the prostate cancer findings from these two studies were not of great concern. The imbalance in clinically diagnosed cases (6 vs. 0)

was diminished with subsequent screening. This screening may have detected some clinically insignificant cancers, however the Gleason and PSA data suggested that cancers diagnosed by screening were comparable to those identified during the trials. In addition, these prognostic factors were similar between SMC021 and placebo subjects. The high incidence of prostate cancers identified in both groups was attributed to the European predominance of study sites, and it is likely that this result would not apply to a U.S. population.

There are limited data available to assess a possible association of calcitonin salmon with prostate cancer, because the drug is not indicated for osteoporosis in men, and use for other indications (Paget's disease, hypercalcemia) is infrequent and usually limited in duration. Off-label uses in men, e.g. treatment of painful bone metastases, are probably also very infrequent.

2.3 Nonclinical Findings

Nonclinical Introduction
The principal nonclinical issue is the finding of synthetic calcitonin salmon related pituitary adenomas in rats after one and two years of subcutaneous exposure. The relevance of this finding to humans remains unknown because this is a very common finding in rats as they age; the pituitary adenomas did not transform into metastatic tumors; there were no other clear treatment related neoplasms; and synthetic calcitonin salmon related neoplasms were not observed in mice after two years of dosing.

Mutagenesis
Synthetic calcitonin salmon i not mutagenic to bacteria and does not cause chromosomal damage in a hamster cell line.

Carcinogenicity
Carcinogenicity was assessed in mice and rats dosed subcutaneously with synthetic calcitonin salmon for up to two years. Current nonclinical carcinogenicity labeling is based upon one-year studies in rats showing an association with pituitary adenomas in two different strains. Carcinogenicity was further assessed in mice and rats that were dosed subcutaneously for two years. No adverse neoplastic findings were observed in mice after two years but synthetic calcitonin salmon related pituitary adenomas were confirmed after two years of dosing in male rats.

<u>Neoplasm Findings</u>
Mice tolerated two years of subcutaneous dosing of synthetic calcitonin salmon at up to 39 times the maximum recommended subcutaneous dose in humans (100 IU/day) and 390 times the maximum recommended intranasal dose in humans (200 IU/day) without adverse injection site pathology, systemic toxicity, changes in body weight gain, hematology or increases in neoplasms. Dose multiples between mice and humans were based on body surface area conversion and an additional 20-fold conversion factor to account for decreased clinical exposure via the intranasal route.

The only clear neoplastic finding in Sprague Dawley (SD) rats dosed subcutaneously with

synthetic calcitonin salmon was an increase in pituitary adenomas in females after one year of dosing and in males after one and two years (Table 4 and Table 5 below). Pituitary adenomas were also elevated in male but not female Fisher 344 rats dosed for one year at ≥ 80 IU/kg/day (Table 5) (Brown et al. 1993). The pituitary adenomas were severe enough to cause morbidity and death in many cases. In female SD rats, the incidence of pituitary adenomas after two years was so high in all groups (80% and 92% including non- synthetic calcitonin salmon treated rats) that a treatment related effect could not be distinguished from natural background incidence. The lowest dose in male SD rats with elevated pituitary adenomas after two years of dosing (1.7 IU/kg/day) is approximately 1/6th the exposures at the maximum recommended subcutaneous dose in humans (100 IU/day) based on body surface area conversion and ~1.6 times the exposure at the maximum recommended intranasal dose in humans (200 IU/day) based on body surface area conversion and a 20-fold conversion factor to account for decreased clinical exposure via the intranasal route.

Table 4: Summary of Pituitary Adenoma Data in SD-Rats Dosed Subcutaneously

Summary of Pituitary Adenoma Data in SD-Rats Dosed Subcutaneously										
52 Weeks (Study JBC-RCH-83-1011, conducted 1984-1986)										
	Male					Female				
Dose (IU/kg/day)	0	1.25	5	20	80	0	1.25	5	20	80
No. Rats Examined	18	19	20	20	13	19	20	18	19	20
No. of rats with pituitary adenoma	0	1 (5%)	2 (10%)	11 (55%)	11 (85%)	1 (5%)	1 (5%)	1 (6%)	1 (5%)	3 (15%)
52-Weeks (Study HWA-2315-116, conducted 1991-1992)										
	Male					Female				
Dose (IU/kg/day)	0	0.2	1	6	36	0	0.2	1	6	36
No. Rats Examined	10	8	8	10	11	9	8	8	10	10
No. of rats with pituitary adenoma	1 (10%)	4 (50%)	2 (25%)	6 (60%)	11 (100%)	3 (33%)	2 (25%)	1 (13%)	3 (30%)	7 (70%)
105 Weeks (Study CHV-2315-119, conducted 1992-1994)										
	Male						Female					
Dose (IU/kg/day)	P	V	0.5	1.7	5	10	P	V	0.5	1.7	5	10
No. Rats Examined	50	50	50	50	50	50	50	50	50	50	50	50
No. of rats with pituitary adenoma	21 (42%)	25 (50%)	29 (58%)	37* (74%)	40* (80%)	43* (86%)	41 (82%)	40 (80%)	46 (92%)	40 (80%)	42 (84%)	43 (86%)

P – placebo (0.2% acetic anhydride, 0.2% sodium acetate trihydrate and 0.75% sodium chloride)
V – vehicle (0.9% saline)
* Statistically significant $p \leq 0.01$. Statistical analysis not provided for the 1 year toxicity studies.
Table adapted from the Sponsor's Table 2-1 in their position paper submitted on 7-29-2008 (SN026).

Table 5: Comparison of Pituitary Adenomas in SD and Fisher 244 Rats

Published Study† in 1993 Comparing Pituitary Adenomas in SD and Fisher 344 Rats Dosed Subcutaneously with ssCT for 52 Weeks								
Sprague Dawley								
	Male				Female			
Dose (IU/kg/day)	0	1.25	5	80	0	1.25	5	80
No. Rats Examined	42	42	42	42	42	42	42	42
No. of rats with pituitary adenoma	5 (12%)	17 (40%)*	20 (48%)**	36 (86%)**	14 (33%)	14 (33%)	15 (36%)	28 (67%)*
Fisher 344								
	Male				Female			
Dose (IU/kg/day)	0	1.25	5	80	0	1.25	5	80
No. Rats Examined	42	42	42	42	42	42	42	42
No. of rats with pituitary adenoma	4 (10%)	5 (12%)	3 (7%)	28 (67%)**	2 (5%)	3 (7%)	2 (5%)	7 (17%)
Pituitary adenomas were localized to the adenohypophysis Statistically significant * $p \leq 0.01$ and ** ≤ 0.001. † Data summarized from Brown et. al. Proliferative pituitary lesions in rats treated with salmon or porcine calcitonin. *Toxicol Pathol* (1993); **21**(1):81-86.								

Mechanistic Assessment of Pituitary Neoplasms in Rats

Pituitary adenomas are a common tumor in aged rats with historical background rates for two year old SD rats ranging between 34-80% (mean 57%) for males and 53-94% (mean 76%) for females. The mechanism for the increase in naturally occurring pituitary adenomas as rats age is unknown but may be related to endocrine imbalance associated with aging (e.g. declining estrogen exposure). The mechanism for the synthetic calcitonin salmon -dependent reduction in the latency period for this common benign neoplasm in rats is unknown. It is also unknown whether the increase in pituitary adenomas is a direct effect of synthetic calcitonin salmon signaling in the pituitary or a secondary effect due to synthetic calcitonin salmon signaling in other tissues.

There are five principle hormone producing cell types in the pituitary: corticotrophs (ACTH), gonadotrophs (LH or FSH), lactotropes (prolactin), somatotropes (growth hormone), and thyrotropes (TSH). LH, FSH, and TSH are heterodimeric proteins that share a common alpha subunit and unique beta subunits. A study was conduced to address the question of whether synthetic calcitonin salmon causes the formation of uncommon hormone secreting neoplasms (ACTH, LH, FHS, GH, or TSH) or whether it increases the abundance of the more common spontaneous prolactin (prolactinoma) or alpha-secreting pituitary tumors.

Twenty male and female SD and Fisher 344 rats were dosed subcutaneously for one year with synthetic calcitonin salmon at 80 IU/kg/day and assessed for pituitary histology, tumor incidence, and serum hormone levels (Jameson et al. 1992). Immunohistochemistry was used only in male SD rats to assess the production of hormones in pituitary tissue.

Similar to the findings of Brown et al. in the table above, pituitary adenomas were elevated in male and female SD rats and male Fisher 344 rats but not female Fisher 344 rats (only male SD incidence was provided in this study). In the SD male rats, pituitary adenomas were

observed in 25% of the control rats and 80% of the synthetic calcitonin salmon treated rats (Table 6). Immunohistochemistry analysis demonstrated that 25% of the pituitary adenomas in vehicle exposed male SD rats produced prolactin and none produced the alpha subunit. In contrast, in the synthetic calcitonin salmon treated SD males, all of the pituitary adenomas produced the common alpha subunit but only 6% of the adenomas produced prolactin. GH, LHβ, FSHβ, and TSHβ were not detected in the male SD tumors in the control or synthetic calcitonin salmon groups. Thus, it appears that calcitonin primarily induces alpha producing adenomas.

Table 6: Pituitary Pathology Incidence in Male SD Rats After One Year

Pituitary Pathology Incidence in Male SD Rats After One Year (80 IU/kg/day SC)						
	Control (N = 20)			**Calcitonin Salmon (N = 20)**		
	Histology	Immunohistology		Histology	Immunohistology	
		α-Subunit	Prolactin		α-Subunit	Prolactin
Hyperplasia	7 (35%)	1 (5%)	7 (35%)	2 (20%)	2 (20%)	1 (5%)
Adenoma	5 (25%)	0	5 (25%)	16 (80%)	16 (80%)	1 (5%)
Hyperplasia or Adenoma	12 (60%)	1 (5%)	12 (60%)	18 (90%)	18 (90%)	2 (10%)
One lesion in the control group and two in the treated group were positive for both α-subunit and prolactin. Table adapted from Jameson et al. Glycoprotein hormone alpha-subunit-producing pituitary adenomas in rats treated for one year with calcitonin. *Am J Pathol* (1992); **140**(1):75-84.						

Correlating with the immunohistochemistry findings, serum alpha subunit levels were extremely variable but elevated 20-fold in male SD and 4-fold in Fisher 344 rats. However, they were not elevated in females of either strain. Serum TSH was elevated 2-fold in male and female SD rats but it was not affected in Fisher 344 rats. Correlating with the 2-fold increase in serum TSH, the thyroid weight was reduced 43% and total body weight was reduced 24% in male SD rats (female data not provided). Serum levels of prolactin, growth hormone, ACTH, FSH, or LH were not altered by synthetic calcitonin salmon in either sex of both strains of rats. Estrogen levels were not evaluated.

Summary

In animal carcinogenicity studies, calcitonin treatment was associated with development of an increased number of benign neoplasms in the pituitary in two strains of rats by month 12. Dose-related pituitary neoplasms were elevated in the male sex of one strain of rats at doses predicted to be below or near the maximum recommended subcutaneous and intranasal dose respectively. Although the background incidence of pituitary adenomas in rats is very high, synthetic calcitonin salmon appears to preferentially promote the growth of alpha-secreting pituitary adenomas above background levels in male but not female rats. It is unknown if this is due to a direct effect of synthetic calcitonin salmon on the pituitary or if it is secondary to the physiological effect of synthetic calcitonin salmon elsewhere. No adverse neoplastic findings were reported in mice dosed for up to two years with synthetic calcitonin salmon at doses 39 to 390 times the maximum recommended subcutaneous and intranasal doses respectively. These data suggest that the increased incidence of pituitary adenomas following synthetic calcitonin salmon exposure is likely unique to rats. The relevance of the pituitary adenomas to humans treated with synthetic calcitonin salmon is unknown.

2.4 Review and Utility of Postmarket Adverse Events Reports

This section summarizes high level assessments of postmarketing reports of malignancy following calcitonin exposure, as reviewed in 2011 and 2012 by Analysts in CDER's Office of Surveillance and Epidemiology (OSE), Division of Pharmacovigilance II (DPV II).[19,20]

Data from postmarketing sources have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. A reported event may have been due to an underlying disease process, a different drug, another coincidental factor, or combination of factors. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Specific limitations of postmarketing data in relation to malignancy include the fact that duration of therapy is often omitted from reports. Additionally, reporters may be less likely to attribute causality, and subsequently report, adverse events that occur long after initiation of therapy, such as malignancy.

Overall, DPV II did not identify any potential signal for prostate cancer or other malignancies in the postmarketing data. We were unable to characterize the relationship of events of malignancy to calcitonin exposure primarily due to inherent limitations of spontaneously reported safety information. Brief summary findings from data mining scores and Adverse Event Reporting System (AERS) database searches are provided below.

Data mining Results

This section summarizes FDA's review of data mining scores for calcitonin relevant to malignancy. Data mining refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. Empirica Signal is the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. MGPS analyzes the records in AERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events in AERS.[a] As these data mining scores are based on postmarketing data, limitations previously described also apply to data mining scores. Further, drug and event causality cannot be inferred from EBGM scores.

The Empirica Signal database was searched using calcitonin and the System Organ Class (SOC) Neoplasms benign, malignant, and unspecified in the Medical Dictionary for Regulatory Activities (MedDRA) terminology.[19] Based on data mining scores for data through May 19, 2011, there were 2 potential safety signals, specifically metastatic renal cell carcinoma and benign laryngeal neoplasm. Upon detailed review, the data mining score for

[a] These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively.

metastatic renal cell carcinoma included duplicate reports and appears to represent a single case. In summary, the data mining scores reviewed did not identify any noteworthy signals for calcitonin and malignancy.

Reports in the Adverse Event Reporting System (AERS) Database

FDA uses a computerized information database (Adverse Event Reporting System or AERS) for post-marketing safety surveillance of drug and therapeutic biologic products. This database stores individual safety reports describing suspected adverse drug reactions. Adverse events in AERS are coded to terms in the MedDRA dictionary.

On June 6, 2011,[19] an AERS database search was performed using the following MedDRA High Level Terms: 1) Prostatic Neoplasms Malignant and 2) Prostatic Neoplasms and Hypertrophy. The search retrieved one postmarketing report involving prostate cancer, in which a patient with preexisting prostate cancer and bone metastases received the drug. The patient experienced hallucinations and delirium 8 hours after his first intranasal administration of Miacalcin. The patient died due to underlying prostate cancer less than 4 weeks after using a single dose of Miacalcin.

On July 31, 2012,[20] an additional AERS database search was performed using the Standardized MedDRA Query (SMQ) Malignancies (broad scope). The search retrieved 70 postmarketing reports potentially involving malignancy. DPV reviewed the cases and excluded reports that were received in duplicate, reports of benign conditions, or reports with limited information (i.e., malignancy could not be confirmed). Following the exclusions, we identified 40 cases of malignancy, including five cases describing use of calcitonin for hypercalcemia of malignancy. The most commonly reported malignancy types were breast cancer (8 cases), unspecified (6 cases), gastrointestinal tract (4 cases) and reproductive tract (4 cases). All other cancer types were reported 3 times or fewer. The finding that the most commonly reported malignancy was breast cancer is not unexpected given the use of calcitonin in postmenopausal women.

2.5 Meta-analysis of Malignancies from Randomized Controlled Trials

As part of their evaluation of the prostate cancer signal noted in the osteoarthritis trials, Novartis conducted trial-level meta-analyses to evaluate the potential risk of malignancy in patients treated with all forms of calcitonin salmon. This section summarizes FDA's statistical and epidemiologic evaluation of the Novartis's meta-analyses and summarizes FDA's independent meta-analyses of the clinical trials. Because all trials with the injectable calcitonin salmon formulation were open label trials, the FDA's analyses focuses mostly on the analysis of trials in the nasal spray formulation for which Miacalcin is currently marketed in the United States. The complete FDA epidemiology review is provided in Appendix C: Epidemiology Review.

Selection of Trials Included in the Meta-analyses

Novartis conducted a literature search in Embase, PubMed, and internal records to identify trials for the meta-analysis. They searched for all randomized controlled, double-blind trials, regardless of indication. The literature search did not identify any additional published studies, so the meta-analysis included 20 Novartis-funded studies only: 17 for the nasal formulation and 3 for the oral formulation. No randomized, controlled, double-blind clinical trials were available for the calcitonin salmon injectable formulation. It should be noted that Novartis's original meta-analyses included 17 nasal formulation trials and 3 oral formulation trials. However, Novartis's background document for the Advisory Committee includes an 18th nasal spray trial in their meta-analyses. Data from this trial were not available to FDA for substantive review and this trial is not incorporated into FDA's meta-analyses or our review of the company's earlier meta-analyses.

All trials included in the meta-analysis were double–blind, randomized, controlled trials, with the exception of one open-label study (506) which compared calcitonin salmon nasal spray 50 IU daily plus calcium supplementation to calcium supplementation alone.

Description of Trials Included in Meta-analysis

Study Population and Geography of included Randomized Controlled Trials

Subjects for the nasal spray trials were recruited from a total of 18 countries, primarily Europe but some included the U.S. Enrollment was limited to a single country for 15 trials; CT320 enrolled patients from the U.S. and the U.K. while study 2402 included participants from 7 European countries. U.S. participants were included in 4 single country nasal spray trials, and 1 multi-country nasal spray study. All 3 of the oral formulation trials were multinational. U.S. participants were included in oral studies C2302 and A2303.

The nasal spray trials were typically small; there were 8 trials which had calcitonin exposed groups numbering below 100. The largest nasal spray trial was CT320, which randomized 844 patients to the calcitonin group. The oral trials were larger, randomizing 2334, 488 or 521 patients to calcitonin salmon.

Inclusion and Exclusion Criteria of Individual Randomized Controlled Trials

Nearly all of the nasal spray trials limited the population to women who were either peri-menopausal or post-menopausal. Only two of the nasal spray trials included men (CT311 and CT312); these trials examined the use of calcitonin in steroid-induced osteoporosis. Two of the three oral trials also included men, and evaluated use of calcitonin in osteoarthritis. Two nasal spray trials, SMCO522 and MIA-16, enrolled patients who were older, above 60 years of age. Restrictions for malignancy, either prior to study entry, malignancy at baseline, or "diseases affecting bone metabolism, including malignancy" were applied in 10 of the included nasal spray randomized controlled trials (RCTs) and all 3 of the oral RCTs. Other studies applied a restriction for presence of disease affecting bone metabolism (to include malignancies). In 2 of the nasal spray RCTs, no malignancy exclusion was applied. Ten

studies expressly excluded patients with current malignancy. Two trials did not specify malignancy exclusion criteria (CT310 and CT312). In CT320, patients with an occurrence of malignancy within the previous 5 years were excluded, but the trial did enroll patients who had basal cell or squamous cell carcinoma at baseline.

Calcitonin exposure- dose and duration of included Randomized Controlled Trials

The shortest nasal spray trial treatment duration included in the meta-analysis was study 2402, which had a 6 month treatment period. Thirteen trials had a 24 month treatment period, 5 had a 36 month treatment period, and 1 trial (CT320) had a 60 month treatment period. Daily calcitonin nasal spray treatment doses ranged from 50 IU daily to 400 IU daily and most trials included multiple calcitonin treatment arms, with each arm evaluating a different calcitonin dose. Only 6 trials evaluated a single dose of calcitonin. In addition to a daily dosing schedule, trial SMCO514 included a 200 IU three times weekly arm. Besides calcitonin, use of calcitonin plus calcium was utilized for trials SMCO503 through SMCO511. In trial MIA-16, in addition to the calcitonin salmon and placebo groups, patients were randomized to two additional arms: nandrolone or nandrolone plus placebo. Nandrolone is an anabolic steroid that was being investigated for use in osteoporosis treatment. Data from the nandrolone exposed groups were not included in the analysis.

The oral trials utilized a dose and duration of 0.8 mg once daily for 36 months (A2303) or 0.8mg twice daily for 24 months (C2301, C2302).

Assessment of malignancy in the included Randomized Controlled Trials

For both the oral and nasal spray trials, malignancy was captured as an adverse event and was not a pre-specified safety endpoint for any of the included studies. The method of malignancy assessment was similar across all trials, consisting of periodic reporting at patient visits and via physical exams. The study reports submitted to the FDA do not document the exact adverse event reporting procedures used (e.g. were all events reported, or just those judged to be attributable to calcitonin treatment?) Additionally, there was no adjudication of malignancies.

Data Sources

Novartis submitted trial-level summaries of number of events and number of patients available for the meta-analyses. The lack of patient-level data limits the ability to evaluate subgroups (e.g. influence of prior malignancies), perform time to event analyses, or examine the effect of exposure duration. Additionally, it is difficult to assess internal consistency and quality of the data.

Statistical Analyses

This section summarizes the statistical analyses conducted by Novartis and the FDA to assess the potential risk of malignancies associated with calcitonin use compared to placebo.

Novartis Statistical Analyses

The main statistic used by Novartis for estimating the overall risk of malignancies was the odds ratio (calcitonin/placebo) using the Peto method, stratified by trial. Trials with no events in both treatment arms (zero-event trials), were not included in Novartis's analyses. Note that the Peto method implicitly excludes zero-event trials as they do not contribute to either the method's pooled estimate or variance of the estimate. Novartis's meta-analyses were performed for all 20 trials (nasal spray and oral formulations combined) and for the 17 nasal spray formulation trials only (the 18th trial included in the Advisory Committee background package is not reviewed for reasons previously discussed). Odds ratios (OR) and corresponding 95% confidence intervals (CIs) for all malignancies were also estimated within each dose level (100 IU, 200 IU, and 400 IU) for trials in the nasal spray formulation only. A value of one on the OR scale is suggestive of equal risks in the calcitonin and placebo arms.

To examine the effect of duration of treatment, Novartis calculated exposure adjusted risk ratios from study level data using Poisson meta-analysis which utilizes the sum of exposures from all patients in a treatment group instead of counting the number of patients. An additional analysis provided counts of study subjects who had completed the studies at 6 month intervals, and provided the proportion of subjects with a malignancy adverse event at each time interval.

In separate analyses of malignancies in the three oral formulation trials, Novartis conducted the exposure-adjusted risk and risk ratio, that is, the incidence rate and incidence rate ratio using Poisson regression. Refer to the Novartis background package for details on all Poisson analyses and results based on the oral trials only.

FDA's Statistical Analyses

FDA's primary analyses of malignancies were based on the 17 clinical trials in nasal spray formulation only (16 double blind and 1 open label trial). The trials in the oral formulation were not considered for inclusion in these analyses for various reasons including different route of administration, unapproved formulation, and different trial objectives. The main statistic in the FDA analyses was the Mantel-Haenszel (MH) fixed-effect risk differences (RD), without continuity corrections, stratified by trial. Note that the risk difference is well-defined for zero-event trials and thus, these trials were included in the FDA's analyses. These analyses were conducted overall across all trials and within each dose for the respective trials. A value of zero on the RD scale is suggestive of equal risks in the calcitonin and placebo arms

The FDA also conducted separate sensitivity analyses:

1. Excluding the largest trial CT320 of 5-year duration from analysis of all nasal spray trials
2. Excluding open label trial SMCO 506 from analysis of double blind nasal spray trials
3. Excluding the largest trial CT320 of 5-year duration from analysis of all double blind nasal spray trials
4. DerSimonian and Laird random-effects analyses of all nasal spray trials.

Note that for sensitivity analyses not included in the reports submitted by Novartis, the FDA used the Novartis's Peto method to estimate odds ratios for comparison to the MH risk differences.

Study Results

This section presents the results of the statistical analyses conducted by the FDA and Novartis. There are many limitations to consider when interpreting these findings: lack of adjudication of malignancies, unknown event time (i.e. if event occurred while patient on drug), varying trial designs, trials not prospectively designed to assess malignancy risks, and lack of patient-level data. Therefore, it is important to note that while these results may be suggestive of a potential cancer risk associated with calcitonin use compared to placebo, FDA cannot conclude that there is a definitive cancer signal (or lack thereof) based on the data analyzed.

Nasal Spray Formulation Trials Only

This section describes Novartis's and the FDA's analyses results for malignancy risks for all trials, and by dosing level, in the nasal spray formulation.

Table 7 shows the results for the FDA's and Novartis's original meta-analyses of all malignancies in the nasal spray formulation trials. There were 4 trials with no events in either calcitonin or placebo arms, which were included in the FDA's analyses by risk differences but excluded from Novartis's analyses of odds ratios (ORs for these trials are represented as "undefined" in the table). Figure 1 extracted from "Response to LoOI Question 4: Dose response and treatment duration analysis", shows Novartis's results of the 13 non-zero event trials. Overall, there were 122/2666 (4.6%) malignancies in calcitonin-treated patients and 28/1264 (2.2%) in placebo-treated patients. The results of all trials suggested higher risk of malignancies for patients treated with calcitonin compared to those treated with placebo; specifically OR=1.6, 95% CI (1.1, 2.3) and RD=1.6%, 95% CI (0.5, 2.8), in Novartis's and the FDA's analyses, respectively. These results include a single open-label trial SMCO 506, which was excluded from the FDA's analyses of double-blind trials; consistent results were obtained as shown in the table. Sensitivity analyses of all nasal spray trials based on random-effects methods also yielded consistent results; RD=1.8%, 95% CI (0.9, 2.8).

As shown in this table, the overall results are heavily influenced by trial CT320 in which the largest number of malignancies occurred. Note that this trial was the largest nasal spray trial,

the only long-term trial of duration 5 years, and the one that studied post-menopausal women only. In this trial, there were 81/944 (8.6%) malignancies that occurred in the calcitonin-treated patients and 16/311 (5.1%) that occurred in patients treated with placebo. FDA conducted sensitivity analyses by excluding trial CT320 from the analysis of all trials and analysis of double blind trials. These sensitivity analyses also suggested a higher risk of malignancy in calcitonin-treated patients compared to placebo; however the null values (one on the OR scale and zero on the RD scale) were not excluded from the confidence intervals. Without patient-level data, it is unclear the extent to which the differences in the time to malignancies differs in trial CT320 compared to the other trials.

Table 7: FDA's and Novartis's Original Meta-analyses Results of All Malignancies
(All Nasal Spray Trials)

Trial ID	Calcitonin n/N (%)	Placebo n/N (%)	Odds Ratio[1] (95% CI)	Risk difference[2] (95% CI)
2402	0/149 (0.0)	0/147 (0.0)	undefined	0.0
CT211	3/31 (9.7)	3/15 (20.0)	0.4 (0.1,2.5)	-10.3(-33.1,12.4)
CT310	4/211 (1.9)	1/68(1.5)	1.3(0.2,10.0)	0.4 (-3.0,3.8)
CT311[3]	8/244 (3.3)	4/79 (5.1)	0.6 (0.2,2.3)	-1.8 (-7.1,3.5)
CT312[3]	11/201 (5.5)	3/102 (2.9)	1.8 (0.6,5.5)	2.5 (-2.0, 7.1)
CT320	81/944 (8.6)	16/311 (5.1)	1.6 (1.0,2.6)	3.4 (0.4, 6.5)
MIA 16[4]	1/32 (3.1)	0/30 (0.0)	6.9 (0.1,350.5)	3.1 (-5.3, 9.2)
SMCO 005	1/32 (3.1)	0/29 (0.0)	3.7 (0.0,370.3)	3.1 (-5.3, 9.2)
SMCO 503	0/26 (0.0)	0/26 (0.0)	undefined	0.0
SMCO 504	1/29 (3.4)	0/29 (0.0)	7.4 (0.2,372.4)	3.5 (-3.2,10.1)
SMCO 506	3/147 (2.0)	1/141 (0.7)	2.6 (0.4,18.9)	1.3 (-1.3, 4.0)
SMCO 511	2/60 (3.3)	0/60 (0.0)	7.5 (0.5,121.6)	3.3 (-1.2, 7.8)
SMCO 514	2/71 (2.8)	0/46 (0.0)	5.3 (0.3,91.1)	2.8 (-1.0, 6.7)
SMCO 517	0/168 (0.0)	0/83 (0.0)	undefined	0.0
SMCO 520	0/65 (0.0)	0/32 (0.0)	undefined	0.0
SMCO 522	4/156 (2.6)	0/52 (0.0)	3.9 (0.4,353.5)	2.6 (0.1, 5.0)
SMCO 524	1/100 (1.0)	0/33 (0.0)	3.8 (0.0,353.5)	1.0 (-0.1, 3.0)
All trials	122/2666(4.6)	28/1264 (2.2)	1.6 (1.1, 2.3)	1.6 (0.5, 2.8)
DB trials*	119/2519 (4.7)	27/1123(2.4)	1.6 (1.1, 2.3)	1.6 (0.4, 2.9)
All w/o CT320*	41/1722(2.4)	12/953 (1.3)	1.6 (0.9, 2.9)	0.9 (-0.2, 1.9)
DB w/o CT320*	38/1575 (2.4)	11/812 (1.4)	1.5 (0.8, 2.8)	0.8 (-0.3, 1.9)

[1] Novartis odds ratio estimates for each trial and overall (based on Peto Method which excludes zero-event trials) obtained from Figure 3.1a in "Response to LoOI Question 4: Dose response and treatment duration analysis". The null value is an OR of 1.
[2] FDA's risk difference estimates for each trial and overall (based on MH fixed-effect method). CIs are not provided for individual trials with no events. The null value is a RD of 0.
[3]Trials including males
[4] Trial includes patients randomized to nandrolone and calcitonin + nandrolone which were omitted from analyses
*FDA's analyses
n=number of patients with malignancies, N=total number of patients
DB=double-blind trials excluding open-label trial SMCO 506, w/o=without

Figure 1: Forest Plot of Novartis's Original Meta-Analysis of Malignancies

(Non-zero Nasal Spray Trials)

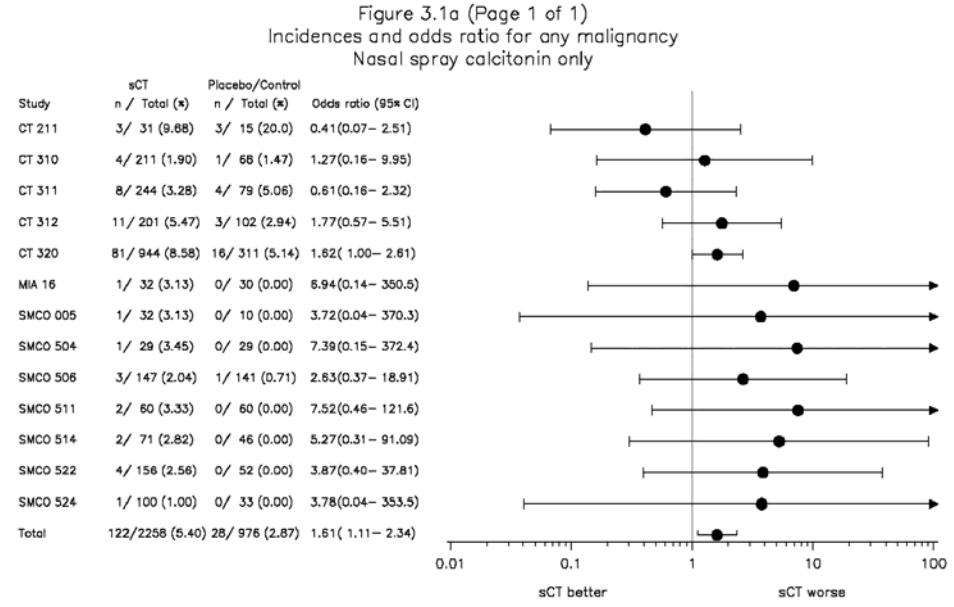


Table 8 shows the daily dose level analyses of all malignancies for the 100 IU, 200 IU and 400 IU doses. Given the small number of malignancies in trials administering the 50 IU dose (5 in calcitonin-treated patients and 1 in placebo-treated patients); these trials were not considered for the FDA's dose level analyses. Note that Novartis also did not report results for the 50 IU dose. As shown in Table 8, the overall risks for all dose levels suggested higher risks in calcitonin-treated patients compared to placebo; consistent results are obtained in the Novartis's and FDA's analyses. While the confidence intervals in the 200 IU (the approved dose of calcitonin nasal spray) do not include the null values, FDA cannot conclude that the risk of malignancy is highest in this dose. Note that not all trials investigated all three doses for adequate comparison of dose effect. Therefore, there might be confounding of trial characteristics and dose-level, which cannot be thoroughly assessed. Additionally, there are other limitations of these dose level analyses, namely reduction in sample size and the same placebo arm is used in multiple analyses with no adjustments for multiplicity.

Table 8: FDA's and Novartis Results of Dose Level Meta-Analyses of Malignancies (All Nasal Spray Trials)

Daily Dose/Trial ID	Calcitonin n/N (%)	Placebo n/N (%)	Odds Ratio[1] (95% CI)	Risk difference[2] (95% CI)
100 IU Dose				
CT310	0/71(0.0)	1/68 (1.5)	0.1 (0.0, 6.5)	-1.5 (-4.3, 1.4)
CT311	4/83 (4.8)	4/79 (5.1)	1.0 (0.2, 3.9)	-0.2 (-6.9, 6.4)
CT320	26/316 (8.2)	16/311(5.1)	1.6 (0.9, 3.1)	3.1 (-1.0, 7.0)
SMCO005	0/10 (0.0)	0/10 (0.0)	undefined	0.0
SMCO503	0/26 (0.0)	0/26 (0.0)	undefined	0.0
SMCO504	1/29 (3.5)	0/29 (0.0)	7.4 (0.1, 372.4)	3.5 (-3.2, 10.1)
SMCO511	2/60 (3.3)	0/60 (0.0)	7.5 (0.5, 121.6)	3.3 (-1.2, 7.9)
SMCO520	0/33 (0.0)	0/32 (0.0)	undefined	0.0
SMCO522	0/52 (0.0)	0/52 (0.0)	undefined	0.0
SMCO524	0/33 (0.0)	0/33 (0.0)	undefined	0.0
All Trials	**32/684 (4.7)**	**21/671 (3.1)**	**1.6 (0.9, 2.7)**	**1.6 (-0.5, 3.6)**
200 IU Dose				
2402	0/149 (0.0)	0/147(0.0)	undefined	0.0
CT211	3/16 (19.0)	3/15 (20.0)	0.9 (0.2, 5.3)	-1.3 (-2.9, 2.7)
CT310	3/72 (4.2)	1/68 (1.5)	2.6 (0.4, 19.0)	2.7 (-2.7, 8.1)
CT311	1/82 (1.2)	4/79 (5.1)	0.3 (0.1, 1.7)	-3.8 (-9.2, 1.5)
CT312	7/102 (6.9)	3/102 (2.9)	2.3 (0.7, 8.2)	3.9 (-2.0, 9.8)
CT320	24/316 (7.6)	16/311 (5.1)	1.5 (0.8, 2.9)	2.5 (-1.4, 6.3)
SMCO005	1/11 (9.1)	0/10 (0.0)	6.8 (0.1, 341.5)	9.1 (-7.9, 2.6)
SMCO514**	2/36 (5.6)	0/46 (0.0)	10.0(0.6, 166.7)	5.6 (-1.9, 13.0)
SMCO517	0/84 (0.0)	0/83 (0.0)	undefined	0.0
SMCO520	0/32 (0.0)	0/32 (0.0)	undefined	0.0
SMCO522	2/52 (3.8)	0/52 (0.0)	7.5 (0.5, 122.1)	3.9 (-1.4, 9.1)
SMCO524	1/34 (2.9)	0/33 (0.0)	7.2 (0.1, 361.7)	2.9 (-2.7, 8.6)
All Trials	**44/986 (4.5)**	**24/978 (2.5)**	**1.6 (1.0, 2.7)**	**1.7 (0.1, 3.3)**
400 IU Dose				
CT211	0/15 (0.0)	3/15 (20.0)	0.1 (0.0, 1.2)	-20.0 (-40.2,0.2)
CT310	1/68 (1.5)	1/68 (1.5)	1.0 (0.1, 16.2)	0.0 (-4.1,4.1)
CT311	3/79 (3.8)	3/79 (3.8)	0.7 (0.2, 3.4)	-1.3 (-7.7, 5.2)
CT312	4/99 (4.0)	3/102 (2.9)	1.4 (0.3, 6.2)	1.1 (-4.0,6.2)
CT320	31/312 (9.9)	16/311 (5.1)	2.0 (1.1, 3.6)	4.8 (0.7,8.9)
MIA16	1/32 (3.1)	0/30 (0.0)	6.9 (0.1, 350.5)	3.1 (-2.9, 9.2)
SMCO524	0/33 (0.0)	0/33 (0.0)	undefined	0.0
All Trials	**40/638 (6.3)**	**26/638 (4.1)**	**1.5 (0.9, 2.5)**	**2.0 (-0.4, 4.5)**

[1] Novartis odds ratio estimates for each trial and overall (based on Peto Method which excludes zero-event trials) obtained from Figure 3.3b1 and Figure 3.3b2 in Response to FDA Questions 16-January-2013 for 200 IU and 400 IU, respectively. 100 IU results based on FDA's analysis using Peto method due to omission of trial SMCO005 in Novartis analyses.

[2] FDA's risk difference estimates for each trial and overall based on MH fixed-effect method). CIs are not provided for individual trials with no events.

**Trial includes patients given 200 IU dose MWF that is not included in 200 IU daily dose analysis

n=number of patients with malignancies, N =total number of patients in arm

Nasal Spray and Oral Formulation Combined

Table 9 shows the FDA's and Novartis's results from the meta-analyses of all malignancies in the nasal spray and oral formulation trials. These results also suggest a higher risk of malignancy for patients treated with calcitonin compared to those treated with placebo; specifically OR=1.4, 95% CI (1.1, 1.7) and RD=1.0%, 95% CI (0.3, 1.7), in Novartis's and the FDA's analyses, respectively.

Table 9: FDA's and Novartis Meta-analyses Results of All Malignancies

(All Oral and Nasal Spray Trials)

Formulation/ Trial ID	Calcitonin n/N (%)	Placebo n/N (%)	Odds Ratio[1] (95% CI)	Risk difference[2] (95% CI)
Nasal Spray				
2402	0/149 (0.0)	0/147 (0.0)	undefined	0.0
CT211	3/31 (9.7)	3/15 (20.0)	0.4 (0.1,2.5)	-10.3(-33.1,12.4)
CT310	4/211 (1.9)	1/68(1.5)	1.3(0.2,10.0)	0.4 (-3.0,3.8)
CT311[3]	8/244 (3.3)	4/79 (5.1)	0.6 (0.2,2.3)	-1.8 (-7.1,3.5)
CT312[3]	11/201 (5.5)	3/102 (2.9)	1.8 (0.6,5.5)	2.5 (-2.0, 7.1)
CT320	81/944 (8.6)	16/311 (5.1)	1.6 (1.0,2.6)	3.4 (0.4, 6.5)
MIA 16[4]	1/32 (3.1)	0/30 (0.0)	6.9 (0.1,350.5)	3.1 (-5.3, 9.2)
SMCO 005	1/32 (3.1)	0/29 (0.0)	3.7 (0.0,370.3)	3.1 (-5.3, 9.2)
SMCO 503	0/26 (0.0)	0/26 (0.0)	undefined	0.0
SMCO 504	1/29 (3.4)	0/29 (0.0)	7.4 (0.2,372.4)	3.5 (-3.2,10.1)
SMCO 506	3/147 (2.0)	1/141 (0.7)	2.6 (0.4,18.9)	1.3 (-1.3, 4.0)
SMCO 511	2/60 (3.3)	0/60 (0.0)	7.5 (0.5,121.6)	3.3 (-1.2, 7.8)
SMCO 514	2/71 (2.8)	0/46 (0.0)	5.3 (0.3,91.1)	2.8 (-1.0, 6.7)
SMCO 517	0/168 (0.0)	0/83 (0.0)	undefined	0.0
SMCO 520	0/65 (0.0)	0/32 (0.0)	undefined	0.0
SMCO 522	4/156 (2.6)	0/52 (0.0)	3.9 (0.4,353.5)	2.6 (0.1, 5.0)
SMCO 524	1/100 (1.0)	0/33 (0.0)	3.8 (0.0,353.5)	1.0 (-0.1, 3.0)
Oral Trials				
A2303	89/2334 (3.8)	87/2331 (3.7)	1.0 (0.8, 1.4)	0.1 (-1.0, 1.2)
C2301[3]	22/585 (3.7)	6/584 (1.0)	3.2 (1.5, 6.8)	2.7 (1.0, 4.5)
C2302[3]	21/520 (4.0)	14/508 (2.8)	1.5 (0.8, 2.9)	1.3 (-0.9, 3.5)
All Trials	**254/6105 (4.2)**	**135/4687 (2.9)**	**1.4 (1.1, 1.7)**	**1.0 (0.3, 1.7)**

[1] Novartis odds ratio estimates for each trial and overall (based on Peto Method which excludes zero-event trials) obtained from Figure 3.1b in "Response to LoOI Question 4: Dose response and treatment duration analysis".

[2] FDA's risk difference estimates for each trial and overall (based on MH fixed-effect method). CIs are not provided for individual trials with no events.

[3]Trials including males

4 Trial includes patients randomized to nandrolone and calcitonin + nandrolone which were omitted from analyses

n=number of patients with malignancies, N=total number of patients

Duration of exposure - malignancy reporting over time

Novartis conducted an analysis of nasal spray studies providing counts of study completers and numbers of malignancies reported at 6 month intervals (Table 10). This analysis does not appear to control for trial differences. At 6 months, the proportion of study completers reporting malignancies in the calcitonin salmon and placebo groups was similar, 0.9% and 0.8% for the calcitonin salmon and placebo groups, respectively. By month 12, the reporting rates in the calcitonin salmon and placebo groups begin to diverge, with a maximum difference occurring at 36 months. By 36-months, the proportion of study completers reporting malignancies was 3.2% in the calcitonin salmon group and 1.2% in the placebo group. After 36 months, only one study was still ongoing and contributed to these analyses.

Table 10 Proportion of study completers reporting an incident malignancy by time period

	Months							
	0	6	12	18	24	36	48	60
Calcitonin nasal completers	2,634	2,377	2,077	1,882	1,770	742	495	383
Malignancy %		0.9%	1.2%	0.7%	0.6%	3.2%	1.4%	3.9%
Completer %		90%	79%	71%	67%	28%	19%	15%
Placebo nasal completers	1,234	1,105	902	826	784	334	154	128
Malignancy %		0.8%	0.2%	0.2%	0.3%	1.2%	0.6%	3.9%
Completer %		90%	73%	67%	64%	27%	12%	10%

For multiple malignancies within a patient, only the first occurrence of malignancy is considered
Eight missing time to events (5 calcitonin, 3 placebo)
Two elevated PSA cases without time to event information (both calcitonin)
Percentage is calculated based on the number of completers at each 6 month period
For the nasal study MIA-16, data by time period is not available

Discussion

Novartis's meta-analysis, as submitted to the FDA, has a number of limitations which affect its ability to adequately assess the potential risk of cancer associated with calcitonin use. Among the issues noted are:

1) Evaluation of only the statistical and not the clinical heterogeneity of included studies,
2) Failure to provide a quality assessment of the included studies, and
3) Inadequate documentation for the methods used in the analysis.

These issues are discussed in greater detail below.

Heterogeneity

A significant concern when interpreting the results of a meta-analysis is the similarity of the trials, both from a qualitative (clinical) perspective as well as from the quantitative (statistical) perspective. Novartis evaluated statistical heterogeneity, but did not evaluate clinical heterogeneity to any significant degree. Novartis assessed heterogeneity using I-squared and Cochran's Q-statistic, tested at a p-value of 0.05 and reported that results of these tests were suggestive of low heterogeneity across the trials included in the meta-analyses. These statistical tests are often criticized as having low power, thereby leading to inaccurate conclusions about the presence of heterogeneity. Therefore, FDA focused on qualitative assessment of heterogeneity.

Clinical heterogeneity seeks to determine the qualitative similarity of the included studies, including study design, inclusion and exclusion criteria, source populations, primary outcomes of interest, assessment of adverse events, and other characteristics contributing to differences between the individual point estimates. In the nasal analysis, the trial designs were similar; most were small, single center trials in post-menopausal women and all but one were randomized clinical trials comparing calcitonin salmon treatment to placebo. However, differences in the study populations were noted. Two trials included men (CT311 and CT312); these trials were undertaken to evaluate the treatment of osteoporosis induced by corticosteroids. Another source of clinical heterogeneity is from trial 2402 in which osteoporosis was not a requirement for inclusion. Study 320 had more lenient exclusion criteria for malignancy when compared to the other studies since patients with basal or squamous cell carcinoma at baseline were allowed to be enrolled. The risk of second malignancies in patients with history of malignancies is likely different compared to patients who have not had history of malignancies. Therefore, analyzing all patients, regardless of malignancy history, could cause difficulties in interpreting the meta-analytic results. Finally, the primary objectives for the studies differed. While the majority of studies examined some aspect of calcitonin efficacy for treatment or prevention of peri-menopausal or post-menopausal osteoporosis, 1 study's objective was to evaluate the prevention of pain associated with forearm fracture, and 2 studies evaluated glucocorticoid induced osteoporosis.

Novartis also did not evaluate clinical heterogeneity for the oral studies. For the oral studies, 2 studies examined the prevention of knee osteoarthritis and enrolled both men and women, and the third study examined prevention of postmenopausal osteoporosis and enrolled only women.

Quality of included Randomized Controlled Trials

Assessment of study quality in meta-analysis is a controversial issue. While researchers dispute whether it is appropriate to adjust the meta-analytic estimate for study quality due to issues of subjectivity in quality assessments, a discussion of the quality of the included studies and perhaps a sensitivity analysis is often more appropriate. However, Novartis provided neither. Several biases may have existed in the included trials, including attrition bias and detection bias. Attrition bias may have been present in study 311, for example. Since

41% of calcitonin patients and 32% of placebo patients discontinued early; this inability to assess events in the discontinued patients may have contributed to the lower cancer risk estimate reported in this study. High attrition in both study groups would have decreased the power of the study and the meta-analysis to generate statistically significant risk estimates and may have biased the estimates in an unknown direction.

While it was more common to have higher dropout rates in the calcitonin groups, 3 studies had higher dropout rates in the placebo arm than at least 1 of the calcitonin treatment arms. Study 320 had dropouts occurring earlier in the 200 and 400 IU calcitonin treatment groups. Pooling calcitonin salmon treatment groups also exacerbates the effect of early dropouts in the calcitonin salmon treatment groups. If differential dropout rates occur in treatment groups and if these patients were more likely to develop cancer, the estimate excluding their experience would have been biased towards the null, while the converse would be true for studies with greater placebo dropout. Ultimately, however, it is impossible to determine the extent and direction of this particular bias and the impact on the meta-analysis is unclear.

Inadequate Documentation and Meta-Analysis Quality

Detection bias may have had a role in studies 511 and 514 where the investigators did not provide adequate documentation of adverse event reporting.

Novartis provided the CHMP and the FDA with updated reports to correct errors identified in the analyses. For example, in the dosing level analysis the FDA identified two studies which were not included in the 200 IU forest plot. While these changes did not substantially affect the risk estimates, they do raise questions about the quality and conduct of the meta-analysis.

Several formal meta-analysis guidelines and checklists exist which are intended to assure the quality of meta-analyses, and provide recommendations for essential procedures to be followed with a focus on preparation for publication. While the Novartis's analysis was completed in response to requests from regulators, elements of these guidelines are still applicable. Essential to these guidelines is the recommendation for analyses to include well defined and clear study methods. Novartis's analysis lacked this methods documentation. For example, an analysis plan was provided for the oral studies but Novartis did not document whether the plan was followed and what procedures were used in the final analysis. Other notable departures from recommended meta-analytic procedures include:

- Study validity and quality was not assessed (presented above)

- Process for data abstraction was not presented
    - Novartis indicates that they rigorously checked the counts of malignancies obtained from clinical study reports. Since the malignancy counts and the resultant odds ratio differed between the original analysis presented in August 2011 and the one presented in June 2012, perhaps a well-documented, pre-defined data abstraction method would have increased the initial study quality.

Conclusions

The overall meta-analyses conducted by the FDA and Novartis show a trend for a higher risk of malignancy for calcitonin-treated patients compared to placebo. There are a number of limitations that makes a causal relationship determination between calcitonin and malignancy difficult. These limitations include incomplete study methods documentation, high rates of early discontinuation and differential follow-up in the included studies, to name a few. Certainly, for the nasal spray trials, the odds ratio of 1.6 (risk difference of 1.6%) is within the range which raises questions of possible uncontrolled confounding. These results are heavily influenced by trial CT320 in which the largest number of malignancies occurred. Note that this trial was the largest nasal spray trial and the only long-term trial of duration 5 years. Sensitivity analyses conducted by the FDA that excluded CT320 still showed a higher risk of malignancy in calcitonin-treated patients compared to placebo (0.9% risk difference, 1.6 odds ratio); however the null values were not excluded from the confidence intervals for both estimates. Without patient-level data, it is unclear to what extent these differences in the time to malignancies differ in trial CT320 compared to the other trials.

The potential for a cancer risk with calcitonin salmon therapy cannot be ignored. The majority of all calcitonin salmon trials showed an increased risk estimate. There were 4 trials for which no events were reported in either calcitonin- or placebo-treated patients.

Novartis and the FDA conducted a series of dose-level analyses in an attempt to characterize the increased risk. The primary meta-analysis compared the combined calcitonin arms containing different doses within each study, with the information for placebo. From an epidemiologic perspective, the analysis of combined dose levels assumes that the risk is not related to dose. Both Novartis's and the FDA's analyses fail to demonstrate a dose response relationship. Establishment of a dose response relationship is an important but not a necessary element to determine association. The lack of a dose response does not necessarily rule out an association as the threshold for a response may be below the dose levels tested.

Novartis also conducted a series of duration of exposure analyses in an attempt to characterize the increased risk. An imbalance in malignancies reported between calcitonin salmon and placebo groups occurred by month 12 and continued through month 36. Similarly, in nonclinical studies calcitonin treatment was associated with early development and detection of an increased number of benign neoplasms in the pituitary in two strains of rats.

Further evaluation of this effect in humans is problematic. The declining use of calcitonin in the U.S. is an indicator that additional epidemiologic studies examining the potential risk of cancer associated with the use of calcitonin salmon will be difficult to complete with sufficient power in the U.S. This is especially true since the overall sample size will be limited by the need to validate outcomes through chart review or via cancer registries. Use of either of these validation methods will require the use of specific datasets which will likely result in cohorts that are a fraction of the size of the total U.S. population of users.

3 Salmon Calcitonin: Efficacy

3.1 Overview of the Efficacy Issues

Since 1994, all products approved for treatment of postmenopausal osteoporosis have been required to demonstrate efficacy in fracture reduction. Calcitonin salmon, initially approved prior to 1994, is the only product currently approved and marketed to treat postmenopausal osteoporosis (PMO) that has not demonstrated definitive evidence of efficacy in reducing fractures. The question of fracture efficacy becomes critical when assessing the risks and benefits of calcitonin in light of the potential cancer risk. The purpose of this review is to summarize the evidence for efficacy of calcitonin salmon in treating postmenopausal osteoporosis, especially the evidence regarding fractures.

3.2 Calcitonin Salmon Injection

The trials used for the basis of approval for calcitonin salmon injection were conducted in the 1970's and consisted of two pivotal 2-year postmenopausal osteoporosis studies. The studies were independent of each other but followed the same protocol, so they will be discussed here together. The primary efficacy endpoint of both studies was total body calcium measured by neutron activation analysis and single photon absorptiometry (SPA) of the radius as a secondary endpoint. In 1980, FDA guidelines did not require evidence of fracture efficacy for approval of osteoporosis drugs. The data and analyses are as presented in the 1984 Summary Basis of Approval (a document previously released under the Freedom of Information Act) for this supplemental New Drug Application, and a publication (Gruber, 1984) based on the one of the studies.

Subjects in these two studies were postmenopausal Caucasian women age 50-74 years old, ambulatory, with vertebral osteopenia (by x-ray criteria) and/or at least one atraumatic compression fracture; total body calcium <85% of expected normal; and no evidence of conditions (other than osteoporosis) involving bone or likely to affect bone. Subjects were randomized to Calcimar 100 IU daily (SC or IM) at bedtime, or control. The studies were not blinded, as control subjects did not receive placebo injections. All subjects received daily supplements of 1200 mg calcium carbonate and 400 units of vitamin D.

Study 1 enrolled 50 subjects, all women with PMO, with a mean age 65 years and an average of 3 baseline vertebral fractures. Five subjects did not complete the 2-year study. There were 45 subjects (24 Calcimar, 21 control) evaluated for efficacy. Study 2 enrolled 34 women with PMO (age 50-74 years old per protocol; demographic data unavailable). There were 9 dropouts, and one subject with osteomalacia was excluded from the analysis. There were 24 subjects (10 Calcimar, 14 control) analyzed for efficacy.

The total body calcium (TBCa) data are presented in Table 11 below. In both studies, TBCa increased from baseline with Calcimar, and decreased from baseline with control, at each timepoint. With Calcimar treatment, TBCa peaked at 18-20 months in Study 1 and at 12 months in Study 2, then declined by 24-26 months though remaining above baseline.

Table 11: Total Body Calcium (PMO): percent change from baseline, by treatment group and visit

	6 months	12 months	18-20 months	24-26 months
		Study 1		
Calcimar, n	24	24	24	24
% change (SEM)	+**1.22** (0.9)	+**2.06** (1.1)	+**2.18** (0.8)	+**1.39** (1.1)
Control, n	21	21	20	21
% change (SEM)	**-0.51** (1.1)	**-1.28** (1.3)	**-2.23** (0.9)	**-1.43** (0.9)
Difference (Calcimar-control)	+1.73	+3.34	+4.41	+2.82
		Study 2		
Calcimar, n	9	10	10	10
% change (SEM)	+**2.14** (0.7)	+**5.17** (1.8)	+**2.54** (1.6)	+**2.14** (1.6)
Control, n	13	13	12	14
% change (SEM)	**-0.45** (1.3)	**-1.01** (1.7)	**-2.51** (1.2)	**-2.10** (0.9)
Difference (Calcimar-control)	+2.59	+6.18	+5.05	+4.24

Source: Summary Basis of Approval for NDA 017497/S-024 and NDA 017769/S-008, Table 1, 12/21/1984

Bone mineral content (BMC) of the non-dominant radius by single photon absorptiometry (SPA) was also evaluated in both studies, at the same time intervals. A Norland-Cameron bone densitometer, with a ^{125}I source, measured BMC at 2 sites, distal radius (10% radius, which is a mixed ~85% cortical/ ~15% trabecular site) and a site more proximal (20% radius, which is a ~90% cortical site), in units of g/cm radial length. At these radial sites, Calcimar and control groups had small changes from baseline, with no significant difference between groups at any timepoint, in either study.

Thoracic and lumbar spine X-rays (AP/lateral) were also obtained yearly. For the two studies combined (34 Calcimar and 35 control subjects), in the first year, there was a total of 6 new vertebral compression fractures in the Calcimar group and 5 in the control group. In the second year, there were 7 new fractures in each group. Worsening of existing fractures was said to be more frequent in the Calcimar group in study 1, but more frequent in control subjects in study 2.

In study 1, iliac crest bone biopsies were also performed in 42 subjects at baseline and 30 subjects at 2 years. At baseline, percent total bone area was significantly correlated with total body calcium (r=.45, p=.004). In the Calcimar group relative to baseline and to control, there were trends toward an increase in percent trabecular bone area and a decline in percent resorbing surface. There was also a slight but significant decrease in the rate of bone apposition with Calcimar relative to control, but no difference in the overall rate of bone formation. Normal bone histology and presumably architecture were preserved, with no evidence of a defect in mineralization.

Because of the concern for using total body calcium as a surrogate for fracture risk, the Applicant committed to conduct a postmarketing fracture study when Calcimar was approved for treatment of postmenopausal osteoporosis. Study RHCG-CT-401 was designed to fulfill the postmarketing commitment. This was an open-label, randomized study of women with postmenopausal osteoporosis and baseline vertebral fractures. The primary objective was to

demonstrate a reduction with Calcimar injection in the number of new vertebral fractures and changes in fracture scores over 3 years of treatment. The plan was to enroll 300 subjects, 150 per treatment group, for a treatment period of 3 years. It was estimated that this sample size would have 90% power to detect a 20% difference between treatment groups in rates of first new fractures, at the .05 level of significance.

Subjects were postmenopausal women more than 45 years old, ambulatory, with an established diagnosis of osteoporosis without an established etiology, defined as a degree of osteopenia inappropriate for age and sex and 1-3 vertebral fractures by X-ray criteria at baseline, and absence of evidence of other conditions or drugs which may lead to secondary osteoporosis or bone loss. Other osteoporosis treatments either approved (i.e. estrogens) or experimental were not allowed within 6 months of entry or during the study. Paget's disease of bone and chronic thiazide diuretic use were also criteria for exclusion.

Subjects were randomized to receive Calcimar 100 units SC (0.5 mL of 200 IU/mL solution), daily at bedtime, or no treatment. The Calcimar dosage could be reduced to 50 units daily if needed to control nausea or vomiting, a known adverse reaction to calcitonin injection. All subjects were to receive twice a day supplements of calcium 500 mg and vitamin D 200 IU. The study was open-label because it was assumed that it would be difficult, if not unethical, to require control subjects to receive daily placebo injections for 3 years. According to protocol, subjects were to be randomized (within each study site) in "matched pairs" based on age and the total vertebral index score.

There was one efficacy endpoint for the trial, vertebral fractures. Spine x-rays were collected on a yearly basis and interpreted by one treatment-blinded radiologist. The method used to define prevalent fracture was a modification of a classification system published by Meunier, in which each vertebra from T-3 thru L-5 was assigned a score of 1 (normal); 2 (biconcave); 3 (variably defined as wedging or endplate fracture); or 4 (variably defined as crush/collapse or as wedged, compressed or fractured). Vertebrae with scores of 3 or 4 were considered fractured. For incident fractures, a wedge or compression fracture was defined by a $\geq$ 20% decrease in height measurement from the previous X-ray and/or a change in shape including depression of the inferior or superior end plate. Each film was assigned a vertebral index as the sum of the scores (1-4) for all vertebrae. Only newly fractured vertebrae (i.e. those with a baseline score of 1, which progressed to either 3 or 4) were included in the primary endpoint; worsening of existing fractures was not evaluated. Some vertebral BMD data were obtained outside protocol and were later analyzed.

A brief interim report on the status of this study indicated that study enrollment had been much slower than anticipated: over a >4-year period, only half of the planned 300 subjects had enrolled, and half of these had dropped out. The Applicant attributed this to poor acceptance and tolerance of the daily injections. Furthermore, it was reported that more fractures had occurred in the Calcimar group relative to control. After discussion, FDA requested that study enrollment be suspended, and requested a more detailed report.

A total of 151 subjects had been enrolled; the number enrolled per study site ranged from 1 to 53. Among these there were 21 subjects "randomized not treated", in most cases because

the central radiologist did not confirm the presence of 1-3 baseline fractures. Of the remainder, 65 had completed the 3-year study, 56 had dropped out and 9 remained active in the study (Table 12). Most of the dropouts occurred during the first year (i.e. before the first post-baseline X-ray), and despite apparent efforts to contact these subjects for follow-up, only 95 subjects had any post-baseline X-rays for the efficacy evaluation. The percentages of subjects completing 1, 2 and 3 years respectively were 60%, 47% and 34% for the Calcimar group, and 66%, 54% and 43% for the control group.

Table 12: Study RHCG-CT-401: Disposition

	Calcimar	Control	Total
Randomized	86	65	151
Completed 3-year study	35	30	65
Discontinued in < 3 yrs	45	32	77
Never received treatment	13	8	21
Withdrew due to AEs (not specified)	16	8	24
Lost to follow-up	6	6	12
"Other" (not specified)	10	10	20
Remaining in study at time of analysis	6	3	9

In reviewing the study progress, the Applicant concluded that the randomization scheme had not been adhered to. Thus, more subjects had been assigned to Calcimar than control (86 vs. 65), especially among subjects with 2 or 3 baseline fractures (27 vs. 17, and 21 vs. 14 respectively), which was not consistent with the study plan to randomize by pairs matched for vertebral fracture index. All study sites, except one, had a larger number of subjects randomized to Calcimar than control. In addition, 5 subjects were switched by investigators after randomization from their assigned treatment to the alternate (4 from control to Calcimar, 1 from Calcimar to control), yet remained in the study.

Demographic data were recorded for 135 of 151 randomized women. The mean age was 67 years old, and the mean number of years since menopause was 21. All but 2 subjects (both control) were Caucasian. The average subject was 63" in height and weighed 139 lbs. The mean number of baseline vertebral fractures among randomized subjects was 1.9 for Calcimar, and 1.8 for control. The mean baseline vertebral index was 20.5 for Calcimar, and 20.2 for control. Mean baseline spinal BMD (for subjects with data) was slightly lower in the Calcimar group (0.81 vs. 0.83 g/cm^2).

Fracture efficacy results:
Out of 151 randomized subjects, there were 95 (52 Calcimar, 43 control) subjects with post-baseline X-rays available for analysis (ITT_E) (Table 13). Among these, there were more Calcimar subjects, relative to control, who had incurred new vertebral fractures (23.1% vs. 11.6%), and the rate of new fractures was higher with Calcimar (181 vs. 133 per 1000 subject years, RR 1.73). These treatment group differences were not statistically significant.

Table 13: Study RHCG-CT-401: New vertebral fractures, by treatment group (ITT_E ‡)

	Calcimar	Control
Subjects with post-baseline X-rays, N	52	43
Mean number of baseline fractures	1.94 ± 0.85	1.72 ± 0.83
Exposure (subject-years)	121.3	105.3
Subjects with new fractures, n (%)	**12/52 (23.1%)**	**5/43 (11.6%)**
RR for new fracture (95% CI)*	1.15 (0.96, 1.39)	
p-value*	0.135	
Total number of new fractures	22	14
Fracture rate (per 1000 subj-yr)	**181**	**133**
RR for new fractures (95% CI)**	1.73 (0.51, 5.92)	
p-value**	0.381	
Adjusted fracture rate (per 1000 subj-yr)***	162	165

‡ ITT_E = subjects randomized and treated, with at least one post-baseline X-ray
* p-value by Sponsor's Cox proportional hazards model stratified by baseline fractures
** p-value by Sponsor's logistic regression analysis (adjusts for number of baseline fractures)
*** adjusted for baseline fractures by Sponsor; calculation verified by this reviewer
Source: Tables 12, 13 and 14, interim report

It was also apparent that the Calcimar group had a greater proportion of higher risk (2 or 3 baseline fracture) subjects, relative to control (Table 13 and Table 14). This resulted from the imbalance in baseline fractures at randomization, which then had become more pronounced during the study: control subjects who discontinued without a post-baseline X-ray had a higher mean number of baseline fractures (1.9) compared to Calcimar subjects who discontinued (1.7). Thus within the efficacy analysis subset, Calcimar subjects had a mean of 1.9 fractures at baseline, and control subjects had a mean of 1.7; and more Calcimar subjects had 3 fractures at baseline (33% vs. 23%). As the Applicant observed, this imbalance would tend to create a bias toward more new fractures in the Calcimar group. A re-calculation of fracture rates was conducted to correct for the number of baseline fractures; this resulted in adjusted rates of new fractures of 162 and 165 per 1000 subject-years for Calcimar and control respectively.

Table 14: Study RHCG-CT-401: New vertebral fractures, by baseline fracture status and treatment group (ITT_E)

	Calcimar Total N=52			**Control** Total N=43		
	number of baseline fractures			number of baseline fractures		
	1	2	3	1	2	3
N (%)	20 (38%)	15 (29%)	17 (33%)	22 (51%)	11 (26%)	10 (23%)
Exposure (subj-yrs)	43.5	37.6	40.1	53.0	30.4	21.9
Subjects with new fractures, n (%)	0 (0%)	5 (33%)	7 (41%)	1 (5%)	1 (9%)	3 (30%)
Number of new fractures	0	10	12	1	2	11
Fracture rate (per 1000 subj-yrs)	0	266	299	19	66	502
Cumulative percent fracture free at EOS*	100.0	60.6	51.3	94.1	88.9	61.0
* EOS (end of study) results from Kaplan-Meier curves Source: Table 12, interim report						

Vertebral index (sum of scores [1-4] for all 15 vertebrae [T-3 to L-5] on a given film) data were also analyzed as a secondary endpoint. The mean vertebral index at baseline was 20.46 for Calcimar, and 20.20 for control. The mean increases in this index from baseline, mostly reflecting new fractures, were greater for the Calcimar cohort relative to control (0.64 vs. 0.38 at year 1; 1.17 vs. 0.91 at year 2; and 1.69 vs. 0.68 at year 3); these treatment group differences were not statistically significant.

Vertebral BMD data obtained by dual photon absorptiometry (DPA), although not included in the protocol, were collected on 55, 84, 61 and 45 out of the 151 enrolled subjects at baseline and years 1, 2 and 3 respectively. (DPA was not available at the largest study site until the end of year 1, thus the smaller number scanned at baseline.) Only 20 subjects (10 in each treatment group) had BMD data at all 4 timepoints. Because these data were collected and analyzed retrospectively at FDA request, there was no standardization of methods.

Among subjects in the fracture efficacy analysis subset who also had BMD data, mean baseline BMD was slightly lower for Calcimar compared to control subjects (0.81 vs. 0.84 g/cm^2), and there were 8/25 Calcimar subjects, compared to 4/22 control subjects, who were in the lowest category (BMD < 0.70 g/cm^2).

During the study, BMD increased by a mean of ~3% in Calcimar subjects at years 1 and 2, then declined at year 3, though remaining somewhat higher than control subjects, who showed small declines from baseline (Table 15). None of these trends were found to be statistically significant.

Table 15: **Study RHCG-CT-401: Vertebral BMD, mean percent change from baseline by treatment group and year (all randomized)**

	Subjects with BMD data at baseline and timepoint		Subjects with BMD data at every timepoint	
	Calcimar	**Control**	**Calcimar**	**Control**
Baseline				
n			10	10
Mean BMD (g/cm^2)			0.83	0.90
Year 1				
n	18	15	10	10
Mean % change	**+3.15**	**-0.37**	**+2.98**	**-0.88**
Year 2				
n	16	14	10	10
Mean % change	**+3.30**	**-0.50**	**+3.53**	**-0.30**
Year 3				
n	12	10	10	10
Mean % change	**+0.68**	**-0.89**	**+0.66**	**-0.89**
Source: Tables 17-19 and 21, interim study report				

The findings from this interim analysis were presented before the Endocrinologic and Metabolic Advisory Committee on July 24, 1991. The Advisory Committee discussed the problems with the randomization process and the lack of difference between treatment groups after accounting for baseline fracture status. It was concluded that due to the study's numerous flaws, the fracture data were unreliable and inconclusive. The bone density data shows that calcitonin salmon increases regional bone mass. However, it is concerning that the bone mass increment tended to diminish with continued treatment. This had been seen in the original studies of total body calcium, which declined following a peak at 12-20 months. Two published studies were also discussed that showed significant increases in lumbar spine BMD at 1 year, however there were no BMD data available beyond 1 year except for the post hoc data from study RHCG-CT-401, which showed an apparent decline between years 2 and 3. The committee agreed unanimously that there was evidence that calcitonin salmon reduces bone loss, at least over a 2-year period, but no evidence that it reduces fractures. The committee voted narrowly against removing the postmenopausal osteoporosis indication and recommended that a new fracture study with improved design be conducted.

3.3 Calcitonin Salmon Nasal Spray

A nasal spray formulation of calcitonin salmon was developed in order to eliminate the requirement for injection. The studies used for the basis of approval for calcitonin salmon efficacy were three randomized, controlled trials with lumbar spine BMD as the primary endpoint (Table 16). The fracture efficacy trial CT320 was ongoing at the time of approval.

Table 16: Phase 3 trials of calcitonin salmon nasal spray in women with PMO and >5 yr post-menopause

Trial	Location	Duration	Mean baseline LS-BMD T-score	endpoint	Total N rand/ ITT_E	Dosage regimens (IU)	Supplements?
SMCO 522	Denmark	2 yr	-2.5	LS-BMD DXA	196	50, 100, 200, Plac daily	Yes-Ca
SMCO 514	U.K.	2 yr	-2.2*	LS-BMD DPA	112	200 daily, 200 3x/wk, Plac	no
SMCO 516	Denmark	1 yr	-2.0	LS-BMD DPA	40	100 BID, Plac	Yes-Ca
*among subjects > 5 yrs post menopause Rand=randomized; LS-BMD=lumbar spine bone mineral density; Plac=placebo; Ca=calcium DXA=dual xray absorptiometry; DPA=dual photon absorptiometry							

The populations of these 3 studies were somewhat different:

- Study 522 enrolled a homogeneous population of elderly women (mean age 70 years old, range 68-72) who were ≥10 years post menopause (mean 23 years) and not taking estrogens. Vertebral fractures were present at baseline in 13% of subjects.
- Study 514 enrolled subjects who were 6 months to 10 years post menopause, however only the data from the "established menopause" group (>5 yrs post menopause, mean age 58 years old) were included in the NDA efficacy summary.
- Study 516 enrolled only women who were >5 to 20 years postmenopausal, except for one who was 4 yrs postmenopausal.

Table 17 below summarizes the data from each of these 3 pivotal studies pertaining to the approved 200 IU daily dose (or 100 IU twice daily, in study 516); this dose appeared to show a more robust and statistically significant BMD response relative to the other regimens studied (50 IU daily, 100 IU daily, 200 IU 3x/wk). The Applicant concluded that 200 IU daily was the lowest effective dose to treat PMO, and produced significant BMD gains of 2-3% over placebo, which were evident within 6 months and did not appear to wane over 2 years of treatment. The benefit was seen in study 514 although BMD increments were lower in both arms of this study compared to the other studies, which was attributed possibly to the lack of calcium supplements in this study. The results below pertain to valid completers (completed 2 years, per-protocol), but are consistent with the overall ITT_E data.

Table 17: Nasal Calcitonin Salmon (sCT) Phase 3: Lumbar spine BMD, mean percent change from baseline by visit (subjects with established PMO, 2-year valid completers)

	Month 12/ Endpoint	Month 24/ Endpoint
Study 522 (+ calcium supplements)		
sCT 200 IU NS daily (N=41)	**+2.44**	**+2.05**
Placebo (N=40)	+0.45	0.004
Difference (sCT-placebo)	**+1.99**	**+2.05**
p-value†	0.015	0.007 (< 0.0167)*
Study 514 (**no** calcium supplements)		
sCT 200 IU NS daily (N=14)	**+1.03**	**+1.38**
Placebo (N=19)	-1.21	-1.73
Difference (sCT-placebo)	**+2.24**	**+3.11**
p-value†	0.022	0.007 (< 0.025)*
Study 516 (+ calcium supplements)		
sCT 100 IU NS twice daily (N=17)	**+3.2%**	
Placebo (N=20)	-0.4%	
Difference (sCT-placebo)	**+3.6%**	
p-value†	0.04	

†p-values by parametric testing (2-tailed 2-sample t-test)
* $p < 0.0167$ vs. placebo (study 522) or $p < 0.025$ vs. placebo (study 514), per Bonferroni criteria for multiple comparisons of primary endpoint (month 24)

Because study 516 used a different dosage regimen (BID instead of daily) and provided no 2-year data, it was not considered relevant to the NDA, and current Miacalcin nasal spray labeling references only the data from studies 522 and 514. These studies also examined BMD of distal forearm (study 522) and proximal femur (study 514), but did not find statistically significant differences between calcitonin salmon and placebo.

Vertebral fractures were assessed in studies 522 and 514 as a secondary endpoint, though neither was powered adequately to evaluate fracture reduction efficacy. Lumbar spine x-rays were collected on a yearly basis. Only one established-osteoporosis subject in study 514 sustained a new fracture. In study 522, there were sufficient new fractures to permit some analysis. Because previous vertebral fractures are a strong risk factor for additional fractures, the study 522 analysis was limited to subjects with no previous fractures (87% of all subjects). Each of the 3 calcitonin dosage groups had fewer fractures than the placebo group, but none was significantly different from placebo, and there was no evidence of dose response (Table 18).

Table 18: Study 522: Subject incidence of new vertebral fractures (subjects with no baseline fractures)

Method of interpretation	**Placebo NS**	**Calcitonin 50 IU**	**Calcitonin 100 IU**	**Calcitonin 200 IU**	**Calcitonin pooled**
Intent to treat (ITT_E)					
Kleerekoper	6/42 (14%)	1/37	2/42	4/39	7/118 (6%)
Melton	5/40 (13%)	2/36	0/39	3/39	5/114 (4%)
2-year valid completers					
Kleerekoper	6/38 (16%)	1/36	1/38	3/35	5/109 (5%)
Melton	5/36 (14%)	2/35	0/36	2/35	4/106 (4%)

The findings from these studies were presented before the Endocrinologic and Metabolic Advisory Committee on November 18, 1994. The majority of committee members were in favor of approval. At the time of approval, Novartis committed to complete the ongoing PROOF fracture trial.

Study CT320 ("PROOF"): A multi-centered, double-blind, randomized study to investigate the efficacy of Miacalcin® Nasal Spray (salmon calcitonin) in the prevention of osteoporotic vertebral fractures

This was a 5-year study in postmenopausal women with osteoporosis, conducted from 1991-1998 at 47 sites (42 in the US, 5 in the UK). The final study report was submitted to FDA on 3/30/99.

This was a randomized, double-blind, placebo-controlled, parallel group study. Although blinded to treatment, subjects and investigators were given access to the BMD results. The objectives of the study were to determine the efficacy and safety of three doses of Miacalcin nasal spray on the rates of reduction of incident vertebral fracture formation in postmenopausal patients with established osteoporosis. Secondary efficacy endpoints included were to determine effects of treatment on spinal deformity index, nonvertebral fractures, BMD of spine and hip, and bone turnover markers. Three dose levels were evaluated 100 IU, 200 IU and 400 IU daily. The primary focus regarding efficacy was the pairwise comparison of the approved 200 IU dose, following amendment 4 (1996).

The study duration was planned for 5 years. The protocol specified an interim analysis at year 2. This was changed to year 3 (amendment 3) based on the 1994 revision of FDA guidelines which established 3 years as the standard for postmenopausal osteoporosis

efficacy evaluations. In amendment 4, the primary endpoint of the study was changed from new vertebral fractures to new and/or worsening vertebral fractures. Amendment 5 stated that the final analysis would be based on 5-year "all accrued" fracture data.

Subjects enrolled in the study were women who were at least 1 year postmenopausal, verified by FSH/estradiol levels with osteoporosis defined as lumbar spine T-score <-2, radiographic evidence of osteopenia, and 1-5 thoracic/lumbar vertebral compression fractures. Subjects were randomized equally to four daily nasal spray treatment groups: 100 IU, 200 IU, 400 IU, or placebo. Subjects were to self-administer the nasal spray daily (in AM) for 5 yrs. In addition, all were prescribed daily supplements of calcium 1000 mg and vitamin D 400 IU.

Efficacy measures consisted of baseline and annual spine X-rays, BMD and bone turnover markers. A central facility (UCSF) subsequently made the definitive assessments of all x-rays for analysis purposes. X-rays were assessed by standard criteria as follows: Prevalent fractures were defined as a >3 SD reduction in any height ratio (relative to normative data) by quantitative morphometry; and a fracture grade > 0 by semi-quantitative (Genant) criteria. Incident fractures were defined as a >20% and >4 mm decrease in any vertebral height by quantitative morphometry and a change in semi-quantitative grade from 0 to ≥1.

The originally planned sample size of 1040 subjects was based on the assumption that 20% of placebo subjects would have new vertebral fractures within 2 years. The study was estimated to have 80% power to detect a "clinically meaningful" decline in incidence to 10% with treatment. Initially, a 20% dropout rate was assumed; the sample size was later increased to accommodate a higher dropout rate. The primary endpoint of new vertebral fractures was analyzed by life-table methods using a proportional hazards model with the date of the spinal X-ray as the "failure time" and treatment as a variable. The overall efficacy (ITT_E) population consisted of all randomized subjects with a baseline and at least one post baseline X-ray (88% of all subjects). Because data pertaining to the 100 IU and 400 IU groups were only considered supportive, there was no adjustment for multiple comparisons.

Study results

Disposition:

There were 1255 women randomized equally to the four treatment groups. Of these, 783 (62%) completed 3 years, 511 (41%) completed the 5-year study and 744 (59%) discontinued prematurely (in < 5 years). The treatment groups did not differ significantly in rates of, or reasons for, discontinuation (Table 19).

Table 19: **Study CT320 (PROOF): Disposition**

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N randomized	311	316	316	312
Completed ≥ 3 years	190 (61%)	189 (60%)	204 (65%)	200 (64%)
Completed study (5 years)	128 (41%)	124 (39%)	132 (42%)	127 (41%)
Discontinued prematurely (< 5 years)	183 (59%)	192 (61%)	184 (58%)	185 (59%)
Adverse event – "related"	21	19	19	31
Adverse event - "not related"	56	50	51	57
Uncooperative	23	16	23	14
Protocol violation	10	11	14	12
Study drug ineffective	25	25	15	17
Other	48	71	62	54
Source: CSR Text Table 5				

The dropout rate in this study was considered high, even allowing for its long duration relative to many other osteoporosis trials. The lack of blinding of investigators and subjects to BMD results which showed relatively modest increases (see below) has been cited as a possible reason, especially because this drug (Miacalcin Nasal S pray) and Fosamax (alendronate) were both approved for marketing in the U.S. at around the midpoint of the study.

Demographics: There were 1255 women, mean age 68 years old (range 44-94 years old), 97% Caucasian. Although the study enrolled early- as well as late- menopausal women, 97% were >5 years postmenopause (i.e. the labeled target population). The mean number of years post menopause was 22. The mean number of baseline vertebral fractures was 2.0. Of note, 21% of subjects had no baseline fractures at baseline and 5% had more than 5 fractures at baseline; these subjects were evenly distributed among treatment groups. Baseline characteristics were similar between treatment groups. Baseline characteristics of subjects who discontinued the study prior to years 3 or 4 were also similar between treatment groups (Table 20).

Table 20: Study CT320 (PROOF): Demographic and baseline characteristics

	Placebo N=311	Calcitonin 100 IU N=316	Calcitonin 200 IU N=316	Calcitonin 400 IU N=312
Age (yr)				
Mean	68.2	68.2	69.0	67.9
Range	48-91	47-87	44-94	47-88
Years post-menopause (mean)	22.0	22.2	23.0	21.9
Race				
Caucasian	95%	96%	99%	98%
Asian	1%	1%	0%	1%
Other	4%	3%	1%	1%
BMI (mean, kg/m^2)	24.7	24.7	25.0	24.9
Lumbar BMD (mean, g/cm^2)	0.85	0.84	0.85	0.84
% with prevalent vertebral fractures	79.7	74.6	79.0	80.8
Number of vertebral fractures (mean)	1.95	1.82	2.08	2.08
Smoking	15%	16%	14%	12%
Source: CSR Text Tables 11 and 13 and SAS dataset "File 2"				

Exposure

The mean study drug exposure was 3.45 years for calcitonin subjects and 3.16 years for placebo subjects. Table 21 details the number of subjects under treatment during each year of the study, and the number who withdrew during each year. As noted, withdrawals were fairly constant throughout the study in all treatment groups.

Table 21: Study CT320 (PROOF): Subject exposure, by treatment duration (all randomized)

		Number of subjects under treatment during time interval (Number of subjects withdrawing during interval)				
	N rand	Year 1	Year 2	Year 3	Year 4	Year 5
Placebo	311	311 (45)	266 (39)	227 (37)	190 (36)	154 (26)
100 IU	316	316 (45)	271 (43)	228 (39)	189 (35)	154 (30)
200 IU	316	316 (39)	277 (36)	241 (37)	204 (35)	169 (37)
400 IU	312	312 (38)	274 (41)	233 (33)	200 (28)	172 (45)
Total	1255	1255 (167)	1088 (159)	929 (146)	783 (134)	649 (138)
Source: CSR Text Table 16						

Efficacy results – vertebral fractures

ITT_E population – new and/or worsening fractures

The primary endpoint specified in the protocol for study CT320 (Amendment 4) was new and/or worsening vertebral fracture (Table 22). The overall efficacy (ITT_E) population specified for the primary analysis consisted of the 1108 subjects with a baseline and at least one post baseline X-ray (88% of all subjects). For this primary endpoint, the relative risk for subject incidence in the calcitonin salmon 200 IU group relative to placebo (0.75) was not significant (p=0.09).

Table 22: Study CT320 (PROOF): New and/or worsening vertebral fractures, all ITT_E subjects

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	270	273	287	278
n (%) with ≥ 1 new and/or worsening fractures	74 (27.4%)	61 (22.3%)	59 (20.6%)	68 (24.5%)
Relative risk for ≥1 new and/or worsening fracture (95% CI)	-	**0.83** (0.59-1.17)	**0.75** (0.53-1.05)	**0.90** (0.65-1.25)
p-value vs. placebo*	-	0.291	0.094	0.526
Absolute risk reduction	-	5%	7%	3%
Relative risk reduction	-	17%	25%	10%
* Wald p-value (SAS) Source: CSR Text Tables 22, 23				

ITT_E population – new fractures

In the clinical study report, the Applicant changed the primary endpoint from new and worsening vertebral fractures to new vertebral fractures based on scientific considerations regarding the validity of worsening of vertebral fractures. It is not clear whether Type 1 error was controlled for in the new analyses.

During the 5 year study, there were fewer subjects with new vertebral fractures in each calcitonin salmon group (21.6%, 17.8% and 21.9% of 100 IU, 200 IU and 400 IU subjects respectively) compared to placebo (25.9% of subjects) (see Table 23 below). Using time-to-event analysis, the risk of a new fracture was reduced by 15%, 33% and 16% in the 100 IU, 200 IU and 400 IU groups respectively. Only the 200 IU group was significantly different from placebo (p=0.032). The absolute risk reduction in this 200 IU group was 8%, therefore the number needed to treat to prevent one vertebral fracture was about 12.

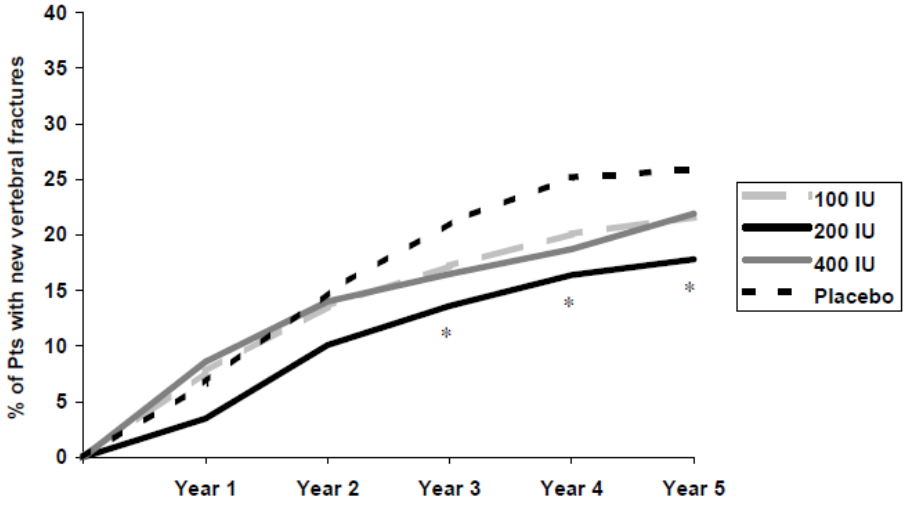
The risk of sustaining multiple new vertebral fractures was also reduced in the 200 IU group by 35% (by odds ratio) relative to placebo. The rate of new fractures in the 200 IU group (78 per 1000 subject X-ray years) was 40% lower than in the placebo group (131 per 1000 subject X-ray years).

Table 23: Study CT320 (PROOF): New vertebral fractures, all ITT_E subjects

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	270	273	287	278
Subjects with ≥ 1 new fracture (fx)				
n (%) with new fractures	70 (25.9%)	59 (21.6%)	51 (17.8%)	61 (21.9%)
Relative risk for ≥1 new fx (95% CI)	-	**0.85** (0.60-1.21)	**0.67** (0.47-0.97)	**0.84** (0.59-1.18)
p-value vs. placebo*	-	0.370	0.032	0.316
Absolute risk reduction	-	4%	8%	4%
Relative risk reduction	-	15%	33%	16%
Subjects with ≥ 2 new fractures				
n (%) with more than one new fracture	33 (12.2%)	34 (12.5%)	24 (8.4%)	30 (10.8%)
Odds ratio for ≥2 new fx (95% CI)	-	1.02 (0.64-1.88)	0.65 (0.38-1.14)	0.87 (0.41-1.30)
* Wald p-value (SAS) Source: CSR, Text Tables 17 and 20				

A Kaplan-Meier plot of the cumulative percentage of subjects with new fractures demonstrates that the trend in favor of the 200 IU group was present throughout the study. (Figure 1 and Table 24).

Figure 2: Cumulative Percentage of Subjects with New Fractures, Kaplan-Meier Estimate



*=p<0.05 vs placebo

Source: CSR Text Figure 2

Table 24: Study CT320 (PROOF): Relative risk (vs. placebo) of new vertebral fracture at the end of each year of treatment

	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
1 year	1.175	0.526	1.333
2 years	0.931	0.681	0.974
3 years	0.831	0.639	0.793
4 years	0.815	0.641	0.737
5 years	0.853	0.674	0.839
Source: CSR Text table 19			

3-year valid completer subjects

This additional analysis population represents a further subset of ITT_E subjects who met all of the following criteria:

- 1-5 baseline vertebral fractures
- At least one post-baseline X-ray
- Stayed on treatment for at least 3 years without an incident fracture, or had an incident fracture prior to 3 years
- Compliant to study drug regimen (> 75%)
- Did not take substantial amount of incorrect study medication
- Did not take substantial amount of a proscribed medication e.g. corticosteroid

There were 626 3-year valid completers, comprising 56.5% of the ITT_E population. Other than the 344 ITT_E subjects who were excluded from this subset because of baseline fracture status, most exclusions (175) were for the third criterion, i.e. lack of 3-year fracture data.

Results for the 3-year valid completers were similar to ITT_E (Table 25).

Table 25: Study CT320 (PROOF): New vertebral fractures, 3-year valid completer subjects

	Placebo NS	Calcitonin 100 IU	Calcitonin 200 IU	Calcitonin 400 IU
N	162	152	157	155
n (%) with new fx	59 (36.4%)	49 (32.2%)	40 (25.5%)	42 (27.1%)
Relative risk (95% CI)	**-**	**0.91** (0.62-1.33)	**0.66** (0.44-0.99)	**0.71** (0.48-1.05)
Absolute risk reduction	-	4%	11%	9%
Relative risk reduction	-	9%	34%	29%
Source: CSR Text Table 37				

Non-vertebral fractures

Nonvertebral fractures, which the study was not powered to evaluate, were less numerous in all 3 calcitonin salmon groups relative to placebo, particularly hip/femur fractures; the greatest numerical difference however was seen only for the 100 IU group (Table 26).

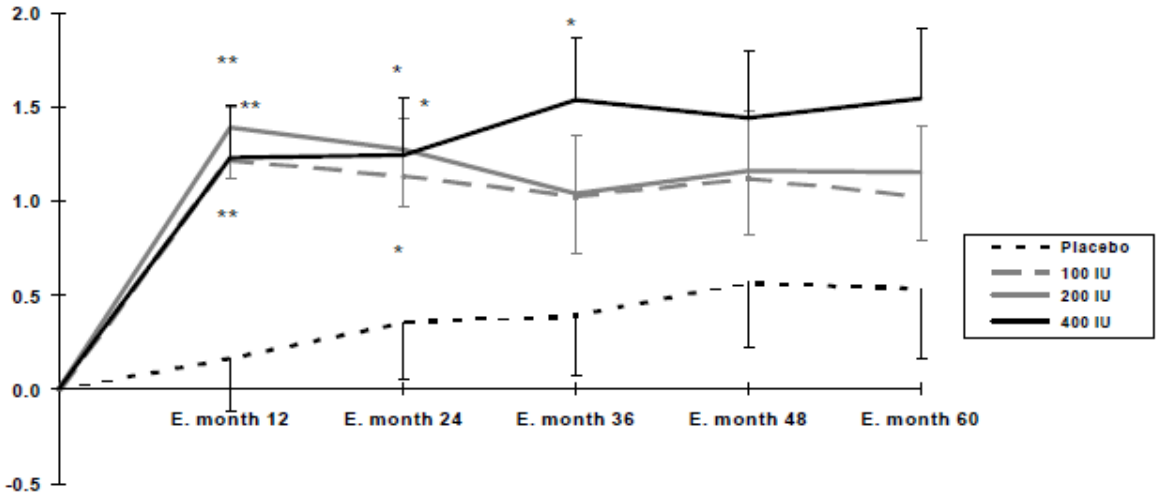
Table 26: Study CT320 (PROOF): Non-vertebral fractures (ITT_E)

	Placebo N=305	**Calcitonin 100 IU** N=313	**Calcitonin 200 IU** N=315	**Calcitonin 400 IU** N=312	**Calcitonin Pooled** N=940
All nonvertebral fractures	48 (15.7%)	32 (10.2%)	46 (14.6%)	41 (13.1%)	119 (12.7%)
Relative risk	-	0.64	0.88	0.81	0.78
Upper limb fractures (humerus, radius, ulna, wrist)	16 (5.2%)	6	13	14	33 (3.5%)
Relative risk	-	0.36	0.75	0.84	0.65
Hip and femur fractures	9 (3.0%)	1	5	7	13 (1.4%)
Relative risk	-	0.11	0.52	0.75	0.46
Source: CSR Text Tables 39, 41,44					

Bone mineral density – lumbar spine

BMD was evaluated annually by DXA with coordination and interpretation by a central facility (UCSF). Lumbar spine mean BMD increased ~1-1.5% relative to baseline in all three calcitonin salmon groups in the first year. There was little further change during the 4 subsequent years other than a small trend in favor of the 400 IU group over 100 IU and 200 IU in years 3-5 (see Table 27 and Figure 3 below). In the placebo group, BMD also increased above baseline. At all timepoints, BMD increases in all three calcitonin salmon groups were larger than placebo.

Figure 3: Lumbar spine BMD mean percent change from baseline +/- SE (LOCF)



Source: CSR Text Figure 15

The BMD were presented as last observation carried forward (LOCF) methodology (Table 27). What becomes lost in this approach is the number of dropout that occurred later in the trial. If evaluated by subjects who completed the timepoint visit, it appears that placebo subjects who were remaining in the study at the 4th and 5th years experienced average BMD increases very comparable to the calcitonin salmon groups (Table 28):

Table 27: Study CT320 (PROOF): Lumbar spine BMD, mean percent increases from baseline (LOCF) (ITT_E)

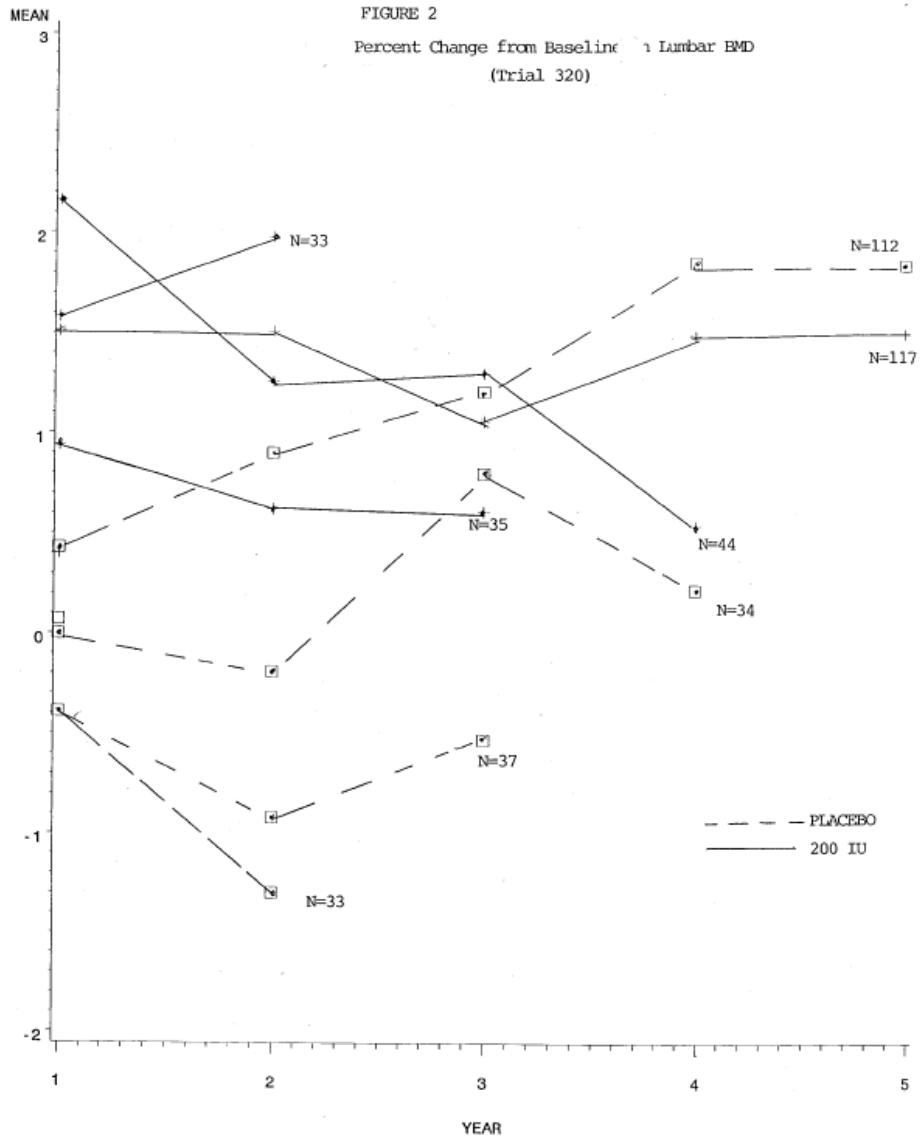
	Baseline (g/cm^2)	Endpoint month 12	Endpoint month 24	Endpoint month 36	Endpoint month 48	Endpoint month 60
Placebo, n	273	258	268	268	268	268
	0.848	**0.167**	**0.359**	**0.397**	**0.571**	**0.537**
100 IU, n	279	259	273	273	273	273
	0.838	**1.218**	**1.133**	**1.028**	**1.124**	**1.029**
200 IU, n	287	270	280	280	280	280
	0.852	**1.388**	**1.273**	**1.038**	**1.158**	**1.155**
400 IU, n	277	267	274	274	274	274
	0.842	**1.233**	**1.242**	**1.538**	**1.442**	**1.545**
Source: CSR Text Table 48						

Table 28: Study CT320 (PROOF): Lumbar spine BMD, mean percent increases from baseline at each visit (ITT_E)

	Baseline (g/cm^2)	Month 12	Month 24	Month 36	Month 48	Month 60
Placebo, n	273	254	196	168	135	112
	0.848	**0.141**	**0.049**	**0.749**	**1.448**	**1.873**
100 IU, n	279	252	201	172	137	111
	0.838	**1.256**	**1.300**	**1.383**	**1.433**	**1.531**
200 IU, n	287	266	216	180	154	117
	0.852	**1.369**	**1.396**	**1.025**	**1.217**	**1.520**
400 IU, n	277	260	218	183	149	119
	0.842	**1.287**	**1.376**	**1.612**	**1.708**	**1.618**
Source: CSR Text Table 48						

Figure 4 is a plot of lumbar spine BMD in the "dropout" cohorts (within 200 IU and placebo treatment groups) as each cohort moves through time. This shows that placebo subjects who either discontinued at 4 yrs or completed at 5 yrs had BMD percent change at that point which was similar to their 200 IU counterparts, erasing differences between the same groups of subjects that existed at years 1-2. The figure also shows that placebo subjects who discontinued after 2 and 3 years had lower BMD than those who remained longer in the study.

Figure 4: Study CT320 (PROOF): Lumbar spine BMD by cohorts defined by time of discontinuation (200 IU and placebo subjects, ITT_E)



Bone mineral density – hip

DXA of the hip was also conducted annually during the study. In contrast to lumbar spine, femoral neck BMD declined in all groups, with no significant differences between any dose of calcitonin salmon and placebo at any point (Table).

Table 29: Study CT320 (PROOF): Femoral neck BMD, mean percent changes from baseline (LOCF)

	Baseline (g/cm^2)	Endpoint month 12	Endpoint month 24	Endpoint month 36	Endpoint month 48	Endpoint month 60
Placebo, n	264	249	260	261	261	261
	0.692	**-0.251**	**-0.630**	**-0.819**	**-1.342**	**-1.945**
100 IU, n	270	257	268	268	268	268
	0.704	**-0.281**	**-0.784**	**-0.971**	**-1.510**	**-1.670**
200 IU, n	282	263	275	275	275	275
	0.695	**+0.380**	**-0.018**	**-0.429**	**-0.892**	**-1.132**
400 IU, n	274	262	271	272	272	272
	0.690	**+0.345**	**-0.253**	**-0.465**	**-1.176**	**-1.375**
Source: CSR Text Table 50						

Similarly, hip trochanter BMD declined in all groups, and there were no statistical differences between any calcitonin salmon dose group and placebo at any point (Table 30).

Table 30: Study CT320 (PROOF): Trochanter BMD, mean percent changes from baseline (LOCF)

	Baseline (g/cm^2)	Endpoint month 12	Endpoint month 24	Endpoint month 36	Endpoint month 48	Endpoint month 60
Placebo, n	264	249	260	261	261	261
	0.600	**0.149**	**0.056**	**-0.407**	**-1.003**	**-1.495**
100 IU, n	270	257	268	268	268	268
	0.606	**0.580**	**-0.033**	**0.034**	**-0.548**	**-0.649**
200 IU, n	282	263	275	275	275	275
	0.596	**1.223**	**0.660**	**-0.375**	**-0.774**	**-0.835**
400 IU, n	274	262	271	272	272	272
	0.596	**0.886**	**0.319**	**-0.053**	**-0.435**	**-0.641**
Source: CSR Text Table 54						

Overall, when assessing the BMD trends in the PROOF study with the trends in fractures a consistent pattern supporting the 200 IU dose is not seen. Lumbar spine BMD tended to increase in all calcitonin salmon dose groups compared to placebo, and there were trends toward fewer vertebral fractures in all 3 groups, however BMD increase was greater with 400 IU while the only significant decline in fractures was with 200 IU. Only the 100 IU group showed a trend toward reduced extremity fractures, however this group displayed no BMD advantage at any skeletal site.

In summary, study CT320 appears to show a statistically significant 33% reduction in new vertebral fractures with the approved 200 IU dosage of nasal spray calcitonin salmon (Miacalcin) in women with PMO. The p-value was not very low (p=0.03), and it is unknown how these findings are impacted by the large number of dropouts, including 11% of subjects with no fracture data at all. Analysis of 3-year valid-completer 200 IU subjects also showed a similar 34% reduction. As expected given the study design, there were insufficient numbers of nonvertebral fractures to establish or rule out a benefit, though there was a trend toward fewer hip fractures.

Fracture results were supported by an increase in lumbar spine BMD in all calcitonin salmon dosage arms. Findings were consistent with previous studies of injectable and nasal calcitonin salmon (as described above) suggesting that total body calcium and vertebral BMD may reach a plateau after about a year of calcitonin treatment. The clinical implications of this phenomenon are unknown. Femoral neck BMD was consistent with a previous study (514) showing no evidence of significant benefit at this skeletal site.

The most disconcerting aspect of the study findings is the lack of dose response: the 100 IU and 400 IU doses of calcitonin salmon, unlike 200 IU, did not show a significant reduction in of reduced vertebral fractures. The biologic plausibility of such a result is unclear. In particular, it is difficult to explain why the 400 IU dose, which resulted in lumbar spine BMD effects at least as favorable as 200 IU, appeared to have less of an effect, if any, on fractures.

Study results may have been confounded by the high dropout rate. Subjects who dropped out before years 3 and 4 had similar baseline characteristics between treatment groups. However, it appears that placebo subjects who discontinued had lower spinal BMD at the time of withdrawal than calcitonin salmon subjects who discontinued, and lower BMD than placebo subjects who remained in the study. Thus, it has been speculated that the availability of these interim BMD results to investigators may have caused preferential withdrawal of subjects at higher fracture risk, which may have biased the primary endpoint.

Because of the ambiguous PROOF trial fracture data, the findings were not approved for inclusion in the Miacalcin labeling. The current labeled indication for treatment of postmenopausal osteoporosis is unchanged from the 1995 original, which states that approval is based on increase in spinal BMD. There are no statements regarding an effect, or lack thereof, on fracture incidence.

3.4 Calcitonin Salmon Oral Formulation

Oral calcitonin salmon formulations have been investigated by several sponsors. Bioavailability of orally administered calcitonin salmon, like nasally administered calcitonin salmon, appears to be substantially lower than parenteral calcitonin salmon, however the relationship between plasma levels and efficacy of calcitonin salmon is unknown.

SMC021 (Novartis) is a tablet formulation of recombinant calcitonin salmon 0.8 mg (4800 IU), with the absorption enhancer 5-CNAC 200 mg. The recently completed phase 3 fracture trial described below was conducted to investigate potential efficacy and safety in treating postmenopausal osteoporosis.

Study SMCO21A-2303: A Randomized, Double-Blind, Multi-Center, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Salmon Calcitonin in the Treatment of Osteoporosis in Postmenopausal Women Taking Calcium and Vitamin D

This is a 3-year postmenopausal osteoporosis study, conducted from 2007-2011 at 16 sites in the U.S., Europe, China, Hong Kong and Brazil. A draft study report was submitted to FDA on 6/8/12.

This was a phase 3, 3-year, randomized, double-blind, placebo-controlled, parallel group study. It was planned to enroll approximately 4500 women age 55-85 years with postmenopausal osteoporosis, defined as a BMD T-score ≤ -2.5 (lumbar spine, femoral neck or total hip), with no more than 2 baseline mild or moderate (but not severe) vertebral fractures (Genant criteria), or a BMD T-score ≤ -1.5 with 1 or 2 baseline vertebral fractures (Genant, any grade). The primary efficacy objective was to demonstrate a reduction in the proportion of study subjects with new vertebral fractures with the active treatment SMC021, relative to placebo. Secondary efficacy objectives included nonvertebral fractures (hip, forearm/wrist, humerus, rib, clavicle, ankle), hip fractures, new and/or worsening vertebral fractures, spinal deformity index (Genant method), new clinical fractures (any site except skull, face, fingers, toes), new fractures (any site), and BMD changes at L1-L4, total hip, femoral neck. Subjects were randomized 1:1 to receive SMC021 0.8 mg calcitonin salmon tablet, or placebo daily, 30-60 minutes before dinner, for 36 months. Subjects also received daily morning supplements of calcium 800-1000 mg and vitamin D 400-800 IU.

Efficacy measures consisted of lateral thoracic/lumbar spine X-rays for fracture assessment at screening and months 12, 24 and 36. These were scored (blinded to treatment) on a standard semi-quantitative (SQ) scale (Genant): prevalent fractures were grades 1, 2 or 3; new fractures (the primary endpoint) were a change from 0 at screening to 1, 2 or 3; and worsening fractures were a change from 1 or 2 at screening to a higher grade. Nonvertebral fractures were confirmed by review of X-rays, radiology reports and discharge summaries. BMD (DXA) of L1-L4, total hip and femoral neck was obtained at baseline and months 12, 24 and 36 in all subjects. Unlike the PROOF study, subjects were to remain blinded to BMD results.

The planned sample size of 4500 subjects was based on non-vertebral fractures. This sample size was estimated to provide 90% power to detect a 30% reduction in such fractures with treatment at a 5% level of significance, assuming a 15% dropout rate over 3 years. A smaller sample size (1936 subjects) would have been needed to demonstrate a 40% reduction in vertebral fractures, from an expected rate of 4% per year in placebo subjects. Interim efficacy analyses were conducted at 1 year (for futility) and at 2 years. For the final (3 year) analysis, efficacy endpoints were analyzed for the modified intent to treat (MITT) population, defined as all randomized and treated subjects who had a baseline and at least one follow-up X-ray. The primary efficacy analysis of proportions of subjects with new vertebral fractures was compared between MITT treatment groups using a logistic regression model controlling for treatment group and age at baseline. BMD was compared between treatment groups using a repeated measures ANCOVA model with treatment group, age, visit and baseline value as explanatory variables.

Study results

Disposition: There were 4665 subjects randomized and treated. Subjects assigned to SMC021 were less likely than placebo subjects to complete 36 months of study drug (68% vs. 74%). This was primarily due to higher incidence of discontinuation due to nonserious adverse events (16% vs. 9%), mostly during the first year (Table 31). After 12 months, discontinuations were similar between treatment groups. About 90% of subjects underwent at least one post-baseline X-ray, constituting the modified ITT population (MITT).

Table 31: Study SMCO21A2303: Disposition

	SMC021	Placebo	Total
N randomized/treated (ITT)	2334	2331	4665
Completed study drug	1578 (68%)	1732 (74%)	3310 (71%)
Subjects with off-drug Month-36 assessments	269 (12%)	204 (9%)	473 (10%)
Discontinued study drug	756 (32%)	599 (26%)	1355 (29%)
Adverse event	367 (16%)	215 (9%)	582 (13%)
Lost to follow up	241	228	469
Non-compliance	58	59	117
Ineffective treatment	43	55	98
Death	18	14	32
Other	15	15	30
Source: CSR Table 10-1			

Exposure data demonstrates the higher discontinuation rate in the SMC021 arm early in the study, with stabilization of dropouts after the first year (Table 32):

Table 32: Study SMC021A2303: Overall exposure by treatment duration (ITT)

Exposure duration	SMC021 N=2334	Placebo N=2331
≥ 1 day	100%	100%
≥ 3 months	89%	94%
≥ 6 months	85%	91%
≥ 12 months	80%	86%
≥ 18 months	75%	82%
≥ 24 months	73%	79%
≥ 34 months	69%	75%
Source: CSR Table 12-1		

The overall dropout rate of 29% was higher than the 15% anticipated during study planning, but compares favorably to a 38% dropout rate during the first 3 years of the PROOF study. The much larger number of subjects in the A2303 study, distributed among only 2 treatment arms instead of 4, also gives this study a considerable statistical advantage.

Demographics
All subjects were postmenopausal women, with an average age of 66 years; 67% were white. The population was moderately osteoporotic by baseline T-scores; 22% had a prevalent vertebral fracture (Table 33):

Table 33: Study SMCO21A2303: Demographics and baseline characteristics (ITT)

	SMC021 N=2334	**Placebo** N=2331	**Total** N=4665
Age (yr)			
Mean	66.5	67.0	66.8
Range	55-86	50-85	50-86
Years post-menopause (mean)	19	19	19
Race ethnicity (%)			
White	66.6	66.3	66.5
Black	1.7	1.3	1.5
Asian	12.8	12.9	12.8
Hispanic	18.9	19.5	19.2
BMI (mean, kg/m2)	26.1	26.0	26.1
Lumbar BMD (mean, g/cm^2)	0.87	0.87	0.87
% with T-score ≤ -2.5			
Femoral neck	19.2	21.0	20.1
Total hip	12.3	14.7	13.5
Lumbar spine	65.6	66.3	65.9
% with prevalent vertebral fractures	20.7	23.0	21.9
% with ≥ 2 prevalent vertebral fractures	4.5	6.0	5.3
Smoking	10%	11%	11%
Source: CSR Table 11-2, ABASE dataset			

Compared to the PROOF study population, subjects were about 2 years younger on average; were more likely to be Asian or Hispanic because of a more international distribution of study sites; and were similar in baseline BMD, but with a much lower prevalence of baseline vertebral fractures by semi-quantitative criteria (22% vs. 79%), therefore a lower fracture risk.

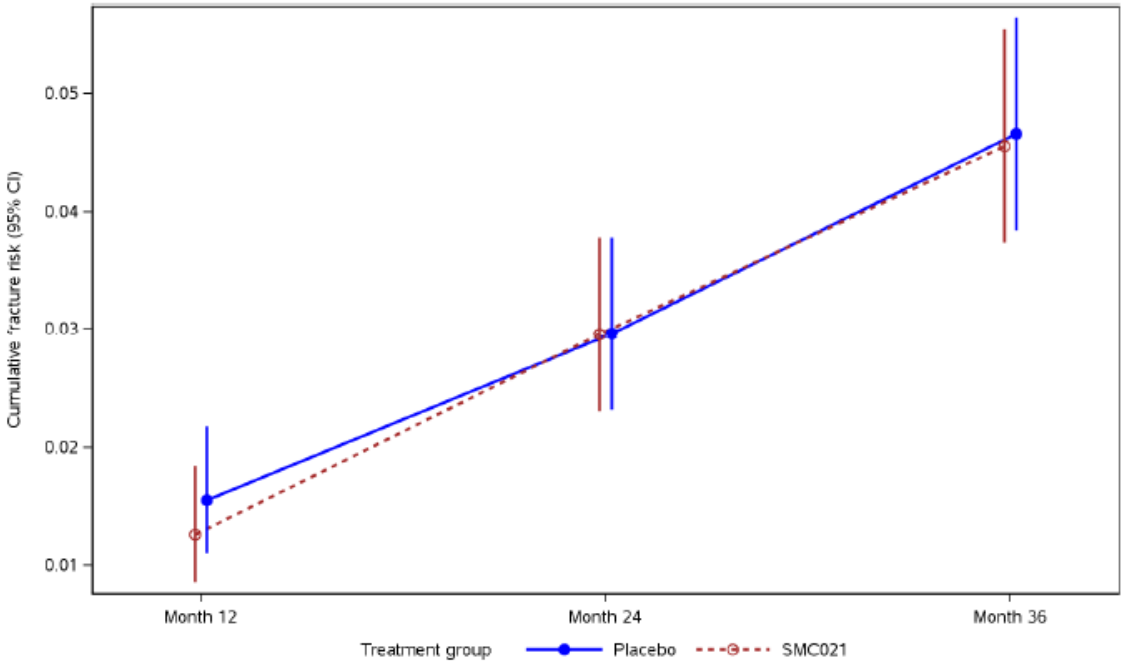
Efficacy results – vertebral fractures
The primary endpoint of vertebral fractures was assessed in the modified ITT population consisting of 88.4% of SMC021 subjects and 91.2% of placebo subjects.

During the 3-year study, new vertebral fractures occurred in 94/2064 subjects (4.55%) in the SMC021 treatment group and 99/2125 subjects (4.66%) in the placebo group. Relative risk was 0.98 with a 95% confidence interval of 0.742 to 1.288 (p=0.94). Kaplan-Meier estimates of cumulative risk for a first new vertebral fracture were nearly identical for the 2 treatment groups (Table 34 and Figure 5).

Table 34: Study SMCO21A2303: New vertebral fractures by treatment group (MITT)

	SMC021	Placebo
N	2064	2125
n (%) with new fractures	94 (4.55%)	99 (4.66%)
Relative risk (95% CI)	0.98 (0.742-1.288)	
Odds ratio (95% CI)	0.99 (0.740-1.321)	
p-value (Chi^2)	0.94	
n (%) with ≥2 new fractures	11 (0.53%)	17 (0.80%)
Odds ratio and p-value are from logistic regression controlling for treatment group and age at baseline Source: CSR Table 11-4		

Figure 5: Study SMCO21A2303: Cumulative risk for first new vertebral fracture by year and treatment (MITT)



Groups are shifted to enhance readability
Cumulative risk and 95% confidence intervals were calculated using Kaplan-Meier estimates for the discrete timepoints
Source: CSR Figure 11-1

There were no significant treatment group differences in new fractures within subgroups defined by baseline T-scores or prevalent fractures, geographic region, race or ethnicity.

Nonvertebral fractures

There were numerically fewer subjects with new nonvertebral fractures (3.21% vs. 3.52%) or new clinical fractures (4.76% vs. 5.11%) in the SMC021 group relative to placebo, but the differences were small and not statistically significant (Table 35). There were no major

imbalances in fractures of the wrist (42 with SMC021 vs. 37 with placebo); humerus (11 vs. 14); ribs (6 vs. 12); ankle (10 vs. 6); or pelvis (2 vs. 3).

Table 35: Study SMCO21A2303: New non-vertebral and clinical fractures by treatment group (ITT)

	SMC021 N=2334	**Placebo** N=2331
Non-vertebral fractures		
n (%) with new fractures	75 (3.21%)	82 (3.52%)
Relative risk (95% CI)	0.91 (0.671-1.243)	
Hazard ratio (95% CI)	0.966 (0.705-1.321)	
p-value (Chi^2)	0.82	
Clinical fractures		
n (%) with new fractures	111 (4.76%)	119 (5.11%)
Relative risk (95% CI)	0.93 (0.724-1.199)	
Hazard ratio (95% CI)	0.978 (0.754-1.266)	
p-value (Chi^2)	0.86	
Hazard ratio and p-value from Cox regression controlling for treatment group and age at baseline Source CSR Tables 11-5 and 11-6		

Hip/femur fractures

There were 22 hip/femur fractures (5 with SMC021 and 17 with placebo). In the SMC021 cohort, all 5 were identified as femoral neck fractures. In the placebo cohort there were 8 femoral neck fractures, 6 intertrochanteric hip fractures, 2 subtrochanteric femur fractures and 1 distal femur fracture. The draft study report indicates hip fracture incidences of 0.1% vs. 0.7% per patient-year exposure for SMC021 and placebo respectively.

Bone mineral density – Lumbar spine

Unlike fractures, lumbar spine BMD (a secondary endpoint) showed a significant though small difference between treatments throughout the study. Similar to the PROOF study, BMD in the calcitonin group increased 1.24% from baseline, and there was little change in the second and third years (Table 36):

Table 36: Study SMC021A2303: Lumbar spine BMD: LS mean % change from baseline (ITT)

	SMC021	**Placebo**	**Difference (95% CI)**	**p-value***
Month 12	(n=1839)	(n=1981)		
	1.24	0.05	+1.19 (0.96, 1.42)	<.0001
Month 24	(n=1690)	(n=1824)		
	1.17	0.07	+1.10 (0.84, 1.37)	<.0001
Month 36	(n=1860)	(n=1941)		
	1.02	0.18	+0.83 (0.54, 1.13)	<.0001
* p-value by repeated measures ANCOVA (Sponsor) Source: CSR Table 11-7				

Bone mineral density – hip
Total hip and femoral neck BMD declined in both treatment arms during the study; there were small differences favoring SMC021 throughout. Substantial declines (>7%) in BMD from baseline to month 36/endpoint occurred in 3.5% and 5.4% of subjects for total hip and femoral neck respectively; these were evenly distributed between the treatment arms (Table 37 and Table 38).

Table 37: Study SMC021A2303: Total hip BMD: Mean % change from baseline (ITT)

	SMC021	Placebo	Difference	p-value*
Month 12	(n=1808)	(n=1949)		
	+0.605	+0.098	+0.507	<0.001
Month 24	(n=1660)	(n=1807)		
	-0.049	-0.560	+0.511	<0.001
Endpoint/ Month 36	(n=1579)	(n=1729)		
	-0.793	-1.107	+0.314	<0.001
* p-value by t-test assuming equal variances Source: ABMDHIP dataset, analysis by clinical reviewer				

Table 38: Study SMC021A2303: Femoral neck BMD: Mean % change from baseline (ITT)

	SMC021	Placebo	Difference	p-value*
Month 12	(n=1810)	(n=1950)		
	+0.338	-0.253	+0.591	<0.001
Month 24	(n=1660)	(n=1807)		
	-0.221	-0.856	+0.635	<0.001
Endpoint/ Month 36	(n=1579)	(n=1729)		
	-0.935	-1.377	+0.442	0.0026
* p-value by t-test assuming equal variances Source: ABMDHIP dataset, analysis by clinical reviewer				

Study SMC021A2303 – Summary/ discussion of efficacy
This adequate and well controlled study of an oral tablet formulation of recombinant calcitonin salmon failed to demonstrate a significant reduction in vertebral fractures in women with PMO over 3 years of treatment.

The design of study A2303 differed in many respects from the PROOF study. The new study was much larger, and enrolled a more geographically and racially diverse population. In addition, A2303 subjects had a much lower baseline prevalence of vertebral fractures (22% vs. 79%, using apparently the same SQ criteria), therefore a lower fracture risk. This was reflected in the incident fracture rates in placebo subjects during the respective studies: 26% over 5 years in the PROOF study vs. 4.7% over 3 years in the A2303 study. Study A2303 was powered to show a nonvertebral fracture difference, and this should result in adequate power to detect a difference in vertebral fracture as well. However this trial showed no fracture benefit.

The PROOF and A2303 studies were in agreement with each other, and with previous studies of injectable and nasal calcitonin, in demonstrating increases in lumbar spine BMD in the range of 1.0-1.5% over placebo. Also consistent with past calcitonin salmon studies, this increase occurred within the first year of treatment, with little change thereafter. This consistency of BMD findings is difficult to reconcile with the inconsistent fracture data.

The A2303 findings were interesting in that the development of calcitonin antibodies appeared to have a negative effect on BMD, which has not been reported previously. However, the proportion of subjects who developed antibodies (~10%) appears to be too small to have driven the fracture results, and was lower than the proportion of antibody-positive subjects in the PROOF study (~30%).

4 Summary

Osteoporosis is a systemic skeletal disease that affects a large number of the U.S. population. There is significant morbidity and mortality associated with osteoporotic fractures, particularly hip fractures. Since 1994, therapies approved for the treatment of postmenopausal osteoporosis have been required to demonstrate efficacy in reducing fractures.

The original safety signal of an imbalance in prostate cancer in patients treated with oral calcitonin salmon-CNAC led to a larger evaluation of calcitonin therapy and the occurrence of malignancy. The meta-analysis of all double-blind controlled trials with the calcitonin salmon nasal formulation suggested an increased risk of malignancy in calcitonin-treated patients compared to placebo, specifically, the Odds Ratio was 1.6, 95% CI (1.1, 2.3) and the Risk Difference was 1.6%, 95% CI (0.4, 2.9). However, Novartis's meta-analysis presents a number of limitations that makes a causal relationship determination between calcitonin and malignancy difficult. The odds ratio of 1.6 is within the range which raises questions of possible uncontrolled confounding. These results are heavily influenced by trial CT320 in which the largest number of malignancies occurred. Sensitivity analyses conducted by the FDA that excluded CT320 still showed a higher risk of malignancy in calcitonin-treated patients compared to placebo (1.6 OR, 0.9% RD) however the null values were not excluded from the confidence intervals for both estimates.

The potential for a cancer risk with calcitonin salmon therapy cannot be ignored. The majority of all calcitonin salmon trials showed an increased risk estimate. Novartis and the FDA conducted a series of dose-level analyses in an attempt to characterize the increased risk. Both Novartis's and the FDA's analyses fail to demonstrate a dose response relationship, but the lack of a dose response does not necessarily rule out an association.

Novartis also conducted a series of duration of exposure analyses in an attempt to characterize the increased risk. An imbalance in malignancies reported between calcitonin salmon and placebo groups occurred by month 12 and continued through month 36. Similarly, in nonclinical studies calcitonin treatment was associated with early development of an increased number of benign neoplasms in the pituitary in two strains of rats.

At this time, the potential for a cancer risk associated with calcitonin use appears plausible, and certainly cannot be ruled out with the data reviewed. In this situation, when assessing the

risks and benefits of calcitonin salmon therapy for treatment of postmenopausal osteoporosis, the question of the fracture reduction efficacy becomes critical.

Three fracture trials have been conducted, each using a separate formulation of calcitonin salmon.

The first, Study RHCG-CT-401, was a randomized, open label study evaluating new vertebral fractures in postmenopausal women with osteoporosis and vertebral fractures at baseline treated with injectable salmon calcitonin. The study was plagued with enrollment and randomization difficulties. An interim report was unfavorable toward the injectable calcitonin salmon but it was concluded that due to the study's numerous flaws, the fracture data were unreliable and inconclusive.

The second, Study CT320 or the PROOF trial, was a 5-year, randomized, double-blind, placebo-controlled, parallel group fracture study evaluating calcitonin salmon nasal in postmenopausal women with osteoporosis and vertebral fractures at baseline. A statistically significant 33% reduction in new vertebral fractures was achieved with only one of the three doses, the approved 200 IU dosage of nasal spray calcitonin salmon (Miacalcin). The p-value was not very low ($p=0.03$), and it is unknown how these findings are impacted by the large number of dropouts, including 11% of subjects with no fracture data at all. In addition, fracture efficacy was not achieved with the 400 IU dose, despite lumbar spine BMD effects at least as favorable as 200 IU dose. The lack of a dose response curve with the three calcitonin salmon doses evaluated is disconcerting. The 100 IU and 400 IU doses of calcitonin salmon, unlike 200 IU, displayed only nonsignificant trends of reduced vertebral fractures. The biologic plausibility of such a result is unclear. In particular, it is difficult to explain when evaluated in the context of the BMD changes achieved with each dose, which were comparable. This calls into question the reliability of the fracture results of this trial and the use of bone mineral density as a surrogate endpoint for fracture risk reduction with calcitonin.

Finally, Study SMCO21A-2303 is a 3-year randomized, double-blind, placebo-controlled, parallel group fracture study evaluating oral calcitonin salmon-CNAC therapy in postmenopausal women with osteoporosis and vertebral fractures at baseline. The primary endpoint was new vertebral fractures. Small increases in lumbar spine BMD were observed when compared to placebo, but the trial did not demonstrate a significant reduction in vertebral fractures.

Intervention to reduce the risk of fracture is the standard for treatment of postmenopausal osteoporosis. Despite three fracture trials conducted, there remain significant questions regarding calcitonin salmon's effectiveness in reducing fractures in postmenopausal women. This lack of effectiveness when combined with the potential for a cancer risk associated with calcitonin salmon therapy raises concerns about the overall risk and benefit assessment for calcitonin salmon products in the treatment of postmenopausal osteoporosis.

We welcome the committee's discussion and analyses of these issues.

5 Appendix A: Product Labeling

NOVARTIS

Miacalcin®

(calcitonin-salmon)

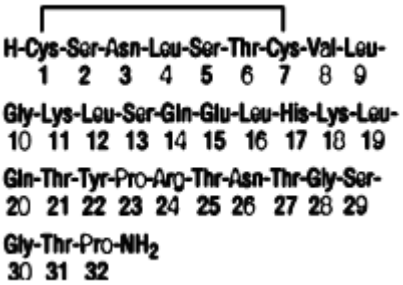
Injection, Synthetic

Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin® (calcitonin-salmon) Injection, Synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in sterile solution for subcutaneous or intramuscular injection. Each milliliter contains: calcitonin-salmon 200 I.U., acetic acid, USP, 2.25 mg; phenol, USP, 5.0 mg; sodium acetate trihydrate, USP, 2.0 mg; sodium chloride, USP, 7.5 mg; water for injection, USP, qs to 1.0 mL.

The activity of Miacalcin Injection is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute for Biological Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action. The actions of calcitonin on bone and its role in normal human bone physiology are still incompletely understood.

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

an apparent decrease in their resorptive activity. Decreased osteocytic resorption may also be involved. There is some evidence that initially bone formation may be augmented by calcitonin through increased osteoblastic activity. However, calcitonin will probably not induce a long-term increase in bone formation.

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

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

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

Calcitonin-salmon, presumably by an initial blocking effect on bone resorption, causes a decreased rate of bone turnover with a resultant fall in the serum alkaline phosphatase and urinary hydroxyproline excretion in approximately 2/3 of patients treated. These biochemical changes appear to correspond to changes toward more normal bone, as evidenced by a small number of documented examples of: 1) radiologic regression of Pagetic lesions, 2) improvement of impaired auditory nerve and other neurologic function, 3) decreases (measured) in abnormally elevated cardiac output. These improvements occur extremely rarely, if ever, spontaneously (elevated cardiac output may disappear over a period of years when the disease slowly enters a sclerotic phase; in the cases treated with calcitonin, however, the decreases were seen in less than one year.)

Some patients with Paget's disease, who have good biochemical and/or symptomatic responses initially, later relapse. Suggested explanations have included the formation of neutralizing antibodies and the development of secondary hyperparathyroidism, but neither suggestion appears to explain adequately the majority of relapses.

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

Circulating antibodies to calcitonin after 2-18 months' treatment have been reported in about half of the patients with Paget's disease in whom antibody studies were done, but calcitonin treatment remained effective in many of these cases. Occasionally, patients with high

antibody titers are found. These patients usually will have suffered a biochemical relapse of Paget's disease and are unresponsive to the acute hypocalcemic effects of calcitonin.

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

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

Transient increases in sodium and water excretion may occur after the initial injection of calcitonin. In most patients, these changes return to pretreatment levels with continued therapy.

Gastrointestinal Tract: Increasing evidence indicates that calcitonin has significant actions on the gastrointestinal tract. Short-term administration results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated.

Metabolism: Information from animal studies with calcitonin-salmon and from clinical studies with calcitonins of porcine and human origin suggest that calcitonin-salmon is rapidly metabolized by conversion to smaller inactive fragments, primarily in the kidneys, but also in the blood and peripheral tissues. A small amount of unchanged hormone and its inactive metabolites are excreted in the urine.

The absolute bioavailability of salmon calcitonin is approximately 66% and 71% after intramuscular (i.m.) or subcutaneous (s.c.) injection, respectively. After subcutaneous administration, peak plasma levels are reached in approximately 23 minutes. The terminal half-life is approximately 58 minutes for i.m. administration and 59-to 64 minutes for s.c. administration. The apparent volume of distribution is 0.15-0.3 L/kg.

It appears that calcitonin-salmon cannot cross the placental barrier and its passage to the cerebrospinal fluid or to breast milk has not been determined.

INDICATIONS AND USAGE

Miacalcin® (calcitonin-salmon) Injection, Synthetic is indicated for the treatment of symptomatic Paget's disease of bone, for the treatment of hypercalcemia, and for the treatment of postmenopausal osteoporosis.

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

In these patients, the biochemical abnormalities were substantially improved (more than 30% reduction) in about 2/3 of patients studied, and bone pain was improved in a similar fraction. A small number of documented instances of reversal of neurologic deficits have occurred, including improvement in the basilar compression syndrome, and improvement of spinal cord and spinal nerve lesions. At present, there is too little experience to predict the likelihood of improvement of any given neurologic lesion. Hearing loss, the most common neurologic lesion of Paget's disease, is improved infrequently (4 of 29 patients studied audiometrically).

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

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

Hypercalcemia: Miacalcin Injection is indicated for early treatment of hypercalcemic emergencies, along with other appropriate agents, when a rapid decrease in serum calcium is required, until more specific treatment of the underlying disease can be accomplished. It may also be added to existing therapeutic regimens for hypercalcemia such as intravenous fluids and furosemide, oral phosphate or corticosteroids, or other agents.

Postmenopausal Osteoporosis: Miacalcin Injection is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Miacalcin Injection should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of Miacalcin Injection is recommended in conjunction with adequate calcium and vitamin D intake to prevent the progressive loss of bone mass. No evidence currently exists to indicate whether or not Miacalcin Injection decreases the risk of vertebral crush fractures or spinal deformity. A recent controlled study, which was discontinued prior to completion because of questions regarding its design and implementation, failed to demonstrate any benefit of salmon calcitonin on fracture rate. No adequate controlled trials have examined the effect of salmon calcitonin injection on vertebral bone mineral density beyond 1 year of treatment. Two placebo-controlled studies with salmon calcitonin have shown an increase in total body calcium at 1 year, followed by a trend to decreasing total body calcium (still above baseline) at 2 years. The minimum effective dose of Miacalcin Injection for prevention of vertebral bone mineral density loss has not been established. It has been suggested that those postmenopausal patients having increased rates of bone turnover may be more likely to respond to anti-resorptive agents such as Miacalcin Injection.

CONTRAINDICATIONS

Clinical allergy to synthetic calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), *including very rare reports* of death attributed to anaphylaxis. The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® (calcitonin-salmon) Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

The incidence of osteogenic sarcoma is known to be increased in Paget's disease. Pagetic lesions, with or without therapy, may appear by X-ray to progress markedly, possibly with some loss of definition of periosteal margins. Such lesions should be evaluated carefully to differentiate these from osteogenic sarcoma.

PRECAUTIONS

Drug Interactions

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

General

The administration of calcitonin possibly could lead to hypocalcemic tetany under special circumstances although no cases have yet been reported. Provisions for parenteral calcium administration should be available during the first several administrations of calcitonin.

Laboratory Tests

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

Coarse granular casts and casts containing renal tubular epithelial cells were reported in young adult volunteers at bed rest who were given calcitonin-salmon to study the effect of immobilization on osteoporosis. There was no other evidence of renal abnormality and the urine sediment became normal after calcitonin was stopped. Urine sediment abnormalities have not been reported by other investigators.

Instructions for the Patient

Careful instruction in sterile injection technique should be given to the patient, and to other persons who may administer Miacalcin® (calcitonin-salmon) Injection, Synthetic.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

An increased incidence of pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley rats administered calcitonin-salmon at dosages of 20 and 80 I.U./kg/day and in Fisher 344 rats given 80 I.U./kg/day. The relevance of these findings to humans is unknown. Calcitonin-salmon was not mutagenic in tests using *Salmonella typhimurium, Escherichia coli,* and Chinese Hamster V79 cells.

Pregnancy: Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given in doses 14-56 times the dose recommended for human use. Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women. Miacalcin Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

Pediatric Use

Disorders of bone in children referred to as juvenile Paget's disease have been reported rarely. The relationship of these disorders to adult Paget's disease has not been established and experience with the use of calcitonin in these disorders is very limited. There is no adequate data to support the use of Miacalcin Injection in children.

ADVERSE REACTIONS

Gastrointestinal System

Nausea with or without vomiting has been noted in about 10% of patients treated with calcitonin. It is most evident when treatment is first initiated and tends to decrease or disappear with continued administration.

Dermatologic/Hypersensitivity

Local inflammatory reactions at the site of subcutaneous or intramuscular injection have been reported in about 10% of patients. Flushing of face or hands occurred in about 2-5% of patients. Skin rashes, nocturia, pruritus of the ear lobes, feverish sensation, pain in the eyes, poor appetite, abdominal pain, edema of feet, and salty taste have been reported in patients treated with calcitonin-salmon. Administration of calcitonin-salmon has been reported in a few cases to cause serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), *including very rare reports* of death attributed to anaphylaxis. (see WARNINGS).

In addition, the following adverse events were reported with Miacalcin Injection.

Body as a Whole – General Disorders: influenza-like symptoms, fatigue, edema (facial, peripheral, and generalized),

Musculoskeletal/Collagen: arthralgia, musculoskeletal pain

Cardiovascular: hypertension

Gastrointestinal: abdominal pain, diarrhea,

Immune System Disorders: hypersensitivity, anaphylactic and anaphylactoid reactions, anaphylactic shock

Urinary System: polyuria

Central and Peripheral Nervous System: dizziness, headache, tremor.

Vision: visual disturbance

OVERDOSAGE

A dose of l000 I.U. subcutaneously may produce nausea and vomiting as the only adverse effects. Doses of 32 units per kg per day for 1-2 days demonstrate no other adverse effects.

Data on chronic high-dose administration are insufficient to judge toxicity.

DOSAGE AND ADMINISTRATION

Paget's Disease: The recommended starting dose of Miacalcin® (calcitonin-salmon) Injection, Synthetic in Paget's disease is 100 I.U. (0.5 mL) per day administered subcutaneously (preferred for outpatient self-administration) or intramuscularly. Drug effect should be monitored by periodic measurement of serum alkaline phosphatase and 24-hour urinary hydroxyproline (if available) and evaluations of symptoms. A decrease toward normal of the biochemical abnormalities is usually seen, if it is going to occur, within the first few months. Bone pain may also decrease during that time. Improvement of neurologic lesions, when it occurs, requires a longer period of treatment, often more than one year.

In many patients, doses of 50 I.U. (0.25 mL) per day or every other day are sufficient to maintain biochemical and clinical improvement. At the present time, however, there are insufficient data to determine whether this reduced dose will have the same effect as the higher dose on forming more normal bone structure. It appears preferable, therefore, to maintain the higher dose in any patient with serious deformity or neurological involvement.

In any patient with a good response initially who later relapses, either clinically or biochemically, the possibility of antibody formation should be explored. The patient may be tested for antibodies by an appropriate specialized test or evaluated for the possibility of antibody formation by critical clinical evaluation.

Patient compliance should also be assessed in the event of relapse.

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

Hypercalcemia: The recommended starting dose of Miacalcin Injection in hypercalcemia is 4 I.U./kg body weight every 12 hours by subcutaneous or intramuscular injection. If the response to this dose is not satisfactory after one or two days, the dose may be increased to

8 I.U./kg every 12 hours. If the response remains unsatisfactory after two more days, the dose may be further increased to a maximum of 8 I.U./kg every 6 hours.

Postmenopausal Osteoporosis: The minimum effective dose of Miacalcin Injection for the prevention of vertebral bone mineral density loss has not been established. Data from a single one-year placebo-controlled study with salmon calcitonin injection suggested that 100 I.U. (subcutaneously or intramuscularly) every other day might be effective in preserving vertebral bone mineral density. Baseline and interval monitoring of biochemical markers of bone resorption/turnover (e.g., fasting AM, second-voided urine hydroxyproline to creatinine ratio) and of bone mineral density may be useful in achieving the minimum effective dose. Patients should also receive supplemental calcium such as calcium carbonate 1.5 g daily and an adequate vitamin D intake (400 units daily). An adequate diet is also essential.

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

Miacalcin vials should be inspected visually. If the solution is not clear and colorless, or contains any particles, or if the vial is damaged, do not administer the solution.

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Injection, Synthetic is available as a sterile solution in individual 2 mL vials containing 200 I.U. per mL .....NDC 0078-0149-23

Store in refrigerator between 2°C-8°C (36°F-46°F).

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2011-XX
Month Year

NOVARTIS

Miacalcin®

(calcitonin-salmon)

Nasal Spray

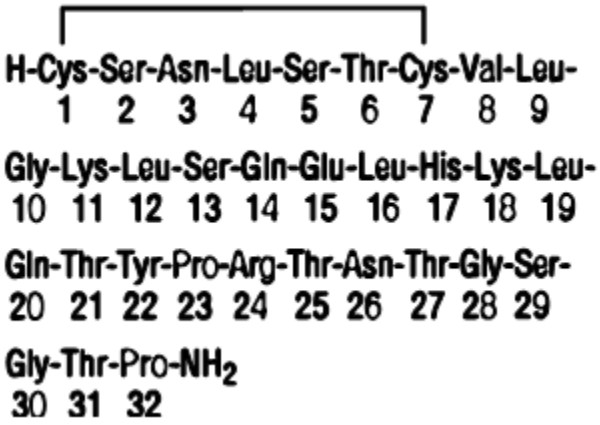
Rx only

Prescribing Information

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

Miacalcin® (calcitonin-salmon) Nasal Spray is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin. This is shown by the following graphic formula:



It is provided in a 3.7 mL fill glass bottle as a solution for nasal administration. This is sufficient medication for at least 30 doses.

Active Ingredient: calcitonin-salmon 2200 I.U. per mL (corresponding to 200 I.U. per 0.09 mL actuation).

Inactive Ingredients: sodium chloride, benzalkonium chloride, hydrochloric acid (added as necessary to adjust pH) and purified water.

The activity of Miacalcin Nasal Spray is stated in International Units based on bioassay in comparison with the International Reference Preparation of calcitonin-salmon for Bioassay, distributed by the National Institute of Biologic Standards and Control, Holly Hill, London.

CLINICAL PHARMACOLOGY

Calcitonin acts primarily on bone, but direct renal effects and actions on the gastrointestinal tract are also recognized. Calcitonin-salmon appears to have actions essentially identical to

calcitonins of mammalian origin, but its potency per mg is greater and it has a longer duration of action.

The information below, describing the clinical pharmacology of calcitonin, has been derived from studies with *injectable* calcitonin. The mean bioavailability of Miacalcin® (calcitonin-salmon) Nasal Spray is approximately 3% of that of injectable calcitonin in normal subjects and, therefore, the conclusions concerning the clinical pharmacology of this preparation may be different.

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

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test system. There is some evidence from the *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

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

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in formation of normal bone.

Postmenopausal Osteoporosis

Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal females. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fractures). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Miacalcin Nasal Spray, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

Calcium Homeostasis

In two clinical studies designed to evaluate the pharmacodynamic response to Miacalcin Nasal Spray, administration of 100-1600 I.U. to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 I.U. did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal females.

Kidney

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

Gastrointestinal Tract

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

Pharmacokinetics and Metabolism

The bioavailability of Miacalcin Nasal Spray relative to intramuscular administration is between 3 and 5%. Miacalcin Nasal Spray is absorbed by the nasal mucosa with a mean Tmax of about 13 minutes. The terminal half-life of calcitonin-salmon has been calculated to be around 18 minutes and no evidence of accumulation was observed with multiple dosing. Plasma exposure was higher following administration of 400 IU nasal spray compared to that after 200 IU dose. As is the case with other polypeptide hormones, there is very little value in monitoring plasma levels of salmon calcitonin since these are not directly predictive of the therapeutic response. Hence, Miacalcin activity should be evaluated by using clinical parameters of efficacy.

INDICATIONS AND USAGE

Postmenopausal Osteoporosis

Miacalcin® (calcitonin-salmon) Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years postmenopause with low bone mass relative to healthy premenopausal females. Miacalcin Nasal Spray should be reserved for patients who refuse or cannot tolerate estrogens or in whom estrogens are contraindicated. Use of Miacalcin Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and vitamin D (400 I.U. per day) intake to retard the progressive loss of bone mass. The evidence of efficacy is based on increases in spinal bone mineral density observed in clinical trials.

Two randomized, placebo-controlled trials were conducted in 325 postmenopausal females (227 Miacalcin Nasal Spray-treated and 98 placebo-treated) with spinal, forearm or femoral bone mineral density (BMD) at least one standard deviation below normal for healthy premenopausal

females. These studies conducted over two years demonstrated that 200 I.U. daily of Miacalcin Nasal Spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic females who were greater than 5 years postmenopause. Miacalcin Nasal Spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as 6 months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of Miacalcin Nasal Spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 1 year of treatment changing to a trend at 2 years that was no longer statistically significant.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few cases of serious allergic-type reactions have been reported in patients receiving Miacalcin® (calcitonin-salmon) Nasal Spray, including cases of anaphylaxis and anaphylactic shock.. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g., bronchospasm, swelling of the tongue or throat, anaphylactic shock), including very rare reports of death attributed to anaphylaxis. The usual provisions should be made for the emergency treatment of such a reaction should it occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of Miacalcin® Injection, Synthetic. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from the Medical Services Department of Novartis Pharmaceuticals Corporation.

PRECAUTIONS

Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done. No drug interaction studies have been performed with Miacalcin® (calcitonin-salmon) Nasal Spray ingredients.

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

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

Periodic Nasal Examinations

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

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

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

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

Information for Patients

Careful instructions on pump assembly, priming of the pump, and nasal introduction of Miacalcin Nasal Spray should be given to the patient. Although instructions for patients are supplied with individual bottles, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 2℃-8°C (36℉-46°F).
- Protect the product from freezing.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- Store bottle in use at room temperature between 15°C-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.
- See DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump for complete instructions on priming the pump and administering Miacalcin Nasal Spray.

You should keep track of the number of doses used from the bottle.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Carcinogenicity, Mutagenicity, and Impairment of Fertility

An increased incidence of nonfunctioning pituitary adenomas has been observed in one-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 I.U. per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body

surface area). The findings suggest that calcitonin-salmon reduced the latency period for development of pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon was tested for mutagenicity using *Salmonella typhimurium* (5 strains) and *Escherichia coli* (2 strains), with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in mammalian V79 cells of the Chinese Hamster *in vitro*.

Laboratory Tests

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

Pregnancy

Teratogenic Effects

Category C

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women with calcitonin-salmon. Miacalcin Nasal Spray is *not* indicated for use in pregnancy.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

Pediatric Use

There are no data to support the use of Miacalcin Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is very limited.

Geriatric Use

In one large multicenter, double-blind, randomized clinical study of Miacalcin Nasal Spray, 279 patients were less than 65 years old, while 467 patients were 65 to 74 years old and 196 patients were 75 and over. Compared to subjects less than 65 years old, the incidence of

nasal adverse events (rhinitis, irritation, erythema, and excoriation) was higher in patients over the age of 65, particularly those over the age of 75. Most events were mild in intensity. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to Miacalcin® (calcitonin-salmon) Nasal Spray (N=341) and to placebo nasal spray (N=131) and reported in greater than 3% of Miacalcin Nasal Spray-treated patients are presented below in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically

Adverse Reaction	Miacalcin® (calcitonin-salmon) Nasal Spray N=341 % of Patients	Placebo N=131 % of Patients
Rhinitis	12.0	6.9
Symptom of Nose†	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with Miacalcin Nasal Spray. Adverse events reported in 1%-3% of patients are identified with an asterisk (*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to Miacalcin Nasal Spray has not been established.

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

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

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

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

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

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

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

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation, tremor

Hearing/Vestibular: tinnitus, hearing loss, earache

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

Vascular: flushing, cerebrovascular accident, thrombophlebitis

Hematologic/Resistance Mechanisms: lymphadenopathy*, infection*, anemia

Psychiatric: depression*, insomnia, anxiety, anorexia

Immune system disorders: Hypersensitivity, anaphylaxis and anaphylactic shock

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

The collective foreign marketing experience with Miacalcin Nasal Spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE

No instances of overdose with Miacalcin® (calcitonin-salmon) Nasal Spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of Miacalcin Nasal Spray up to 1600 I.U., doses up to 800 I.U. per day for 3 days and chronic administration of doses up to 600 I.U. per day have been studied without serious adverse effects. A dose of 1000 I.U. of Miacalcin injectable solution given subcutaneously may produce nausea and vomiting. A dose of Miacalcin injectable solution of 32 I.U. per kg per day for 1 or 2 days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of Miacalcin Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of Miacalcin® (calcitonin-salmon) Nasal Spray in postmenopausal osteoporotic females is one spray (200 I.U.) per day administered intranasally, alternating nostrils daily.

Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of Miacalcin Nasal Spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to Miacalcin Nasal Spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, Miacalcin Nasal Spray should be at room temperature. To prime the pump, the bottle should be held upright and the two white side arms of the pump depressed toward the bottle until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position, and the pump firmly depressed toward the bottle. The pump should not be primed before each daily dose.

HOW SUPPLIED

Miacalcin® (calcitonin-salmon) Nasal Spray

Available as a metered dose clear solution in a 3.7 mL fill clear glass bottle. It is available in a dosage strength of 200 I.U. per activation (0.09 mL per spray). A screw-on pump is provided. The pump, following priming, will deliver 0.09 mL of solution. Miacalcin Nasal Spray contains 2200 I.U. per mL calcitonin-salmon and is provided in an individual box containing one glass bottle and one screw-on pump ..... NDC 0078-0311-54

Store and Dispense

Store unopened bottle in refrigerator between 2℃-8°C (36°F-46°F). Protect from freezing.

Store bottle in use at room temperature between 15℃-30°C (59°F-86°F) in an upright position, for up to 35 days. Each bottle contains at least 30 doses.

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Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2011-XX

Information for the Patient

Miacalcin®

(calcitonin-salmon)

Nasal Spray

What is MIACALCIN® [MEE-uh-KAL-sin] Nasal Spray?

MIACALCIN® Nasal Spray is a medication used for the treatment of osteoporosis after menopause (postmenopausal osteoporosis) in women more than 5 years after menopause with low bone mass who refuse or cannot tolerate estrogens, or in whom estrogens are not an option. Patients who use MIACALCIN® Nasal Spray should be sure to ingest adequate amounts of calcium and vitamin D along with therapy.

How much calcium and vitamin D do I need each day?

When taking MIACALCIN® Nasal Spray, it is recommended that you get at least 1000 mg of calcium and 400 I.U. (International Units) of vitamin D each day. Check with your doctor or healthcare provider to see if you are getting enough calcium and vitamin D in your diet. If not, he or she may recommend that you start taking calcium and vitamin D supplements.

What is osteoporosis after menopause? What causes it?

Postmenopausal osteoporosis is a condition associated with frail, brittle bones. It usually occurs when “old” bone cells are removed from bones faster than they can be replaced by “new” bone cells. As a result, bones get weak and may become susceptible to fractures.

Osteoporosis occurs most frequently in women who have gone through menopause. At menopause, a woman’s body goes through many changes, including a substantial decrease in the amount of estrogen produced. Estrogen in your body helps keep bones strong -- without it, they may become weak.

Postmenopausal osteoporosis begins without notice; however, over time symptoms develop such as:

- Curved spine
- Rounded shoulders
- Loss of height

Untreated, postmenopausal osteoporosis can be painful and disabling. Some women with postmenopausal osteoporosis suffer from broken hips and fractured wrists. Fortunately, osteoporosis after menopause is treatable. Your doctor or healthcare provider can prescribe a medication, like MIACALCIN® Nasal Spray, to treat your condition.

How does MIACALCIN® Nasal Spray work?

The active ingredient in MIACALCIN® Nasal Spray is calcitonin, a man-made protein similar to one found in people, other mammals, and some types of fish and birds.

The way calcitonin affects bone is still being studied, but it is believed to work in the following ways:

- Calcitonin reduces the activity of osteoclasts [AHS-tee-oh-clasts], the cells that remove “old” bone
- Because bone building continues while bone removal is slowed down, the result is an increase in bone mass

When you spray MIACALCIN® Nasal Spray into your nostril, it is rapidly absorbed by the blood vessels lining your nasal passages. It then travels into your bloodstream and on to your bones where it works to stop bone loss and helps your bones become stronger.

How do I use MIACALCIN® Nasal Spray?

The recommended dose of MIACALCIN® Nasal Spray is one spray daily in alternated nostrils -- unless directed otherwise by your healthcare provider. Start with a spray in the left nostril on your first day, followed by a spray in the right nostril on the second day. Continue to alternate nostrils every day. There are at least 30 "doses" of MIACALCIN® Nasal Spray in each bottle.

You should keep track of the number of doses used from the bottle.

After 30 doses, each spray may not deliver the correct amount of medication, even if the bottle is not completely empty.

Who should not take MIACALCIN® Nasal Spray?

MIACALCIN® Nasal Spray should not be used by patients who are allergic to the protein calcitonin-salmon, or by women who are pregnant or nursing.

You should be aware of these warnings and precautions when taking MIACALCIN® (calcitonin-salmon) Nasal Spray.

- No formal studies designed to test drug interactions with calcitonin-salmon have been done; however, no drug interactions have been observed with the use of MIACALCIN® Nasal Spray. You should inform your doctor and pharmacist about the other prescription and nonprescription medications you are taking.
- In clinical studies, nasal symptoms occurred in approximately 9% of postmenopausal patients taking MIACALCIN® Nasal Spray. For this reason, it is recommended that a nasal examination be performed prior to the start of treatment and at any time nasal complaints occur.
- Rare instances of nasal ulceration have occurred with MIACALCIN® Nasal Spray. In some cases, your doctor may decide to temporarily discontinue treatment with MIACALCIN® Nasal Spray until symptoms subside.
- Because calcitonin-salmon is a protein, the possibility of a systemic allergic reaction exists. Patients who are allergic to calcitonin-salmon should not use MIACALCIN® Nasal Spray.
- MIACALCIN® Nasal Spray is safe to use in elderly patients. A slight increase in nasal symptoms has been observed in patients over 65 years of age, however the symptoms are usually mild. No other unusual side effects have been seen in patients over 65 years of age.

Possible side effects

Most patients tolerate treatment with MIACALCIN® Nasal Spray very well; however, like all prescription drugs, MIACALCIN® Nasal Spray may cause some side effects in some people. These side effects are usually mild and generally do not lead to discontinuation of treatment with MIACALCIN® Nasal Spray. The most commonly reported side effects are:

- Nasal symptoms such as runny nose, crusting, or nasal bleeding
- Back/joint pain
- Headache

Anytime you have a medical problem you think may be related to MIACALCIN® Nasal Spray, talk to your doctor or healthcare provider.

Your doctor or pharmacist can demonstrate how to assemble, prime, and use MIACALCIN® Nasal Spray. In addition, detailed directions can be found in your

MIACALCIN® Nasal Spray box. Please read them carefully before assembling and using the spray.

This medication is prescribed for a particular condition. Do not use it for another condition or give the drug to others. Keep MIACALCIN® Nasal Spray and all medicines out of reach of children. This leaflet provides a summary of information about MIACALCIN® Nasal Spray. If you have any questions or concerns about either MIACALCIN® Nasal Spray or osteoporosis, talk to your doctor. In addition, talk to your pharmacist or other healthcare provider.

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Novartis Pharmaceuticals Corporation
East Hanover, NJ 07936

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Month Year/July 2011

HOW TO ASSEMBLE AND USE

Miacalcin® NASAL SPRAY

(calcitonin-salmon) Nasal Solution

ONE SPRAY, ONCE A DAY

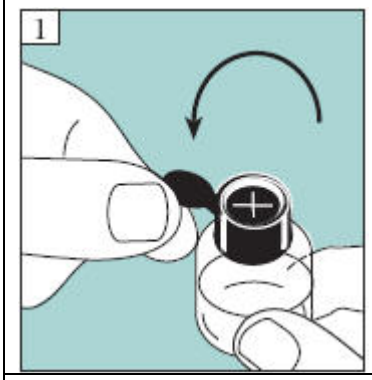
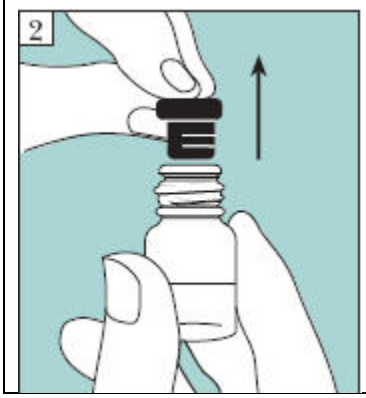
BEFORE USING MIACALCIN® (calcitonin-salmon) NASAL SPRAY

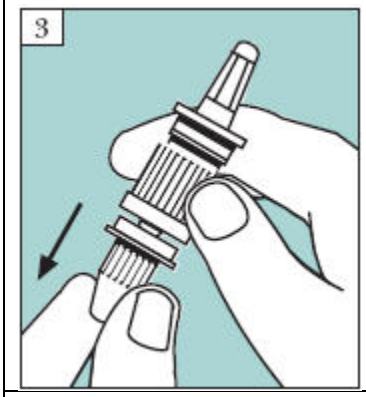
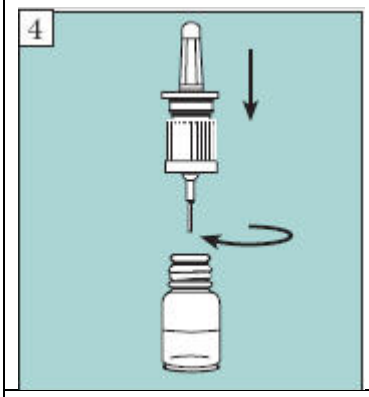
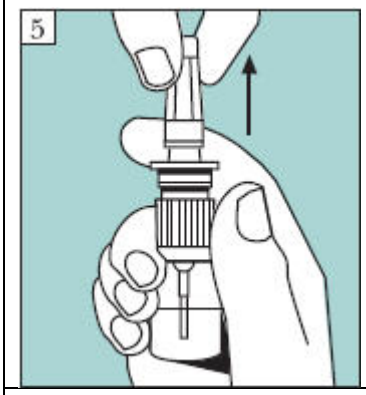
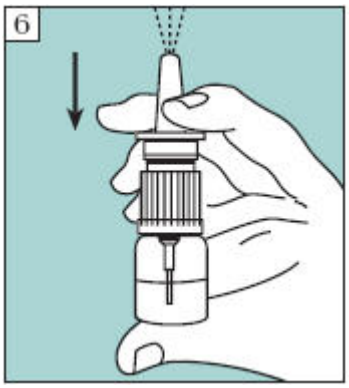
This package contains one bottle of MIACALCIN® (calcitonin-salmon) Nasal Spray and one screw-on pump.

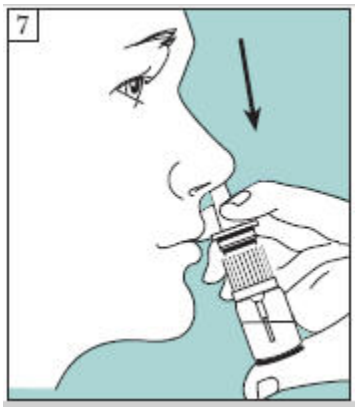
Important Facts About Your Medication:

- The bottle contains the proper amount of medication — be aware that the entire bottle will not be filled with liquid.
- Before opening and assembling your medication bottle, keep it in your refrigerator between 2°C-8°C (36°F-46°F). Do not freeze.
- After opening and assembling a new medication bottle, keep it at room temperature between 15°C-30°C (59°F-86°F) in an upright position.

HOW TO USE MIACALCIN® (calcitonin-salmon) NASAL SPRAY

Putting the Nasal Spray Pump Unit Together 	1. If your bottle and pump unit were already assembled by your pharmacist, go to Step 6. If not, remove the bottle from your refrigerator and allow it to reach room temperature before assembling. Lift up the blue plastic tab and carefully pull the metal safety seal off the bottle.
	2. Keeping the bottle upright, remove the rubber stopper from the bottle.

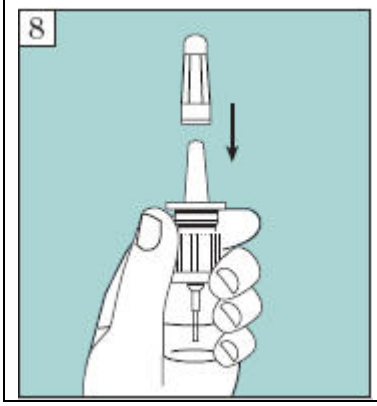
	3. Holding the pump unit, gently remove the opaque plastic protective cap from the bottom of the unit. Note: Do not depress pump when it is not attached to the bottle.
	4. Holding the bottle upright, insert the nasal spray pump unit into the bottle. Then turn the pump clockwise, and tighten it until it is securely fastened to the bottle.
	5. Holding the bottle upright with your index finger on top of one of the two side arms of the pump, gently remove the clear protective cap from the top of the nozzle.
Priming a New Bottle 	6. **To ensure proper delivery of medication, a newly opened and assembled bottle must be primed before you use it for the first time. If your pharmacist assembled the unit for you**, check to see if it has already been primed by pumping the unit once. If a full spray is emitted, the unit has already been primed. If no spray is emitted, you must prime the unit. Holding the bottle upright with your index and middle fingers on the two side arms of the pump, and your thumb on the bottom of the bottle, press the arms down fully **until you see a full spray**. Now the nasal spray is ready for use. **Do not re-prime the pump before each daily use because this will waste your medication.**
Using the Medication	7. The recommended dose of MIACALCIN® (calcitonin-

<table>
<tr><td> 
</td><td>salmon) Nasal Spray is one spray once a day in one nostril.

Keep your head upright and carefully place the nozzle in one nostril.

Tilt the bottle until it is in a straight line with the nasal passage.

Firmly press down on the pump once to spray the medication into your nose. It is not necessary to inhale while this is being done. Please note: Because the mist is so fine, you may not feel it inside your nose. Also, some medication may drip out of your nose. However, in either case, the medication is absorbed. IMPORTANT: Do not “test” the spray unit or prime it before you use your daily dose because this will waste your medication.</td></tr>
<tr><td colspan="2">Cleaning the Pump

Once or twice a week, wipe the nozzle with a clean, damp cloth. Dry the nozzle before replacing the clear protective cap.</td></tr>
<tr><td>Storing the Unit
 
</td><td>8. Holding the bottle with two fingers under the two side arms of the pump, gently replace the protective cap on the nasal spray unit. Be careful not to depress the pump while this is being done. Once the pump is primed, the unit must be kept at room temperature between 15°C-30°C (59°F-86°F) in the upright position until the medication is finished.</td></tr>
</table>

IMPORTANT

- Do not refrigerate the unit between doses.
- Do not store the unit on its side.

Bottles left at room temperature (opened or unopened) for more than 35 days must be discarded.

Refrigerated bottles are good until the expiration date stamped on the bottle and box.

Alternate Nostrils Daily

The first day, start with one spray in the left nostril. The next day, use one spray in the right nostril, and so on.

It is important to receive the correct daily amount of calcium and vitamin D, as directed by your healthcare provider.

IMPORTANT

- **Use MIACALCIN® (calcitonin-salmon) Nasal Spray daily.**

To ensure proper treatment, it is important to use your MIACALCIN® (calcitonin-salmon) Nasal Spray daily even if you have no symptoms of postmenopausal osteoporosis.

What is the Correct Dose of MIACALCIN ®(calcitonin-salmon) Nasal Spray?

A single spray of MIACALCIN® (calcitonin-salmon) Nasal Spray contains one daily dose, which is 200 I.U. of calcitonin-salmon. The fine mist is actually 0.09 mL (milliliter) of solution. Your bottle of MIACALCIN® Nasal Spray contains at least 30 doses. Priming the pump as described in Step 6 does not alter the total number of doses available in a bottle of MIACALCIN® Nasal Spray. The bottle need only be primed once after assembly. Do not re-prime or "test spray" your bottle before you use your daily dose of MIACALCIN® Nasal Spray. This will waste your medication.

For more information on MIACALCIN® Nasal Spray and how to assemble it, please call Novartis Pharmaceutical Corporation at 1-888-669-6682.

Please see your healthcare provider for complete product information for MIACALCIN® Nasal Spray.

July 2011

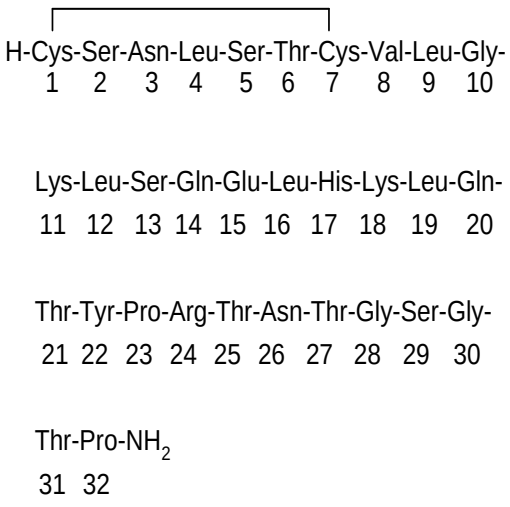
FORTICAL®
calcitonin-salmon
(rDNA origin)
Nasal Spray
For Intranasal Use Only
Rx only

DESCRIPTION

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish.

The active ingredient in FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is a polypeptide of 32 amino acids manufactured by recombinant DNA technology and is identical to calcitonin-salmon produced by chemical synthesis.

This is shown by the following graphic formula:



It is provided in a 3.7 mL fill glass bottle as a solution for intranasal administration with sufficient medication for at least 30 doses. Each spray delivers 200 International Units calcitonin-salmon in a volume of 0.09 mL.

Active Ingredient: Calcitonin-salmon 2200 International Units/mL, corresponding to 200 International Units per actuation (0.09 mL).

Inactive Ingredients: Sodium Chloride USP, Citric Acid USP, Phenylethyl Alcohol USP, Benzyl Alcohol NF, Polysorbate 80 NF, Hydrochloric Acid NF or Sodium Hydroxide NF (added as necessary to adjust pH) and Purified Water USP.

CLINICAL PHARMACOLOGY

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

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

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

Single injections of calcitonin cause a marked transient inhibition of the ongoing bone resorptive process. With prolonged use, there is a persistent, smaller decrease in the rate of bone resorption. Histologically, this is associated with a decreased number of osteoclasts and an apparent decrease in their resorptive activity. *In vitro* studies have shown that calcitonin-salmon causes inhibition of osteoclast function with loss of the ruffled osteoclast border responsible for resorption of bone. This activity resumes following removal of calcitonin-salmon from the test

system. There is some evidence from *in vitro* studies that bone formation may be augmented by calcitonin through increased osteoblastic activity.

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

Bone biopsy and radial bone mass studies at baseline and after 26 months of daily injectable calcitonin indicate that calcitonin therapy results in the formation of normal bone.

***Postmenopausal Osteoporosis*:** Osteoporosis is a disease characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk as patients approach or fall below a bone mineral density associated with increased frequency of fracture. The most common type of osteoporosis occurs in postmenopausal women. Osteoporosis is a result of a disproportionate rate of bone resorption compared to bone formation, which disrupts the structural integrity of bone, rendering it more susceptible to fracture. The most common sites of these fractures are the vertebrae, hip, and distal forearm (Colles' fracture). Vertebral fractures occur with the highest frequency and are associated with back pain, spinal deformity and a loss of height.

Calcitonin, given by the intranasal route, has been shown to increase spinal bone mass in postmenopausal women with established osteoporosis but not in early postmenopausal women.

***Calcium Homeostasis*:** In two clinical studies designed to evaluate the pharmacodynamic response to calcitonin-salmon nasal spray, administration of 100-1600 International Units to healthy volunteers resulted in rapid and sustained small decreases (but still within the normal

range) in both total serum calcium and serum ionized calcium. Single doses greater than 400 International Units did not produce any further biological response to the drug. The development of hypocalcemia has not been reported in studies in healthy volunteers or postmenopausal women.

***Kidney*:** Studies with injectable calcitonin show increases in the excretion of filtered phosphate, calcium, and sodium by decreasing their tubular reabsorption. Comparable studies have not been conducted with FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

Gastrointestinal Tract: Some evidence from studies with injectable preparations suggests that calcitonin may have significant actions on the gastrointestinal tract. Short-term administration of injectable calcitonin results in marked transient decreases in the volume and acidity of gastric juice and in the volume and the trypsin and amylase content of pancreatic juice. Whether these effects continue to be elicited after each injection of calcitonin during chronic therapy has not been investigated. These studies have not been conducted with FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

Pharmacokinetics and Drug Metabolism

The pharmacokinetic properties of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray after multiple dose administration were shown to be similar to that of a commercially available calcitonin-salmon product in healthy volunteers. FORTICAL® Nasal Spray is absorbed rapidly by the nasal mucosa. In normal volunteers approximately 3% (range 0.3%-30.6%) of a nasally administered dose is bioavailable compared to the same dose administered by intramuscular injection. Peak plasma concentrations of drug appear approximately 10 minutes after nasal administration. The terminal half-life (t1/2) of calcitonin-salmon is calculated to be about 23 minutes. There is no accumulation of the drug on repeated nasal administration at 10 hour intervals for up to 15 days. Absorption of FORTICAL® Nasal Spray has not been studied in postmenopausal women.

INDICATIONS AND USAGE

Postmenopausal Osteoporosis – FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is indicated for the treatment of postmenopausal osteoporosis in women greater than 5 years postmenopause with low bone mass relative to healthy premenopausal women. Use of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is recommended in conjunction with an adequate calcium (at least 1000 mg elemental calcium per day) and Vitamin D (400 International Units per day) intake to retard the progressive loss of bone mass. The evidence of efficacy for calcitonin-salmon is based on increases in spinal bone mineral density (BMD) observed in clinical trials.

Two randomized, placebo-controlled trials were conducted in 325 postmenopausal women (227 treated with calcitonin-salmon nasal spray and 98 treated with placebo) with spinal, forearm or femoral BMD at least one standard deviation below the normal value for healthy premenopausal women. These studies conducted over two years demonstrated that 200 International Units daily of calcitonin-salmon nasal spray increases lumbar vertebral BMD relative to baseline and relative to placebo in osteoporotic women who were greater than 5 years postmenopause. Calcitonin-salmon nasal spray produced statistically significant increases in lumbar vertebral BMD compared to placebo as early as 6 months after initiation of therapy with persistence of this level for up to 2 years of observation.

No effects of calcitonin-salmon nasal spray on cortical bone of the forearm or hip were demonstrated. However, in one study, BMD of the hip showed a statistically significant increase compared with placebo in a region composed of predominantly trabecular bone after 1 year of treatment changing to a trend at 2 years that was no longer statistically significant.

CONTRAINDICATIONS

Clinical allergy to calcitonin-salmon.

WARNINGS

Allergic Reactions

Because calcitonin is a polypeptide, the possibility of a systemic allergic reaction exists. A few

cases of serious allergic-type reactions have been reported in patients receiving calcitonin-salmon nasal spray, including cases of anaphylaxis and anaphylactic shock. With injectable calcitonin-salmon there have been a few reports of serious allergic-type reactions (e.g. bronchospasm, swelling of the tongue or throat, anaphylactic shock), including very rare reports of death attributed to anaphylaxis. The usual provisions should be made for emergency treatment if such a reaction should occur. Allergic reactions should be differentiated from generalized flushing and hypotension.

For patients with suspected sensitivity to calcitonin, skin testing should be considered prior to treatment utilizing a dilute, sterile solution of a calcitonin-salmon injectable product. Physicians may wish to refer patients who require skin testing to an allergist. A detailed skin testing protocol is available from Upsher-Smith Laboratories, Inc. by calling toll-free at 1-800-654-2299.

PRECAUTIONS

1. Drug Interactions

Formal studies designed to evaluate drug interactions with calcitonin-salmon have not been done.

Concomitant use of calcitonin and lithium may lead to a reduction in plasma lithium concentrations due to increased urinary clearance of lithium. The dose of lithium may need to be adjusted.

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

2. Periodic Nasal Examinations

Periodic nasal examinations with visualization of the nasal mucosa, turbinates, septum and mucosal blood vessel status are recommended.

The development of mucosal alterations or transient nasal conditions have been reported in up to 9% of patients who received a calcitonin-salmon nasal spray and in up to 12% of patients who

received placebo nasal spray in studies in postmenopausal women. The majority of patients (approximately 90%) in whom nasal abnormalities were noted also reported nasally related complaints/symptoms as adverse events. Therefore, a nasal examination should be performed prior to start of treatment with nasal calcitonin and at any time nasal complaints occur.

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

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

3. Information for Patients

Careful instructions on pump assembly, priming of the pump and nasal introduction of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray should be given to the patient. Although instructions for patients are supplied with the individual bottle, procedures for use should be demonstrated to each patient. Patients should notify their physician if they develop significant nasal irritation.

Get emergency medical help right away if you have any of the following symptoms of a serious allergic reaction:

- trouble breathing
- swelling of your face, throat or tongue
- rapid heartbeat

- chest pain
- feel faint or dizzy

Patients should be advised of the following:

- Store new, unassembled bottles in the refrigerator between 36-46^{o}F (2-8^{o}C).
- Protect the product from freezing.
- Keep the bottle of Fortical® Nasal Spray away from light.
- Before priming the pump and using a new bottle, allow it to reach room temperature.
- After opening a new bottle of Fortical® Nasal Spray, store bottle in use with pump attached at room temperature, 68°F to 77°F (20°C to 25°C), in an upright position. Each bottle contains enough medicine for 30 doses.
- Throw away the empty bottle of Fortical® Nasal Spray after you have used 30 doses.
- See **DOSAGE AND ADMINISTRATION, Priming (Activation) of Pump** for complete instructions on priming the pump and administering FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray.

4. Carcinogenicity, Mutagenicity, Impairment of Fertility

An increased incidence of non-functioning pituitary adenomas has been observed in 1-year toxicity studies in Sprague-Dawley and Fischer 344 Rats administered (subcutaneously) calcitonin-salmon at dosages of 80 International Units per kilogram per day (16-19 times the recommended human parenteral dose and about 130-160 times the human intranasal dose based on body surface area).

The findings suggest that calcitonin-salmon reduced the latency period for development of the pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process.

Calcitonin-salmon was tested for mutagenicity using four strains of *Salmonella typhimurium* and

two strains of *Escherichia coli*, with and without rat liver metabolic activation, and found to be non-mutagenic. The drug was also not mutagenic in a chromosome aberration test in Chinese Hamster ovary cells *in vitro.*

5. Laboratory Tests

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

6. Pregnancy

Teratogenic Effects

Category C.

Calcitonin-salmon has been shown to cause a decrease in fetal birth weights in rabbits when given by injection in doses 8-33 times the parenteral dose and 70-278 times the intranasal dose recommended for human use based on body surface area.

Since calcitonin does not cross the placental barrier, this finding may be due to metabolic effects on the pregnant animal. There are no adequate and well-controlled studies in pregnant women with calcitonin-salmon. FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is not indicated for use in pregnancy.

7. Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on this drug since many drugs are excreted in human milk. Calcitonin has been shown to inhibit lactation in animals.

8. Pediatric Use

There are no data to support the use of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray in children. Disorders of bone in children referred to as idiopathic juvenile osteoporosis have been reported rarely. The relationship of these disorders to postmenopausal osteoporosis has not been established and experience with the use of calcitonin in these disorders is limited.

9. Geriatric Use

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

ADVERSE REACTIONS

The incidence of adverse reactions reported in studies involving postmenopausal osteoporotic patients chronically exposed to calcitonin-salmon nasal spray (N=341) and to placebo nasal spray (N=131), and reported in greater than 3% of calcitonin-salmon nasal spray treated patients are presented in the following table. Most adverse reactions were mild to moderate in severity. Nasal adverse events were most common with 70% mild, 25% moderate, and 5% severe in nature (placebo rates were 71% mild, 27% moderate, and 2% severe).

Adverse Reactions Occurring in at Least 3% of Postmenopausal Patients Treated Chronically

Adverse Reaction	Calcitonin-Salmon Nasal Spray N=341 % of Patients	Placebo N=131 % of Patients
Rhinitis	12.0	6.9
Symptom of Nose†	10.6	16.0
Back Pain	5.0	2.3
Arthralgia	3.8	5.3
Epistaxis	3.5	4.6
Headache	3.2	4.6

†Symptom of nose includes: nasal crusts, dryness, redness or erythema, nasal sores, irritation, itching, thick feeling, soreness, pallor, infection, stenosis, runny/blocked, small wound, bleeding wound, tenderness, uncomfortable feeling and sore across bridge of nose.

In addition, the following adverse events were reported in fewer than 3% of patients during chronic therapy with calcitonin-salmon nasal spray. Adverse events reported in 1%-3% of patients are identified with an asterisk(*). The remainder occurred in less than 1% of patients. Other than flushing, nausea, possible allergic reactions, and possible local irritative effects in the respiratory tract, a relationship to calcitonin-salmon nasal spray has not been established.

Body as a whole – General Disorders: influenza-like symptoms*, fatigue*, edema (facial, peripheral, and generalized), fever

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

Musculoskeletal/Collagen: arthrosis*, myalgia*, arthritis, polymyalgia rheumatica, stiffness

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

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

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

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

Endocrine: goiter, hyperthyroidism

Urinary System: cystitis*, pyelonephritis, hematuria, renal calculus

Central and Peripheral Nervous System: dizziness*, paresthesia*, vertigo, migraine, neuralgia, agitation

Hearing/Vestibular: tinnitus, hearing loss, earache

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

Vascular: flushing, cerebrovascular accident, thrombophlebitis

Hematologic/Resistance Mechanisms: lymphadenopathy*, infection*, anemia

Psychiatric: depression*, insomnia, anxiety, anorexia

Immune System Disorders: hypersensitivity, anaphylaxis and anaphylactic shock

Common adverse reactions associated with the use of injectable calcitonin-salmon occurred less frequently in patients treated with calcitonin-salmon nasal spray than in those patients treated with injectable calcitonin. Nausea, with or without vomiting, which occurred in 1.8% of patients

treated with the nasal spray (and 1.5% of those receiving placebo nasal spray) occurs in about 10% of patients who take injectable calcitonin-salmon. Flushing, which occurred in less than 1% of patients treated with the nasal spray, occurs in 2-5% of patients treated with injectable calcitonin-salmon. Although the administered dosages of injectable and nasal spray calcitonin-salmon are comparable (50-100 units daily of injectable versus 200 units daily of nasal spray), the nasal dosage form has a mean bioavailability of about 3% (range 0.3%-30.6%) and therefore provides less drug to the systemic circulation, possibly accounting for the decrease in frequency of adverse reactions.

The collective foreign marketing experience with calcitonin-salmon nasal spray does not show evidence of any notable difference in the incidence profile of reported adverse reactions when compared with that seen in the clinical trials.

OVERDOSAGE

No instances of overdose with calcitonin-salmon nasal spray have been reported and no serious adverse reactions have been associated with high doses. There is no known potential for drug abuse for calcitonin-salmon.

Single doses of calcitonin-salmon nasal spray up to 1600 International Units, doses up to 800 International Units per day for 3 days and chronic administration of doses up to 600 International Units per day have been studied without serious adverse effects. A 1000 International Units dose of calcitonin-salmon injectable product given subcutaneously may produce nausea and vomiting. A 32 International Units per kg per day dose of calcitonin-salmon injectable product for 1or 2 days demonstrated no additional adverse effects.

There have been no reports of hypocalcemic tetany. However, the pharmacologic actions of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray suggest that this could occur in overdose. Therefore, provisions for parenteral administration of calcium should be available for the treatment of overdose.

DOSAGE AND ADMINISTRATION

The recommended dose of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray in postmenopausal osteoporotic patients is 1 spray (200 International Units) per day administered

intranasally, alternating nostrils daily. Each bottle, filled with 3.7 mL of solution, contains enough medication for 30 doses. Drug effect may be monitored by periodic measurements of lumbar vertebral bone mass to document stabilization of bone loss or increases in bone density. Effects of calcitonin-salmon nasal spray on biochemical markers of bone turnover have not been consistently demonstrated in studies in postmenopausal osteoporosis. Therefore, these parameters should not be solely utilized to determine clinical response to calcitonin-salmon nasal spray therapy in these patients.

Priming (Activation) of Pump

Before the first dose and administration, allow the bottle to reach room temperature. Remove the protective cap and clip from the bottle of FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray. To prime the pump, hold the bottle upright and depress the two white side arms of the pump toward the bottle at least 5 times until a full spray is produced. The pump is primed once the first full spray is emitted. To administer, the nozzle should be carefully placed into the nostril with the head in the upright position and the pump firmly depressed toward the bottle. The pump should NOT be primed before each daily use.

HOW SUPPLIED

FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray is presented as a metered dose solution in a 3.7 mL fill amber glass bottle. It is available in a dosage strength of 200 International Units per activation (0.09 mL). A screw-on pump is provided. Following priming, the pump will deliver solution containing 200 International Units of calcitonin-salmon per activation. FORTICAL® calcitonin-salmon (rDNA origin) Nasal Spray contains 2200 International Units /mL calcitonin-salmon and is provided in individual boxes containing one glass bottle with screw cap and one screw-on pump (NDC# 0245-0008-35).

Store and Dispense

Store unopened bottle in refrigerator between 36°F to 46°F (2°C to 8°C). **Protect from freezing.** After opening, store bottle in use in an upright position at 68°F to 77°F (20°C to 25°C). Excursions permitted to 15°C to 30°C (59°F to 86°F). Throw away the empty bottle of

Fortical® Nasal Spray after you have used 30 doses.

Distributed by

UPSHER-SMITH LABORATORIES, INC.

Minneapolis, MN USA 55447-4709

US Patent RE 40, 182

US Patent 6,103,495

US Patent 6,210,925

US Patent 6,627,438

US Patent 6,737,250

US Patent 5,789,234

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6 Appendix B: Drug Utilization Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

Date:	January 31, 2013
Reviewer(s):	Patty Greene, Pharm.D., Drug Use Data Analyst Division of Epidemiology II (DEPI II)
Team Leader	Grace Chai, Pharm.D. Division of Epidemiology II (DEPI II)
Deputy Director	Laura Governale, Pharm.D., MBA Division of Epidemiology II (DEPI II)
Subject:	Calcitonin-Containing Products Drug Utilization Review
Drug Name(s):	Miacalcin (calcitonin-salmon) and generic equivalents Fortical (calcitonin-salmon recombinant)
Application Type/Number:	Various
Applicant/sponsor:	Various
OSE RCM #:	2012-1682

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

This review examines sales and drug utilization data of calcitonin-containing products in the outpatient retail pharmacy setting from year 2006 through year 2011.

Sales Distribution Data:

- National sales of osteoporosis products decreased by 38% from 62 million packages sold in year 2007 to 38.8 million packages sold in year 2011. Alendronate products accounted for 63% of total sales (24.4 million packages) of osteoporosis products in year 2011.
- In year 2011, sales of calcitonin-containing products accounted for approximately 4.5% of the osteoporosis market.
- Sales distribution data for calcitonin-containing products showed that approximately 1.7 million packages were distributed nationwide in year 2011, a decrease of 48% from 3.3 million packages in year 2006.
- Sales data in year 2011 indicated that approximately 91% of calcitonin-containing product sales were distributed as calcitonin nasal spray products and 9% of total sales were distributed as calcitonin vials.
- Annual sales of calcitonin nasal spray decreased by 50% from 3.1 million bottles sold in year 2006 to 1.6 million bottles sold in year 2011.
- Annual sales of calcitonin vials remained steady and ranged from 152,000 vials to approximately 160,000 vials for the review period.
- In year 2011, the largest proportion of calcitonin-containing products sales were distributed to outpatient retail pharmacy settings at 48% of calcitonin-containing products sales. Non-retail settings accounted for 33% of sales, primarily to long term care settings, and 19% of sales were to mail-order/specialty pharmacies.

Outpatient Retail Prescription Data:

- In year 2011, approximately 795,000 prescriptions were dispensed and 205,000 patients received prescriptions for calcitonin-containing products from outpatient retail pharmacies.
- From year 2006 to year 2011, the overall number of dispensed prescriptions and patients receiving dispensed prescriptions for calcitonin-containing products decreased by 54% (of prescriptions) and 51% (of patients), respectively.
- Nearly 100% of prescriptions were dispensed for calcitonin nasal spray, primarily to female patients (92% of nasal calcitonin prescriptions) during the total review period.

Office-Based Physician Survey Data:

- "Osteoporosis" (ICD-9 733.0) was the most common diagnosis for calcitonin nasal spray at 64% of drug use mentions during the review period.

1 INTRODUCTION

1.1 BACKGROUND

On March 5, 2013, the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management will meet to discuss the efficacy data of calcitonin-containing products for the treatment of osteoporosis. The European Medicines Agency (EMA) recommended against the use of the intranasal calcitonin-containing products for the treatment of osteoporosis in a press release on July 20, 2012. According to the EMA, calcitonin-containing products will only be available as a solution for injection or infusion to prevent acute bone loss due to sudden immobilisation, Paget's disease or hypercalcemia. Treatment is limited to short-term use due to evidence of an increased risk of cancer associated with long-term use of calcitonin-containing products.

This review provides drug utilization data as background information on the use of calcitonin-containing products nationwide in the outpatient retail pharmacy setting for context and discussions at the advisory committee meeting. We examined national patterns of drug utilization for calcitonin-containing products by the volume of sales (packages sold), dispensed prescriptions, and patient exposure. We also included an analysis of diagnoses associated with the use of calcitonin-containing products by formulation (nasal spray vs. injection). Using the currently available proprietary drug utilization databases, this review describes outpatient retail pharmacy utilization for calcitonin-containing products from year 2006 through 2011.

2 METHODS and MATERIALS

2.1 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ data was used to determine the various retail and non-retail channels of distribution for calcitonin-containing products for year 2011.[1] Approximately 48% of calcitonin-containing products sales were distributed to outpatient retail pharmacy settings, 33% to non-retail settings (primarily long term care settings); and 19% were to mail-order/specialty pharmacies. As a result, outpatient retail pharmacy utilization patterns were examined. National estimates of drug utilization in long term care facilities are not available to the Agency. Mail-order/specialty and non-retail pharmacy data were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full data descriptions).

IMS Health, IMS National Sales Perspectives™ was used to determine national estimates of the number of packages (eaches) sold for osteoporosis products (USC Class: 59200: alendronate, risedronate, raloxifene, ibandronate, teriparatide, zoledronic acid (Reclast®), denosumab (Prolia®) and calcitonin-containing products by product formulation from manufacturers into retail and non-retail markets from year 2006 through 2011. Products not labeled for the treatment of osteoporosis were excluded, e.g. denosumab (Xgeva®) and zoledronic acid (Zometa®).

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[1] IMS Health, IMS National Sales Perspectives™. Year 2011. Extracted January 2013. File: NSPC 2012-1682 Calcitonin by form 1-12-13.xls

IMS, Vector One®: National (VONA) was used to obtain crude national estimates of the number of outpatient dispensed prescriptions for calcitonin-containing products by formulation and patient sex from year 2006 through 2011. Calcitonin nasal spray prescriptions dispensed as new, switch/add-on, or continuing using a 12-month look back period from the date of fill were also obtained from the IMS, Vector One®: National (VONA) database. We utilized a 12-month look back period for this analysis to take into account patients new to therapy who were possibly switched from an osteoporosis agent with a longer dosing interval. Prescriptions were classified as *new patient prescriptions* if the prescription for calcitonin nasal spray was dispensed to a patient who, during the *twelve-month* look back period, had not filled any prescriptions for calcitonin nasal spray. Prescriptions were classified as *continuing patient prescriptions* if a calcitonin nasal spray prescription dispensed to a patient who, during the *twelve-month* look back period, had filled the same brand previously. Lastly, prescriptions were classified as *switch/add-on patient prescriptions* if a calcitonin nasal spray prescription dispensed to a patient who, during the *twelve-month* look back period, was never dispensed the brand previously but who had received another osteoporosis drug previously; these prescriptions were either added on to current therapy or switched from one therapy to another.

IMS, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for calcitonin-containing products by product formulation in the outpatient setting from year 2006 through 2011.

Diagnoses associated with the use of calcitonin-containing products by formulation were obtained from the Encuity Research, LLC., and Treatment Answers™ with Pain Panel from year 2006 through 2011.

2.3 PRODUCTS INCLUDED

Table 1: Indications of Calcitonin-Containing Products[2]

Trade Name	Generic Name	Application Number (Approval Date)	Indication	Product Form and Dose
Miacalcin	calcitonin salmon	NDA 20-313 (8/17/1995) ANDA 76-396 (11/17/2008) ANDA 76-979 (6/08/2009)	-Treatment of postmenopausal osteoporosis.	**Nasal Spray:** Dose: 200 I.U. daily

[2]Calcitonin-Salmon Product labels. http://dailymed.nlm.nih.gov/dailymed/about.cfm

		NDA 17-808 (7/31/1986)	-Treatment of Paget's disease of bone -Treatment of hypercalcemia -Treatment of postmenopausal osteoporosis.	**Injection (subq/IM):** Paget's disease: 100 I.U. daily Hypercalcemia: 4-8 I.U./kg every 12 hours Postmenopausal osteoporosis: 100 I.U. every other day
Fortical	calcitonin salmon recombinant	NDA 21-406 (8/12/2005)	- Treatment of postmenopausal osteoporosis in women greater than 5 years postmenopausal with low bone mass relative to healthy premenopausal women.	**Nasal Spray:** Dose: 200 I.U. daily
Calcimar *(Discontinued)*	calcitonin salmon	NDA 17-769 (4/17/1978) NDA 17-497	-Treatment of Paget's disease of bone - Treatment of hypercalcemia	**Injection (subq/IM):** Paget's disease: 100 I.U. daily Hypercalcemia: 4-8 I.U./kg every 12hrs

3 RESULTS

3.1 SALES OF CALCITONIN-CONTAINING PRODUCTS

Figure 1 and Table 1 in Appendix 1 displays the nationally estimated number of packages sold for osteoporosis products from manufacturers to U.S. retail and non-retail channels of distribution, years 2007 through 2011. Approximately 38.8 million packages were distributed nationwide for osteoporosis drug products in year 2011, a 38% decrease from 62 million packages in year 2007. Alendronate was the market leader accounting for approximately 63% of total sales in year 2011. Annual sales of alendronate decreased 31% from 35.2 million packages sold in 2007 to approximately 24.4 million packages sold in year 2011. Meanwhile, sales of zoledronic acid (Reclast®) and denosumab (Prolia®) increased while sales of risedronate (Evista®), teriparatide (Forteo®), ibandronate (Boniva®), and calcitonin-containing products decreased during the examined time period. Calcitonin-containing products accounted for 4.5% of osteoporosis product sales in year 2011.

Figure 2 in Appendix 1 displays the nationally estimated number of packages (spray bottles or vials) sold for calcitonin-containing products by formulation from manufacturers to U.S. retail and non-retail channels of distribution, year 2006 through 2011. Approximately 1.7 million packages were distributed nationwide for calcitonin-containing products in year 2011, a 47% decrease from 3.3 million packages in year 2006. Calcitonin nasal spray accounted for 91% of total sales in year 2011. Annual sales of calcitonin nasal spray decreased 50% from 3.1 million bottles sold in 2006 to 1.6 million bottles sold in year 2011. Meanwhile, sales of calcitonin injection products remained steady over this time period. Annual sales of calcitonin injection products ranged from 152,000 vials to approximately 160,000 vials sold for the review period.

3.2 DISPENSED PRESCRIPTIONS FOR CALCITONIN-CONTAINING PRODUCTS IN U.S. OUTPATIENT RETAIL PHARMACIES

Figure 3 and Table 2 in Appendix 1 show the nationally estimated number of dispensed prescriptions for calcitonin-containing products by formulation from U.S. outpatient retail pharmacies, year 2006 through 2011. During this time period, approximately 7.5 million total prescriptions were dispensed for calcitonin-containing products for the review period. Of these prescriptions, over 99% were dispensed for the calcitonin nasal spray. Overall, dispensed prescriptions of calcitonin-containing products decreased 54% from 1.7 million prescriptions in year 2006 to 791,000 prescriptions in year 2011. Miacalcin® nasal spray was the most commonly dispensed product in year 2006, accounting for 68% (1.2 million prescriptions) of total prescriptions compared to Fortical® nasal spray at 32% (554,000 prescriptions). By year 2008, Fortical® accounted for 60% of dispensed prescriptions and held the majority of the market share through 2010. The first generic calcitonin nasal spray products was approved in November 2008. By year 2011, 52% of nasal calcitonin prescriptions were dispensed for Miacalcin® or generic equivalents. Calcitonin injection prescriptions accounted for a negligible proportion in the outpatient retail pharmacy setting.

Table 3 in Appendix 1 displays the nationally estimated number of dispensed prescriptions for calcitonin-containing products by formulation and patient sex from years 2006 to year 2011, cumulative. For calcitonin nasal spray, female patients accounted for 92% of dispensed prescriptions compared to male patients at 8% of dispensed prescriptions. For calcitonin injection, females accounted for 83% of dispensed prescriptions compared to males at 17% of dispensed prescriptions.

3.3 PATIENT UTILIZATION OF CALCITONIN-CONTAINING PRODUCTS IN U.S. OUTPATIENT RETAIL PHARMACIES

Table 4 in Appendix 1 shows the nationally estimated number of patients who received prescriptions dispensed for calcitonin-containing products by patient age from U.S. outpatient retail pharmacies, year 2006 through 2011. Approximately 1 million total patients received a prescription for calcitonin-containing products for the review period. Overall, patient utilization decreased 51% from 423,000 patients in year 2006 to 205,000 patients in year 2011. Trends in patient utilization were similar to prescription trends for calcitonin-containing products. Over 99% of patients received prescriptions for nasal formulations of calcitonin-containing products throughout the examined time. Patients dispensed calcitonin injection products from outpatient retail pharmacies decreased from approximately 3,000 patients to 1,300 patients, annually, during the review period.

3.4 NEW, SWITCH/ADD-ON, OR CONTINUING DISPENSED PRESCRIPTIONS FOR CALCITONIN-CONTAINING PRODUCTS IN U.S. OUTPATIENT RETAIL PHARMACIES

Figure 4 in Appendix 1 provides the nationally estimated number of prescriptions for calcitonin nasal spray that were dispensed as new, switch/add-on, or continuing patient prescriptions from U.S. outpatient retail pharmacies, from year 2006 through year 2011. Of the 791,000 prescriptions dispensed for calcitonin nasal spray in year 2011, 88% of prescriptions were for patients who were *continuing* on calcitonin nasal spray therapy. Approximately 8% of prescriptions were for patients *new* to therapy, while 4% were for

patients who had *switched from another prescription or added on therapy* within the *12-month* look back period.

3.5 DIAGNOSIS ASSOCIATED WITH THE USE OF CALCITONIN-CONTAINING PRODUCTS

Diagnoses associated with the use of calcitonin-containing products, by product formulation, were analyzed according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied to the estimates (***Table 5 in Appendix 1***). According to physician survey data, drug use mentions for "Osteoporosis" (ICD-9 733.0) was the most common diagnosis for calcitonin nasal spray at 64% of drug use mentions[3] with a point estimate of 650,000 uses (95% CI 530,000-771,000 uses) during the review period. Diagnoses related to vertebral fracture were also commonly reported for calcitonin nasal spray. "Multiple myeloma" (ICD-9 203.0) and "Osteitis Deformans NOS" (Paget's Disease ICD-9 731.0) were reported at <1% of drug use mentions, respectively. Drug use mentions for "Osteoporosis" was also the most common diagnosis for injectable calcitonin-containing products. However, the number of drug use mentions reported was below the acceptable count allowable to provide a reliable estimate of national use, and should therefore be interpreted with caution.

4 DISCUSSION

In a press release in July 2012, the European Medicines Agency (EMA) recommended against the use of the intranasal calcitonin-containing products for the treatment of osteoporosis due to limited efficacy data. We examined sales distribution data for calcitonin-containing products prior to the July 2012 press release, and our findings show that calcitonin-containing products accounted for only 4.5% of total sales for the osteoporosis market in year 2011. Overall, national sales of the osteoporosis products market gradually decreased since year 2007; alendronate accounted for nearly two-thirds of the osteoporosis market in year 2011.

In U.S. outpatient retail pharmacy settings, utilization of calcitonin-containing products decreased by 50% or more during the six-year review period. This trend is consistent with U.S sales from manufacturers to retail and non-retail channels of distribution nationwide. Calcitonin-containing products were primarily dispensed as the nasal spray formulation and the majority of prescriptions were dispensed to female patients. In year 2011, a crude analysis of prescription dispensed to new, continuing, or switch/add-on patients showed that only 8% of calcitonin nasal spray prescriptions were dispensed for patients new to therapy from outpatient retail pharmacies. We utilized a 12-month look back period for this analysis to take into account patients new to therapy who were possibly switched from an osteoporosis agent with a longer dosing interval (i.e. Boniva®, Prolia®, or Reclast®). The dosing interval for these products can range from 3 months to up to one year. Patients switching from a product with a longer dosing interval would

[3] Encuity Research, LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

have been misclassified as patients new to therapy using a shorter look-back period. Medications prescribed for acute conditions typically require a shorter look-back period. Calcitonin-containing products are typically prescribed to patients for chronic treatment of osteoporosis. However, shortening the look-back period may result in greater new patient transactions and decrease the proportion of continuing and switch/add-on patient transactions. Although, our analysis did not include longitudinal patient-level data, they provide a rough sense of prescribing trends to new patients within the examined time.

Results from the diagnoses analysis showed a wide range of diagnoses (ICD-9 codes) associated with drug use mentions for calcitonin-containing products. The vast majority of office-based physicians reported using calcitonin nasal spray for the treatment of osteoporosis or vertebral fractures according to survey data. Our data also showed diagnosis codes for "Backache NOS" (ICD-9 code 724.5) as well as "Lumbago" (ICD-9 code 724.2) which could be suggestive of off-label use. According to the package insert, calcitonin nasal spray is not indicated for use in the treatment of bone pain. However, studies have shown use of calcitonin for vertebral fracture pain.[4] Off-label use of calcitonin nasal spray in Paget's disease or multiple myeloma was not commonly reported and accounted for <1% of drug use mentions for the review period.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that calcitonin-containing products were distributed primarily in the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. We focused our analysis on only the outpatient retail pharmacy setting, therefore these estimates may not apply to other settings of care in which these products are used (e.g. non-retail settings or mail-order/specialty pharmacies).

5 CONCLUSIONS

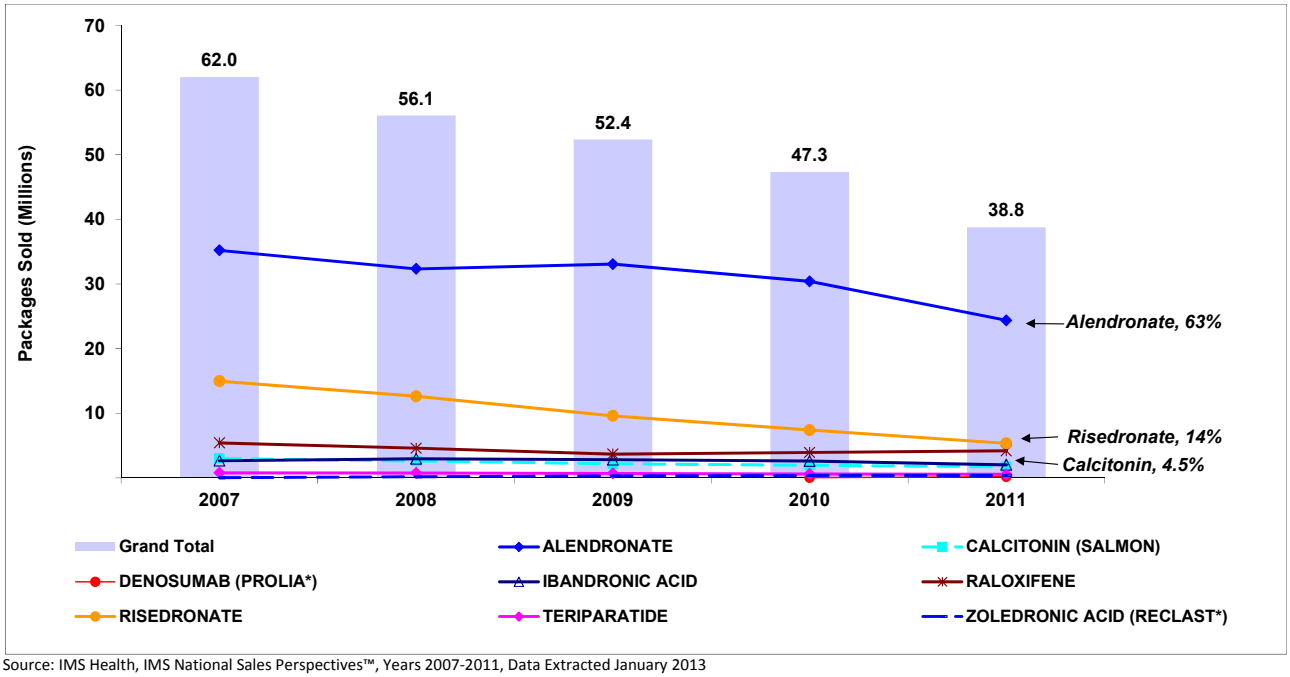
Findings for this analysis show that calcitonin-containing products accounted for approximately 4.5% of the osteoporosis market in year 2011. Over 99% of calcitonin prescriptions dispensed from outpatient retail settings were for the nasal spray formulation. The overall number of dispensed prescriptions and patients receiving dispensed prescriptions from outpatient retail pharmacies for calcitonin-containing products decreased by 54% (of prescriptions) and 51% (of patients), respectively, from year 2006 to year 2011 nationwide. Calcitonin nasal spray was primarily used for the treatment of osteoporosis and off-label use in Paget's disease or multiple myeloma were not commonly reported by office-based physician survey.

[4] Blau LA, Hoehns JD. Analgesic efficacy of calcitonin for vertebral fracture pain. *The Annals of Pharmacotherapy* 2003; 37: 564-70.

6 APPENDICES

6.1 APPENDIX 1: FIGURES AND TABLES

Figure 1. Sales of Osteoporosis Products in Packages† (bottles, IV bags, syringe kits, or vials) Sold to U.S. Channels of Distribution, Y2007-2011



Source: IMS Health, IMS National Sales Perspectives™, Years 2007-2011, Data Extracted January 2013

† Packages = (bottles, IV bags, pre-filled syringe kits, vials)

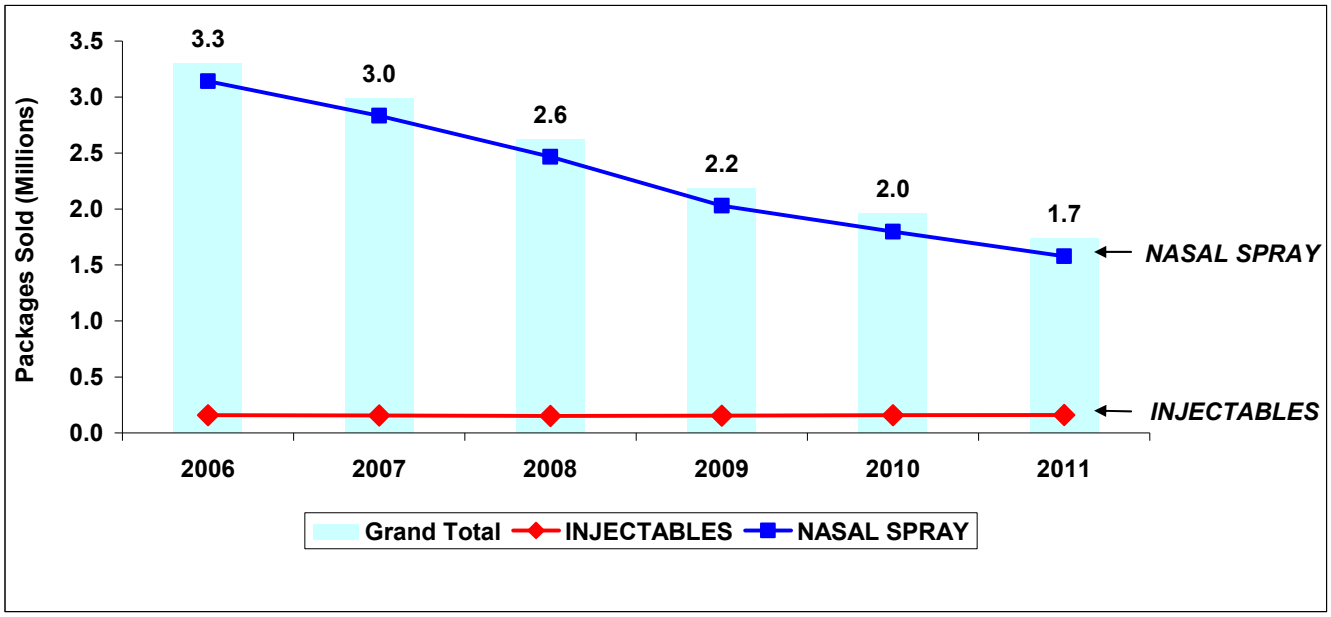
*Only products with approved labeling for the treatment of osteoporosis were included (e.g. Xgeva and Zometa were excluded)

Table 1. Sales of Osteoporosis Products in Packages (bottles, IV bags, syringe kits, or vials) Sold to U.S. Channels of Distribution, Y2007-2011

	2007		2008		2009		2010		2011	
Combined Molecule	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %	Packages (N)	Share %
Total Market	**62,014,711**	**100.0%**	**56,063,391**	**100.0%**	**52,351,990**	**100.0%**	**47,331,466**	**100.0%**	**38,759,882**	**100.0%**
ALENDRONATE (FOSAMAX)	35,203,222	56.8%	32,335,982	57.7%	33,067,999	63.2%	30,394,220	64.2%	24,370,867	62.9%
RISEDRONATE (ACTONEL)	14,968,923	24.1%	12,631,726	22.5%	9,598,905	18.3%	7,402,560	15.6%	5,353,175	13.8%
RALOXIFENE (EVISTA)	5,403,576	8.7%	4,594,703	8.2%	3,683,426	7.0%	3,930,233	8.3%	4,187,052	10.8%
IBANDRONIC ACID (BONIVA)	2,647,560	4.3%	2,951,896	5.3%	2,811,983	5.4%	2,614,360	5.5%	2,017,631	5.2%
CALCITONIN SALMON	2,990,545	4.8%	2,619,099	4.7%	2,184,971	4.2%	1,957,271	4.1%	1,737,584	4.5%
TERIPARATIDE (FORTEO)	780,532	1.3%	763,078	1.4%	693,775	1.3%	615,233	1.3%	537,221	1.4%
ZOLEDRONIC ACID (RECLAST)	20,353	0.0%	166,907	0.3%	310,931	0.6%	388,231	0.8%	390,814	1.0%
DENOSUMAB (PROLIA)							29,358	0.1%	165,538	0.4%

Source: IMS Health, IMS National Sales Perspectives™, Years 2007-2011, Extracted January 2013 File: NSPC 2012-1682 Osteo Market 1-16-13.xls

Figure 2. Sales of Calcitonin-Containing Products in Packages (spray bottles or vials) Sold by Product Formulation to U.S. Channels of Distribution, Y2006-2011



Source: IMS Health, IMS National Sales Perspectives™ Year 2006-2011, Data extracted Jan 2013

Figure 3. Nationally Estimated Number of Dispensed Prescriptions for Intranasal Calcitonin-Containing Products in U.S. Outpatient Retail Pharmacies, Y2006-2011

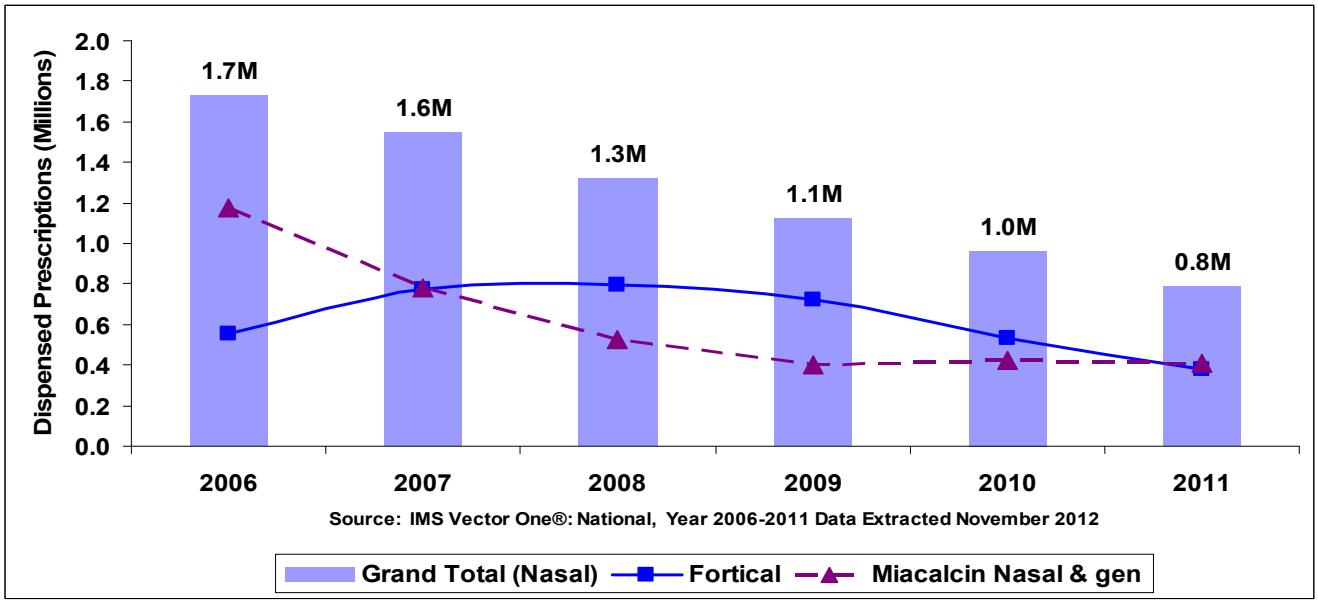


Table 2. Nationally Estimated Number of Dispensed Prescriptions for Calcitonin-Containing Products by Product Formulation in U.S. Outpatient Retail Pharmacies, Y2006-2011

	2006		2007		2008		2009		2010		2011		Total Y2006-2011	
	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %	TRxs N	*Share* %
Grand total	**1,740,897**	***100.0%***	**1,558,527**	***100.0%***	**1,331,126**	***100.0%***	**1,129,562**	***100.0%***	**964,139**	***100.0%***	**794,656**	***100.0%***	**7,518,906**	***100.0%***
Nasal	**1,732,116**	***99.5%***	**1,550,119**	***99.5%***	**1,324,144**	***99.5%***	**1,123,936**	***99.5%***	**959,931**	***99.6%***	**791,352**	***99.6%***	**7,481,597**	***99.5%***
Fortical	554,396	*32.0%*	770,192	*49.7%*	797,396	*60.2%*	722,984	*64.3%*	534,904	*55.7%*	381,018	*48.1%*	**3,760,890**	***50.3%***
Miacalcin Nasal & gen	1,177,720	*68.0%*	779,927	*50.3%*	526,748	*39.8%*	400,952	*35.7%*	425,027	*44.3%*	410,334	*51.9%*	**3,720,708**	***49.7%***
Injectable	**8,781**	***0.5%***	**8,408**	***0.5%***	**6,982**	***0.5%***	**5,625**	***0.5%***	**4,208**	***0.4%***	**3,304**	***0.4%***	**37,309**	***0.5%***

Source: IMS Vector One®: National, Years 2006-2011 Data Extracted November 2012. File: VONA 2012-1682 Calcitonin by product 11-30-12

Table 3. Nationally Estimated Number of Dispensed Prescriptions for Calcitonin-Containing Products by Product Formulation and Patient Sex in U.S. Outpatient Retail Pharmacies, Y2006-2011

	Total Y2006-2011	
	TRxs N	*Share* %
Grand Total	**7,517,418**	***100.0%***
Nasal	**7,480,118**	***99.5%***
Female	6,890,534	*92.1%*
Male	586,108	*7.8%*
Unknown	3,476	*0.0%*
Injectable	**37,300**	***0.5%***
Female	31,103	*83.4%*
Male	6,190	*16.6%*
Unknown	6	*0.0%*

Source: IMS Vector One®: National, Years 2006-2011 Data Extracted January 2013. File: VONA 2012-1682 Calcitonin by form_gender 1-7-13

Table 4. Nationally Estimated Number of Patients Who Received a Prescription for Calcitonin-Containing Products by Product Formulation in U.S. Outpatient Retail Pharmacies, Y2006-2011

	2006		2007		2008		2009		2010		2011		Total Y2006-2011	
	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %	Patient Count N	*Share* %
Grand total	**423,405**	***100.0%***	**383,254**	***100.0%***	**307,036**	***100.0%***	**261,727**	***100.0%***	**242,506**	***100.0%***	**205,524**	***100.0%***	**1,037,642**	***100.0%***
Nasal	**421,452**	***99.5%***	**381,306**	***99.5%***	**305,443**	***99.5%***	**260,395**	***99.5%***	**241,345**	***99.5%***	**204,580**	***99.5%***	**1,031,875**	***99.4%***
Fortical	167,863	*39.8%*	210,964	*55.3%*	200,563	*65.7%*	180,310	*69.2%*	143,737	*59.6%*	101,771	*49.7%*	**595,746**	***57.7%***
Miacalcin Nasal & gen	300,982	*60.2%*	199,765	*44.7%*	128,615	*34.3%*	109,888	*30.8%*	115,553	*40.4%*	115,627	*50.3%*	**612,222**	***42.3%***
Injectable	**2,919**	***0.5%***	**2,949**	***0.5%***	**2,465**	***0.5%***	**1,833**	***0.5%***	**1,567**	***0.5%***	**1,271**	***0.5%***	**10,268**	***0.6%***

Source: IMS Total Patient Tracker. Year 2006-2011 Data Extracted January 2013 File: TPT 2012-1682 Calcitonin by year 1-7-13

*Subtotals may not sum exactly, due to rounding. Due to aging of patients during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories.

For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Figure 4. Nationally Estimated Number of Prescriptions for Calcitonin Nasal Spray Dispensed as New, Switch/add-on or Continuing Prescriptions from U.S. Outpatient Retail Pharmacies, Y2006-2011

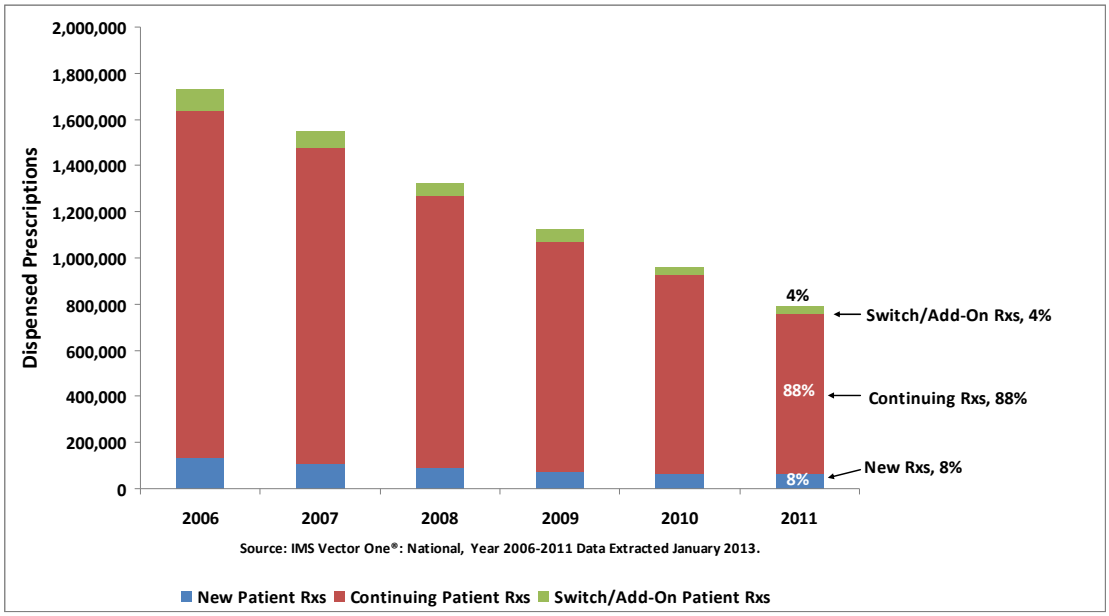


Table 5. Diagnoses Associated with the Use* of Calcitonin-Containing Products by Product Formulation As Reported by Office-Based Physician Practices, Y2006-2011

	01/2006-12/2011		
	Uses (000)	*Share%*	95% Confidence Interval Uses (000)
Grand Total	**1,114**	***100.0%***	**957-1,272**
Calcitonin Nasal	**1,020**	***91.6%***	**869-1,171**
7330 OSTEOPOROSIS	650	*63.8%*	530-771
7339 BONE/CARTIL DIS NEC/NOS	73	*7.1%*	33-113
7245 BACKACHE NOS	49	*4.8%*	16-82
8054 FX LUMBAR VERTEBRA-CLOSE	47	*4.7%*	15-80
8052 FX DORSAL VERTEBRA-CLOSE	31	*3.0%*	5-57
7242 LUMBAGO	22	*2.2%*	<0.5-45
8058 VERTEBRAL FX NOS-CLOSED	19	*1.9%*	<0.5-40
7331 PATHOLOGICAL FRACTURE	18	*1.8%*	<0.5-39
8290 FRACTURE NOS-CLOSED	15	*1.5%*	<0.5-34
7241 PAIN IN THORACIC SPINE	13	*1.2%*	<0.5-29
2754 DIS CALCIUM METABOLISM	12	*1.1%*	<0.5-28
7194 PAIN IN JOINT	10	*1.0%*	<0.5-25
8208 FX NECK OF FEMUR NOS-CL	10	*1.0%*	<0.5-25
8238 FX TIBIA/FIBULA NOS-CLOS	7	*0.7%*	<0.5-19
4940 BRONCHIECTASIS W/O EXAC	7	*0.7%*	<0.5-19
7333 HYPEROSTOSIS OF SKULL	6	*0.6%*	<0.5-18
8062 CL DORSAL FX W CORD INJ	6	*0.6%*	<0.5-18
2030 MULTIPLE MYELOMA	4	*0.4%*	<0.5-12
7310 OSTEITIS DEFORMANS NOS	3	*0.3%*	<0.5-11
6259 FEM GENITAL SYMPTOMS NOS	3	*0.3%*	<0.5-10
7159 OSTEOARTHROSIS NOS	2	*0.2%*	<0.5-10
7395 SOMAT DYSFUNC PELVIC REG	2	*0.2%*	<0.5-10
7240 SPINAL STENOSIS NEC	2	*0.2%*	<0.5-10
7812 ABNORMALITY OF GAIT	2	*0.2%*	<0.5-10
7392 SOMAT DYSFUNC THORAC REG	2	*0.2%*	<0.5-10
3384 CHRONIC PAIN SYNDROME	2	*0.2%*	<0.5-9
V670 SURGERY FOLLOW-UP	1	*0.1%*	<0.5-7
Calcitonin Injectable	**94**	***8.5%***	**48-140**
7330 OSTEOPOROSIS	33	*35.1%*	6-60
8054 FX LUMBAR VERTEBRA-CLOSE	16	*16.6%*	<0.5-34
8058 VERTEBRAL FX NOS-CLOSED	11	*11.7%*	<0.5-27
2754 DIS CALCIUM METABOLISM	11	*11.5%*	<0.5-26
4280 CONGESTIVE HEART FAILURE	10	*10.3%*	<0.5-24
7169 ARTHROPATHY NOS	8	*8.9%*	<0.5-22
2030 MULTIPLE MYELOMA	3	*3.3%*	<0.5-12
8290 FRACTURE NOS-CLOSED	2	*2.5%*	<0.5-10

Source: Encuity Research, LLC., Treatment Answers with Pain Panel, Year 2006-2011 Extracted January 2013. File: PDDA 2012-1682 Calcitonin by Form and Dx 1-8-13
* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Encuity Research, LLC., Treatment Answers™

Encuity Research, LLC., Treatment Answers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

PATTY A GREENE
01/29/2013

GRACE CHAI
01/31/2013
cleared by data vendors

LAURA A GOVERNALE
01/31/2013

7 Appendix C: Epidemiology Review

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Comparison of Multiple Studies or Literature Review

Date:	2-4-2013
Reviewer(s):	CDR David Moeny, MPH, R.Ph Division of Epidemiology II
Associate Director of Science	Rita Ouellet-Hellstrom, Ph.D. M.P.H. Division of Epidemiology II
Subject	Review of calcitonin meta-analysis for malignancy
Drug Name(s):	Salmon calcitonin
Application Type/Number:	Miacalcin Nasal Spray 020313, Miacalcin Injection 17808
Applicant/sponsor:	Novartis
OSE RCM #:	2012-1682
TSI #:	1191

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Calcitonin salmon (CS) is approved for use in Paget's Disease and for the treatment of postmenopausal osteoporosis. A safety signal for prostate cancer in the sponsor's oral product clinical trial prompted a review of malignancy data for all CS products by US and European regulators. The Division of Reproductive and Urologic Products (DRUP) received copies of a meta-analysis submitted to the oral product IND application and requested that the Division of Epidemiology review and comment on the meta-analysis, conduct a literature review, and make recommendations regarding warnings and labeling changes.

The sponsor's analyses were updated several times due to data corrections and regulator requests. We report the estimate contained in the most recent submission. Further, the sponsor's background package analysis includes an additional study not contained in the analyses submitted to the FDA.

The combined, meta-analytic odds ratio for all nasal CS versus placebo reported by the sponsor is 1.6 (95% CI 1.1-2.3) for all malignancies. For the combined oral and nasal analysis, the malignancy odds ratio is 1.4 (95% CI 1.1-1.7).

The combined odds ratios at each dosing level (100IU, 200IU, 400IU) were between 1.5 and 1.6. The time to event analyses also showed no clear relationship by dosing level; the mean time to event was 25.9 months for the 100 IU stratum, 17.7 months for 200 IU, and 23.9 months for 400 IU. An additional analysis of time to event by 6 month intervals showed that the time to event (all cancers) in the CS groups was similar to placebo for nasal calcitonin within the first 6 months, thereafter the incidence in the CS groups exceeded that of placebo.

The sponsor's meta-analysis study has a number of limitations which make concluding a causal relationship between CS and malignancy difficult. Incomplete study method documentation, multiple analysis and data corrections submitted by the sponsor, a failure to assess clinical heterogeneity or study quality, and high rates of early discontinuation and differential follow-up in the included studies present a challenge. While these analyses failed to provide evidence of a dose response, the results of each of these meta-analyses showed a consistent trend towards a possible increased cancer risk with CS treatment with point estimates around 1.4 and 1.6 in all analyses.

Although the results of the meta-analyses and each individual RCTs do not show statistically significant risk estimates, and despite the fact that the studies have limitations, the consistency towards an elevated risk among the included studies, and an increasing incidence rate difference over time supports the conclusion that calcitonin may be associated with a risk of malignancy. Whether this risk is causal, promotional, or a result of uncontrolled confounding cannot be determined with the existing information.

DEPI recommends the risk of malignancy be noted in the label for the nasal calcitonin products. If there is a need for calcitonin, use of the product should be limited to less than 6 months. DEPI further recommends that potential risk be communicated to prescribers and the public through an appropriate communication channel.

1 INTRODUCTION

Recently the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) announced its recommendation to remove the indication for postmenopausal osteoporosis for CS nasal spray. This decision was based on a safety signal observed for malignancy in oral trials, a meta-analysis of the sponsor's clinical trials, and the lack of demonstrated efficacy of calcitonin in the prevention of osteoporotic fractures. The Division of Reproductive and Urologic Products (DRUP) received copies of the sponsor's meta-analysis and is undertaking a review of the risks and benefits of CS as well.

DRUP requests that OPE/DEPI:

- Review and comment on the cancer findings of the meta-analyses of clinical trials investigating intranasal and oral calcitonin for various indications.
- Search and review the literature to identify additional epidemiological studies on cancer and calcitonin (any formulation).
- Comment on whether the weight of the evidence of the cancer risk with calcitonin warrants labeling revision or other risk mitigation strategy or strategies.
- Provide drug use data for calcitonin by formulation and indication

2 BACKGROUND

Calcitonin is a polypeptide hormone secreted by the parafollicular cells of the thyroid gland in mammals and by the ultimobranchial gland of birds and fish. It acts to reduce blood calcium opposing the effects of parathyroid hormone (PTH).
The approved product, calcitonin salmon (CS), is a synthetic polypeptide of 32 amino acids in the same linear sequence that is found in calcitonin of salmon origin, available in both injectable and intranasal spray (NS) product forms. CS (Miacalcin) was approved for marketing on July 3, 1986. Only the injectable product form carries labeling for use in Paget's Disease (for short term, early treatment of hypercalcemic emergencies when a rapid decrease in serum calcium is required.) The intranasal and injectable forms are both approved for the treatment of postmenopausal osteoporosis in females greater than 5 years post-menopause with low bone mass relative to healthy premenopausal females; when estrogen supplementation is not indicated.

The current product label for the nasal product (Miacalcin, Fortical- CS recombinant) includes references to animal carcinogenicity data; no human data is presented. The label states that an increased incidence of non-functioning pituitary adenomas was observed in 1-year rat toxicity studies conducted with exposures of approximately 130-160 times the human labeled dose. The label notes that these studies suggested that CS reduces "the latency period for development of the pituitary adenomas that do not produce hormones, probably through the perturbation of physiologic processes involved in the evolution of this commonly occurring endocrine lesion in the rat. Although administration of calcitonin-salmon reduces the latency period of the development of nonfunctional proliferative lesions in rats, it did not induce the hyperplastic/neoplastic process. "

A safety signal for prostate cancer in the sponsor's oral product clinical program prompted a review of all malignancy data for all CS products by US and European regulators. In response to requests from regulators, the sponsor conducted a meta-analysis of randomized controlledtrials to evaluate the risk of malignancy associated with the use of CS. The

Division of Reproductive and Urologic Products (DRUP) received copies of a meta-analysis undertaken by the sponsor to evaluate this malignancy risk. This analysis and subsequent revisions and clarifications requested by the CHMP were submitted to the FDA by the Sponsor for review.

On July 20, 2012, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a press release[1] stating that there is evidence that long term use of calcitonin containing products is associated with an increased risk of cancer. The CHMP recommended that the nasal CS product be withdrawn from the market. The EMA has not yet decided on whether to implement the CHMP recommendations.

This document provides an independent review of the sponsor's meta-analysis, an overall assessment of the studies included in the meta-analysis, the results of a literature search for published epidemiologic studies which assess the neoplasm risk in association with CS use, and recommendations for labeling changes as warranted.

List of Abbreviations

CS – Calcitonin Salmon
NS- Nasal Spray
EMA- European Medicines Agency
CHMP- Committee for Medicinal Products for Human Use
DEPI- Division of Epidemiology
DRUP- Division of Reproductive and Urologic Products
OR- Odds Ratio

3 REVIEW METHODS AND MATERIALS

This review provides an epidemiologic evaluation of the sponsor's meta-analysis, including evaluating the sponsor's compliance with the guidelines contained in the Quality of Reporting of Meta-Analysis (QUOROM) statement. Comments are provided regarding whether the current product label should be revised as a result of the meta-analysis results.

DEPI conducted an independent literature search in PubMed and Embase databases, using the search terms: calcitonin, malignancy, neoplasm, cancer.

The drug utilization data analyst will provide an independent review for calcitonin drug use to assess current use of the products and this data will only be briefly discussed here.

The following materials were reviewed

- Miacalcic® (synthetic salmon calcitonin) Ampoules and Nasal Spray
  Response to List of Questions Procedure Number: EMEA/H/A-1291
  Release date: 02 August 2011
- Miacalcic® Ampoules and Nasal Spray Synthetic Salmon Calcitonin, Article 31
  Response to List of Outstanding Issues, 23 March 2012
- Miacalcin® (calcitonin-salmon) NDA No. 17-808 and 20-313, Response to FDA Request, 12 October 2012

[1] *European Medicines Agency recommends limiting long-term use of calcitonin medicines*
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/public_health_alerts/2012/07/human_pha_detail_000065.jsp&mid=WC0b01ac058001d126

- Miacalcin® (calcitonin) NDA 020313/S-033, Response to FDA questions, 16 January 2013
- Miacalcic Nasal Spray and Oral Calcitonin, Response to LoOI Question 4: Dose response and treatment duration analysis

4 REVIEW RESULTS

4.1 DEPI LITERATURE SEARCH

An independent search of PubMed and Embase revealed no additional trials or epidemiologic studies examining the outcome of malignancy in association with the use of CS.

4.2 BRIEF SUMMARY OF SPONSOR META-ANALYSIS

The sponsor conducted its own literature search in Embase, PubMed, and its own internal records to identify studies for the meta-analysis. The sponsor searched for all randomized controlled trials, regardless of indication. The literature search did not identify any additional published studies as well, so the analysis includes 20 sponsor-funded randomized controlledtrials (RCT) only: 17 for the nasal formulation and 3 for the oral formulation. It should be noted that the Sponsor's background document includes an 18th nasal spray trial in their meta-analyses. Data from this trial were not available to FDA for substantive review and this trial is not incorporated into FDA's meta-analyses or our review of the company's meta-analyses.

The sponsor conducted separate analyses for the oral and the nasal formulations. A table summarizing the major similarities and differences among the included RCTs can be found in Appendix A of this document and brief summaries of the included trials are provided in Appendix D.

For the nasal formulations analysis, 13 of the 17 RCTs reported at least 1 patient with a malignancy. Of these 13 studies, four showed no elevated risk of malignancy, while the remainder reported point estimates above 1, ranging from 1.39 to 7.52. None of the individual study estimates were statistically significant, likely due to the small number of patients randomized. The overall OR for the meta-analysis that includes all RCTs reporting a malignancy was 1.6 (95% CI 1.1-2.3) when comparing the combined CS dose arms to placebo using the Peto method (the corresponding Peto estimate conducted prior to the identification of errors in the sponsor's malignancy count was 1.5 (95% CI 1.1-2.2). An alternate Mantel-Haenszel analysis that included all 17 studies found an odds ratio of 1.9 (1.3-2.8).

The oral formulation analysis included three trials. The meta-analytic risk estimate for the oral studies was calculated using the incidence rate ratio; the combined, all malignancy IRR was 1.3 (95% CI 1.0 – 1.7).

4.3 STUDIES INCLUDED IN THE META-ANALYSIS

To examine the risk of malignancy among users of CS, the Sponsor provided a separate meta-analysis for the nasal spray and oral calcitonin formulations.

The sponsor, in response to an FDA request, provided the original study reports for the 20 studies included in the meta-analyses. Of the 20 studies retrieved, 17 used the nasal spray formulation and three used the oral formulation (currently in IND status). Brief overviews

of the submitted study reports and DEPI comments are provided in the Appendices A and D. A summary of the major differences and similarities of the submitted studies follows.

Study Design

All studies included in the meta-analysis were double blind randomized controlled trials, with the exception of one open-label study (506) which compared calcitonin NS 50IU daily plus calcium supplementation to calcium supplementation alone.

Study Population and Geography

Subjects for the nasal studies were recruited from a total of 18 countries, primarily Europe but some included the US. Enrollment was limited to a single country for 15 studies; study CT320 enrolled patients from the US and the UK while 2402 included participants from 7 European countries. US participants were included in 4 single country nasal spray studies, and 1 multi-country nasal spray study. All 3 of the oral studies were multinational. US participants were included in oral studies C2302 and A2303. Country information for each of the studies is contained in the study summary table in the Appendix A.

The nasal studies were typically small; there were 8 studies which had calcitonin exposed groups numbering below 100. The largest nasal study was CT320, which randomized 844 patients to the calcitonin group. The oral (A2303, C2301, C2303) studies were larger, randomizing 2334, 585 or 521 calcitonin patients respectively.

Inclusion and exclusion criteria

Nearly all of the NS studies limited the study population to women who were either peri-menopausal or post-menopausal. Only two of the NS studies included men (numbers 311 and 312); these studies examined the use of calcitonin in steroid induced osteoporosis. Two of the three oral studies also included men, and evaluated use of calcitonin in osteoarthritis. Two NS studies, 522 and MIA-16, enrolled patients who were older, above 60 years of age.

Restrictions for malignancy, either prior to study entry, malignancy at baseline, or "diseases affecting bone metabolism including malignancy" were applied in 10 of the included nasal RCTs and all 3 of the oral RCTs. Other studies applied a restriction for presence of disease affecting bone metabolism (which may have included certain malignancies). In two of the nasal RCTs, no malignancy exclusion was applied. Study 320 excluded patients with an occurrence of malignancy within the previous 5 years, but did allow patients who had basal or squamous cell carcinoma at baseline.

Calcitonin exposure- dose and duration

The shortest NS study included in the analysis was study 005, which had a 12 month treatment period. Thirteen studies had a 24 month treatment period, 5 had a 36 month treatment period, and 1 study (study 320) had a 60 month treatment period. Daily NS treatment doses ranged from 50IU daily to 400 IU daily and most studies included multiple dose dependent treatment arms. Only 6 studies evaluated a single dose of calcitonin. In addition to a daily dosing schedule, study 514 included a 200IU 3 times weekly arm. Besides calcitonin, use of calcitonin plus calcium was utilized for studies 503 through 511. In study MIA-16, in addition to the CS and placebo groups, patients were randomized to two additional arms: nandrolone or nadrolone plus placebo. Nandrolone is an anabolic steroid that was being investigated for use in osteoporosis treatment. The sponsor excluded the nandrolone exposed arms in the meta-analysis.

The oral studies utilized a dose and duration of 0.8 mg once daily for 36 months (study A2303) or 0.8mg twice daily for24 months (C2301, C2302).

Most of the meta-analysis RCTs randomized patients to multiple dose arms. The single dose studies in the analysis included the nasal studies 2403, 503, 504, 506, 511, MIA16, and the oral study A2303. Of these studies, 2 were excluded from the primary Peto analysis due to the lack of malignancies.

Assessment of malignancy

For both the oral and nasal studies, a malignancy was captured as an adverse event among many others and was not a pre-specified safety endpoint for any of the included studies. The method of malignancy assessment was similar across all trials, consisting of periodic reporting at patient visits and via physical exams. The provided study reports do not document the exact AE reporting procedures used (e.g. were all events reported, or just those judged to be attributable to calcitonin treatment?)

4.4 META-ANALYSIS METHODS AND MATERIALS

To examine the risk of malignancy among users of CS, the Sponsor provided separate meta-analyses for the nasal spray and oral calcitonin formulations.

Study sources

The initial meta-analysis submission included only the studies using the nasal spray or ampoule formulations. After the initial submission of the nasal spray meta-analysis, the EMEA requested that the sponsor broaden the analysis to include studies for the oral products under development as well. All of the sponsor funded randomized controlled trials were searched. The sponsor also conducted a literature search using the terms (breast cancer and calcitonin) and (breast cancer and Miacalic) to determine if other published studies examining the risk of cancer were available.

No other published studies were identified for inclusion. The sponsor included 17 relevant nasal spray studies in the meta-analysis and 3 for oral products. Four of the nasal studies had no malignancies noted in either the placebo or the treatment groups; these studies were excluded from the primary Peto method analyses.

It should be noted that the Sponsor's background document includes an 18th nasal spray trial in their meta-analyses. Data from this trial were not available to FDA for substantive review and this trial is not incorporated into FDA's meta-analyses or our review of the company's meta-analyses. In this trial, the odds ratio for malignancy was 0.1.

Outcomes and Covariates

The EMEA requested additional analyses examining duration of treatment, the sponsor included the variables study, and possibly sex as covariates for the meta-analytic odds ratio. No other meta-analytic covariates, such as study quality, were included in the meta-analysis. The sponsor also provided this analysis to the FDA.

Analysis

The sponsor did not provide the final study protocol for the meta-analyses as requested by the FDA. Instead, they provided an analytical plan for the oral studies, and indicated that the methods used for the nasal spray analysis were similar to that of the oral studies.

For the nasal spray analysis, the sponsor calculated odds ratios for any malignancy in the primary analysis. The combined, meta-analytic odds for malignancy was obtained using the Peto method. Using this method, studies with no malignancy event in either the calcitonin or control groups were excluded. The sponsor also conducted an alternative Mantel-Haenszel analysis which included the zero event studies. The combined meta-analysis results were stratified by study duration, age group, and cumulative dose. Statistical heterogeneity was evaluated for all malignancies combined, and for individual malignancies using the Cochran's Q test and the I-square statistic. Dose-specific analyses were completed as a subsequent analysis in response to a request from the CHMP. For the oral analysis, absolute and relative risks per study were calculated using standard methods with SAS PROC FREQ, along with asymptotic 95% confidence intervals. This analysis used incidence rates for malignancies and the associated 95% confidence intervals, calculated using Poisson regression with a log link.

The numerator for the incidence rate includes the number of patients who experienced at least one malignancy event and the denominator is the total exposure of patients until first occurrence of a malignancy event or censorship, measured in years. To prevent the miss-attribution of un-exposed time, in cases where an event occurred after the last dosing, only the time from first day until last day of dosing was considered for calculation of the denominator.

Although the statistical analysis plan stated that for the oral studies, the combined meta-analytic estimates would be obtained by adding study as a covariate (i.e., a fixed effects model without interaction), and patient sex as long as it did not prevent model fit (among the oral studies, study A2303 included only females), the variables included in the final analysis are unknown. The sponsor did not provide complete documentation for the methods employed. Risk estimates were obtained using Poisson regression with study as a fixed effect.

4.5 STUDY RESULTS

The sponsor presents 2 forest plots, one for nasal calcitonin studies only; the other includes the oral studies in addition to those for the nasal spray product as well.

The combined, meta-analytic odds ratio for all nasal calcitonin versus placebo is 1.6 (95% CI 1.1-2.3) for all malignancies (figure 3.1a), below). For the combined oral and nasal analysis, the combined odds ratio is 1.4 (95% CI 1.1-1.7).

Using the Peto method, and again excluding RCTs with no reported malignancy, the sponsor calculated the combined odds ratios at each dosing level (100IU, 200IU, 400IU) for studies that reported a malignancy; the estimates were 1.5 (95% CI 0.9-2.7), 1.6 (95% CI 1.0 – 2.7), and 1.5 (95% CI 0.9-2.5) respectively (Table 1, below). The sponsor's analysis failed to demonstrate a dose-response relationship. . Forest plots for these analyses are provided in Appendix B of this document.

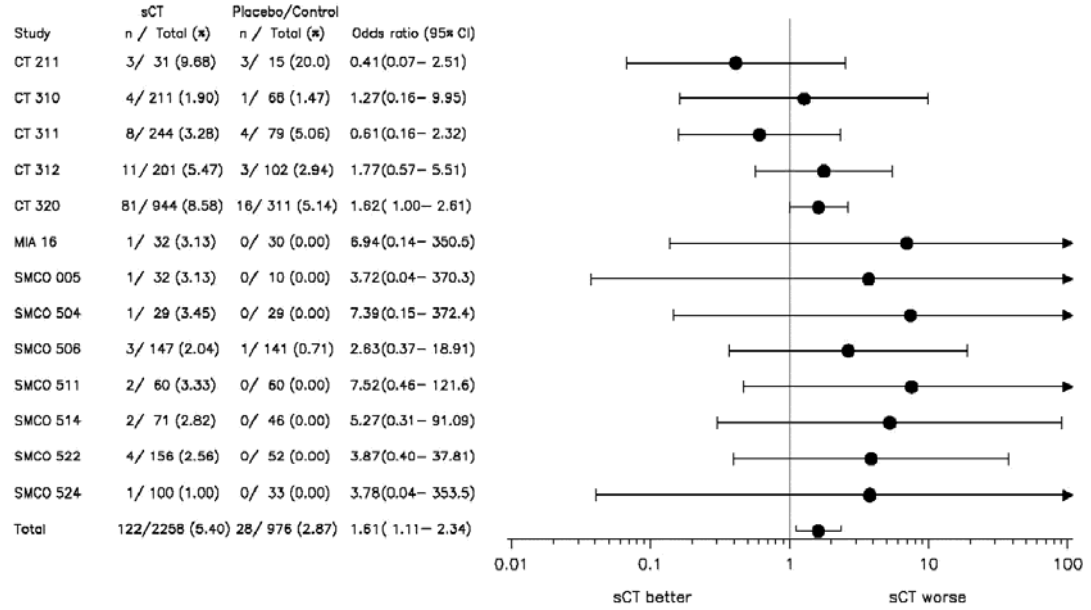
Table 1. Incidences and odds ratio for any malignancy, nasal spray by dose level vs. placebo

	# studies	Calcitonin cases/subjects	Placebo cases/subjects	Odds Ratio*	95% CI
100 IU	4	32/530	21/518	1.5	0.9-2.7
200 IU	9	44/721	27/716	1.6	1.0-2.7
400 IU	6	40/605	27/605	1.5	0.9-2.5
*Odds ratio obtained by Peto method. Only includes studies with at least one event in either treatment group. Source: figures 3.3a, 3.3b, 3.3c, Sponsor submission, June 2012 (provided in Appendix B)					

For the separate analysis of the oral studies, the combined malignancy rate ratio is 1.3 (95% CI 1.0 – 1.7).

In response to a CHMP request, the sponsor provided an analysis and forest plot for the nasal and oral products combined. Although FDA agrees with the sponsor that the oral and nasal spray trials are best analyzed separately, the malignancy odds ratio for nasal and oral products combined is 1.4 (95% CI 1.1-1.7 (Figure 3.1b, below). Including these studies in the forest plot also gives a visual representation to the reader that the oral trial results are somewhat consistent with those of the NS trials.

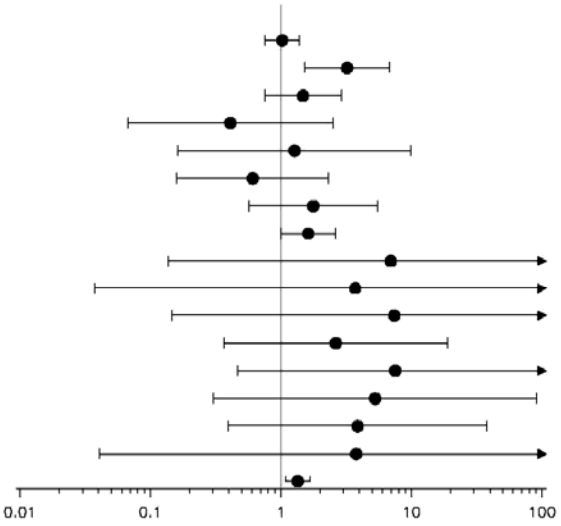
Figure 3.1a (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray calcitonin only



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.
/report/pgm_saf/new_metafigs.sas 30MAY12:19:10 Final Version

Figure 3.1b (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal and Oral calcitonin

Study	sCT n / Total (%)	Placebo/Control n / Total (%)	Odds ratio (95% CI)
A2303	89/2334 (3.81)	87/2331 (3.73)	1.02(0.76– 1.38)
C2301	22/ 585 (3.76)	6/ 584 (1.03)	3.22(1.52– 6.81)
C2302	21/ 520 (4.04)	14/ 508 (2.76)	1.48(0.75– 2.90)
CT 211	3/ 31 (9.68)	3/ 15 (20.0)	0.41(0.07– 2.51)
CT 310	4/ 211 (1.90)	1/ 68 (1.47)	1.27(0.16– 9.95)
CT 311	8/ 244 (3.28)	4/ 79 (5.06)	0.61(0.16– 2.32)
CT 312	11/ 201 (5.47)	3/ 102 (2.94)	1.77(0.57– 5.51)
CT 320	81/ 944 (8.58)	16/ 311 (5.14)	1.62(1.00– 2.61)
MIA 16	1/ 32 (3.13)	0/ 30 (0.00)	6.94(0.14– 350.5)
SMCO 005	1/ 32 (3.13)	0/ 10 (0.00)	3.72(0.04– 370.3)
SMCO 504	1/ 29 (3.45)	0/ 29 (0.00)	7.39(0.15– 372.4)
SMCO 506	3/ 147 (2.04)	1/ 141 (0.71)	2.63(0.37– 18.91)
SMCO 511	2/ 60 (3.33)	0/ 60 (0.00)	7.52(0.46– 121.6)
SMCO 514	2/ 71 (2.82)	0/ 46 (0.00)	5.27(0.31– 91.09)
SMCO 522	4/ 156 (2.56)	0/ 52 (0.00)	3.87(0.40– 37.81)
SMCO 524	1/ 100 (1.00)	0/ 33 (0.00)	3.78(0.04– 353.5)
Total	254/5697 (4.46)	135/4399 (3.07)	1.35(1.09– 1.66)



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.
A2303, C2301, C2302 are oral calcitonin studies.
/report/pgm_saf/new_metafigs.sas 30MAY12:19:10 Final Version

Heterogeneity

The sponsor conducted statistical heterogeneity tests to determine the appropriateness of combining the studies in a meta-analysis. The FDA statistical review discusses the sponsor's heterogeneity testing in detail. The sponsor did not present a clinical heterogeneity assessment.

Time to event and duration of treatment

Two time-to-event analyses were conducted by nasal dose level and by treatment (oral or nasal). The nasal dose level time to event analysis showed no clear relationship by dosing level; the longest median time to event of 23.7 months occurred in the 100 IU stratum, with time to event in the 200 IU group of 13.7 months, and in the 400 IU of 18.0 months. The 25IU and 50IU strata included only 3 RCT arms (n=3 for each dose); the median time to event was 25.6 and 11.0 months, respectively. Time to malignancy event by treatment was assessed using Poisson meta-analysis (Table 2), accounting for total exposure (the sum of exposures from all patients in a treatment group rather than the number of patients). The median time to event for the nasal studies was 16.8 months for both CS and placebo; the median for the oral studies was 16.2 for CS and 16.9 months for placebo.

Table 2. Time to event (months) by treatment (Sponsor table 3-1, Dose response and Treatment Duration Analysis)

	Nasal*		Oral**	
	Calcitonin	Placebo	Calcitonin	Placebo
N	117.0	25.0	130.0	107.0
Mean	21.8	22.4	17.1	17.3
Median	16.8	16.8	16.2	16.9
Minimum	0.03	0.0	0.0	0.0
Maximum	60.3	60.0	36.3	38.6
For multiple malignancies within a patient, the first occurrence of malignancy is considered				
*Eight missing time to event (5 calcitonin, 3 placebo) for nasal trials				
*Two elevated PSA cases without time to event information in calcitonin group				

An additional breakdown for time to event is presented in Appendix C (Sponsor table 3-2) providing counts of completers and numbers of malignancies reported at 6 month intervals. At 6 months, the proportion of malignancies in the CS and placebo groups was similar; for the nasal studies the difference was 0.9% and 0.8%, for treatment and placebo respectively and for the oral studies the difference was 0.7% and 0.5% respectively. As time progressed, the incidence rates in CS and placebo groups begin to diverge, with a maximum difference in malignancy incidence occurring at 36 months while the proportion of patients retained in the calcitonin and placebo groups remained similar. The 36 month incidence rates for the nasal studies were 3.2% in the CS group and 1.2% in the placebo group; for the oral analysis, the 36 month difference was 8.9% and 7.4% for the CS and placebo groups respectively. Consequently, the risk for malignancy was seen between 6 and 12 months of use.

Adjustment for exposure

A Poisson exposure-adjusted risk ratio was calculated for nasal calcitonin and for nasal and oral calcitonin combined. The sponsor indicated that this analysis used the sum of exposure time for patients instead of the number of patients, but does not provide complete documentation for how these estimates were obtained or which, if any, covariates were included. The OR for the nasal studies for CS vs. placebo was 1.6 (95% CI 1.1 – 2.5) and the OR for the combined oral and nasal studies was 1.4 (95% CI 1.1-1.8)[10].

5 DISCUSSION

The meta-analysis, as submitted to the FDA, has a number of limitations which affect its ability to assess the risk of cancer associated with calcitonin use. Among the issues noted are:

1) Evaluation of the statistical but not the clinical heterogeneity of included studies,
2) The failure to maintain the randomization of the source studies due to pooling CS treatment groups (doses across) compared to one placebo group
3) Failure to provide a quality assessment of the included studies, and
4) Inadequate documentation for the methods used in the analysis.

5.1 HETEROGENEITY

A significant concern when interpreting the results of a meta-analysis is the similarity of the studies, both from a qualitative (clinical) perspective as well as from the quantitative (statistical) perspective. In this meta-analysis, the sponsor evaluated statistical heterogeneity, but did not evaluate clinical heterogeneity to any significant degree. Statistical heterogeneity is addressed in depth in the FDA statistical review and will not be further discussed here.

Clinical heterogeneity seeks to determine the qualitative similarity of the included studies such as study design, inclusion or exclusion criteria, source populations, primary outcomes of interest, assessment of adverse events, or other characteristics contributing to differences between the individual point estimates. In the nasal analysis, the trial designs were similar; most were small, single center trials in post-menopausal women and all but one were randomized controlledtrials comparing CS treatment to placebo. However, differences in the study populations were noted. Two studies included men (311 and 312); these studies were undertaken to evaluate the treatment of osteoporosis induced by corticosteroids. Another outlier, with respect to heterogeneity, is study 2402 in which osteoporosis was not a requirement for inclusion (in 2402, no malignancies were reported in either the calcitonin or the placebo groups, so this study was not included in the primary analysis). Study 320 had more lenient exclusion criteria for malignancy when compared to the other studies in that they allowed enrollment of patients with basal or squamous cell carcinoma. This, however, is not expected to bias the estimate of risk because patients and their risk of cancer were likely randomized. Finally, the primary objectives for the studies differed. While the majority of studies examined some aspect of the calcitonin efficacy for treatment or prevention of peri-menopausal or post-menopausal osteoporosis, 1 study's objective was to evaluate the prevention of pain associated with forearm fracture, and 2 studies evaluated glucocorticoid induced osteoporosis. While differences among the included studies do exist, they do not appear to be significant enough to conclude that there was a substantial clinical heterogeneity problem.

The sponsor also did not evaluate clinical heterogeneity for the oral studies. For the oral studies, 2 examined the prevention of knee osteoarthritis and enrolled both men and women, and 1 for prevention of postmenopausal osteoporosis which enrolled only women.

5.2 EXPOSURE: THE DOSE RESPONSE RELATIONSHIP

The sponsor conducted a secondary meta-analysis evaluating the risk of malignancy by dose levels. Their analysis fails to demonstrate a dose-response relationship. The individual point estimates, while not statistically significant due to the loss of sample size, are quite similar to the statistically significant overall combined estimate of 1.6. The dose-response analysis however, only includes studies reporting malignancies. A risk difference analysis that included all studies conducted by FDA's Division of Biostatistics show similar risk estimates. The lack of a dose-response does not necessarily rule out causation as the threshold for a response may be below the dose levels tested for this safety signal. Nonetheless, the sponsor also provides an analysis of exposure duration or time to event assessed as incidence of malignancy in 6 month intervals. The early observance of an increased incidence cancer rate in CS treated groups with NS or oral products raised questions about cancer promotion activity of calcitonin, although this idea is not readily supported by animal data other than an increase in pituitary tumors. Nonetheless, the consistent and possibly widening difference in these rates over time while on treatment with the calcitonin and placebo groups argues for the persistency of a consistent effect.

5.3 QUALITY OF INCLUDED RCTS

Assessment of study quality in meta-analysis is a controversial issue. While researchers dispute whether it is appropriate to adjust the meta-analytic estimate for study quality due to issues of subjectivity in quality assessments, a discussion of the quality of the included studies and perhaps a sensitivity analysis is often more appropriate. However, the sponsor provided neither. Several biases may have existed in the included trials, including attrition bias and detection bias. Attrition bias may have been present in study 311, for example. Since 41% of calcitonin patients and 32% of placebo patients discontinued early; this inability to assess events in the discontinued patients may have contributed to the lower cancer risk estimate reported in this study. High attrition in both study groups would have decreased the power of the meta-analysis to generate statistically significant risk estimates and may have biased the estimates in an unknown direction.

While it was more common to have higher dropout rates in the calcitonin groups, 3 studies had higher dropout rates in the placebo arm than at least 1 of the calcitonin treatment arms. Study 320 had dropouts occurring earlier in the 200 and 400IU calcitonin treatment groups. Pooling CS treatment groups also exacerbates the effect of early dropouts in the CS treatment groups. If differential dropout rates occur in treatment groups and if these patients were more likely to develop cancer, the estimate excluding their experience would have been biased towards the null, while the converse would be true for studies with greater placebo dropout. Ultimately, however, it is impossible to determine the extent and direction of this particular bias and the impact on the meta-analysis is unclear.

5.4 INADEQUATE DOCUMENTATION AND META-ANALYSIS QUALITY

Detection bias may have had a role in studies 511 and 514 where the investigators did not provide adequate documentation of adverse event reporting.

The sponsor provided the CHMP and the FDA with updated reports to correct errors identified in the analyses. For example, in the dosing level analysis the FDA identified two studies which were not included in the 200IU forest plot. The reason for the omission is not known, but the sponsor subsequently included the trials and submitted updated estimates to the FDA. However, FDA later noted that study MIA-16, which utilized dosing of 50IU twice daily was not included in the 100IU forest plot, despite 1 malignancy in the CS group; due to time constraints, an updated analysis was not received from the sponsor. While these changes did not substantially affect the risk estimates, they do raise questions about the documented quality of the studies included in the meta-analysis.

Several formal meta-analysis guidelines and checklists exist which are intended to assure the quality of meta-analyses. In addition to providing investigators guidance, checklists such as the QUORUM guidelines also provide reviewers of meta-analyses a convenient study-quality assessment tool. We utilized the QUORUM checklist to evaluate the sponsor study, recognizing that the guidelines are written with a goal of publication in peer reviewed journals, that the sponsor was not requested to prepare the meta-analysis report in a standard format, and that the nature of the question and answer process with regulatory agencies contributed to non-compliance with these guidelines. The most troubling issue of QUORUM compliance for this analysis is the lack of documentation of study methods, other areas of non-compliance with QUORUM include:

- No abstract is presented
- Study validity and quality was not assessed
- Process for data abstraction was not presented

    - The sponsor indicates that they rigorously checked the counts of malignancies obtained from clinical study reports. Since the malignancy counts and the resultant odds ratio differed between the original analysis presented on August 2011 and the one presented on June 2012, perhaps a well-documented, pre-defined data abstraction method would have increased the initial study quality.
- A meta-analysis trial flow is not presented
- A description of the methods which were used in the study was not presented.
    - The sponsor did provide an analysis plan for the oral studies, but not for the nasal studies. However, there is scant documentation to the methods which were actually used in the meta-analysis. For example, the plan makes references to procedures "if appropriate" but it is unclear whether these procedures were implemented or attempted (e.g. inclusion of patient sex in the statistical models).

Among the nasal studies, study 320 was the largest and longest. As the sponsor notes, this study drives the risk estimate since it also contributes the largest number of malignancy cases, and a substantial portion of these cancer cases are basal cell carcinoma. In the initial submission, the sponsor conducted an analysis which excluded this study. The combined OR when study 320 is included is1.52 whereas when study 320 is excluded, the OR is 1.59. It should be noted that this analysis was conducted prior to the sponsor's discovery that there was a discrepancy in the number of events. The analysis was not repeated in the final, corrected submission.

Nonetheless, despite problems with providing reliable meta-analyses, there is a consistency in the occurrence of malignancy in the CS treatment arms of most (13 out of 17) studies. The primary analysis included only studies in which a malignancy event occurred in either the treatment or placebo group. In all 13 of these studies, at least one event occurred in one of the CS treatment arms, while only 6 of the studies had an event occurring only in the placebo arm. However, there were 4 studies with no reported malignancy in either arm and these need to be considered in the final analysis.

Some studies have shown that bisphosphonates may lower the risk for breast cancer as well as osteoporosis[2][3]. The duration of this effect is not known. Although the patients recruited for the RCTs and included in the meta-analysis did not use CS prior to randomization, since calcitonin may be used as a second or third line agent, it is possible that some women could have used first line bisphosphonates prior to the start of the baseline period. Studies that include older participants would more likely include some with prior bisphosphonate use, potentially decreasing the precision risk estimate, but not biasing the study if randomization was adequate.

[2] P A Newcomb, *Bisphosphonates for osteoporosis treatment are associated with reduced breast cancer risk, British Journal of Cancer* (2010) **102**, 799–802.

[3] G Rennert, *Use of Bisphosphonates and Risk of Postmenopausal Breast Cancer*, *JCO* August 1, 2010 vol. 28 no. 22 3577-3581

5.5 SUMMARY OF DRUG UTILIZATION

The Drug Use Data Analyst completed a separate drug utilization review[4]. In summary, CS represents approximately 5% of the osteoporosis market. The use, in terms of patients who received a prescription from a retail pharmacy and in terms of wholesale distribution has decreased by roughly 50% between 2006 and 2011. In year 2011, approximately 205,000 patients received a calcitonin product through a retail pharmacy. Approximately 80% of prescription dispensed represented continuing users.

The declining use of calcitonin in the US is an indicator that additional epidemiologic studies examining the risk of malignancy in association with the use of CS will be difficult to complete with sufficient power in the US. This is especially true since the overall size will be limited by the need to validate outcomes through chart review or via cancer registries. Use of either of these validation methods will require the use of specific datasets which will likely result in US cohorts that are a fraction of the size of the total US population of bisphosphonate users.

6 CONCLUSIONS

The sponsor's meta-analysis study presents a number of limitations that makes a causal relationship determination between calcitonin and malignancy difficult. These limitations include incomplete documentation of study methods, high rates of early discontinuation in the treatment and placebo arms, and differential follow-up in the included studies. Certainly, the reported combined odds ratio of 1.6 is within the range which raises questions of possible uncontrolled confounding. The sponsor also conducted a series of dose and duration of exposure analyses in an attempt to characterize the increased risk. These analyses failed to provide statistically significant evidence of a dose response relationship. Nonetheless, consistent reports of malignancy in 13 of 17 RCTs, mostly in the CS treatment arms cannot be ignored. All the 13 studies that were included in the meta-analysis had malignancy events in the CS treated group while 7 of the placebo groups were malignancy free, demonstrating a consistent increase in risk among calcitonin users. These reports resulted in point estimates which were consistently elevated to similar levels of between 1.4 and 1.5 for the CS treatment arm compared to placebo.

The potential for an increased risk with calcitonin salmon therapy cannot be ignored. The observance of an increased cancer incidence rate in calcitonin salmon treated groups raised early questions about cancer promotion activity of calcitonin. This idea was not supported by animal data other than an increase in pituitary tumors in rats.

Nonetheless, the consistent and widening difference in these cancer incidence rates over time among the calcitonin treated versus placebo groups argues for the persistency of a consistent effect.

Finally, while the methodological issues discussed in the biostatistics review emphasize the limits for interpretability of the combined estimates and the credibility of the results of the meta-analysis, the consistent trend towards an increased cancer risk among CS treated patients compared to placebo in the RCT studies suggest a real effect.

[4] Patty Greene, *Calcitonin-Containing Products Drug Utilization Review*, January 31, 2013, RCM 2012-1682

At this time, a cancer risk associated with calcitonin use appears plausible, and certainly cannot be ruled out with the available data. Whether this risk is causal, promotional, the result of uncontrolled confounding, or a failure of randomization cannot be determined with the existing information.

7 RECOMMENDATIONS

DEPI recommends that the potential increase in the risk of malignancy be noted in the label for the nasal calcitonin products. Because use of the product is declining over time, additional studies to characterize the cancer risk cannot be done easily in the US. It is unknown if use is declining in other countries as well. If there is a need for calcitonin, the data reviewed suggest that use of the product should be limited to less than 6 months. Finally, the potential risk should be communicated to prescribers and the public through an appropriate communication channel.

APPENDIX A – Randomized ControlledTrial Summary Table

Table 1. Key features of studies included in the meta-analysis, odds ratio for malignancy occurrence and 95% confidence intervals

Trial ID	Odds Ratio	95% Confidence Interval	Indication Evaluated **	Duration of Treatment Period	Patients randomized to calcitonin / control	Calcitonin Treatment	Population geographic location as US or other (total # of countries included)	Malignancy exclusion	DEPI comment
Nasal Studies									
005	3.8	(0.1-103.5)	PMO	12 months	32/10	50, 100, 200IU daily	Other (1)	Current malignancy	• Shortest duration study in the analysis • BMI statistically different by treatment arm
211	0.9	(0.2-5.4)	PMO	24 months	31/15	200, 400IU daily	US (1)	History of carcinoma within the previous 2 years	Higher placebo dropout (27% placebo, 13% CS)
2402 *			Strength & pain post arm fracture	24 months	149/148	200IU daily	Other (7)	History of carcinoma within the previous 2 years	Higher placebo dropout (20% placebo, 11% CS,)
310	1.0	(0.1-9.6)	PMO	24 months	211/68	100, 200, 400IU daily	US (1)	History of malignant disease within 5 years (or evidence of recurrence)	Higher placebo dropout (31% placebo, 26% CS)
311	0.51	(0.1-2.1)	Steroid induced osteoporosis	36 months	244/79	100, 200, 400IU daily	US (1)	None	High dropout, especially in CS group (32% plac,41% CS)

312	1.39	(0.5-4.2)	Steroid induced osteoporosis	36 months	201/102	200IU or 400IU daily	US (1)	None	High dropout (34% placebo, 36% CS)
320	1.47	(0.9-2.4)	PMO	60 months	844/311	100, 200, 400IU daily	US (2)	Within 5 yr, evidence of recurrence except skin CA	No exclusion for malignancy, ~59% dropout all groups
503*			PMO	24 months	26/26	100IU daily	Other (1)	Current malignancy	
504	7.39	(0.2-372.4)	PMO	24 months	29/29	50IU 2x daily	Other (1)	Current malignancy	
506	2.63	(0.4-18.9)	Bone loss in early PMO	36 months	147/141	50 IU daily	Other (1)	Current malignancy	Investigators not blinded to exposure
511	7.52	(0.5-121.6)	Bone loss in peri-menopause	36 months	60/60	100IU daily	Other (1)	Disease affecting bone metabolism e.g. malignancy	AE assessment poorly documented
514	5.27	(0.3-91.1)	Early & established PMO	24 months	117/78	200IU daily or 3x/wk	Other (1)	Disease affecting bone metabolism e.g. malignancy	• AE assessment poorly documented, • No malignancy exclusion
517*			PMO	24 months	168/83	50, 200 IU daily	Other (1)	Clinically relevant neoplastic disease	High dropout (49% placebo, 43% calc)
520*			Prevention of PMO	24 months	65/32	100, 200IU daily	Other (1)	Recent or current malignancy	
522	3.87	(0.4-37.8)	Established PMO in elderly	24 months	174/40	50, 100, 200IU daily	Other (1)	Current malignancy	

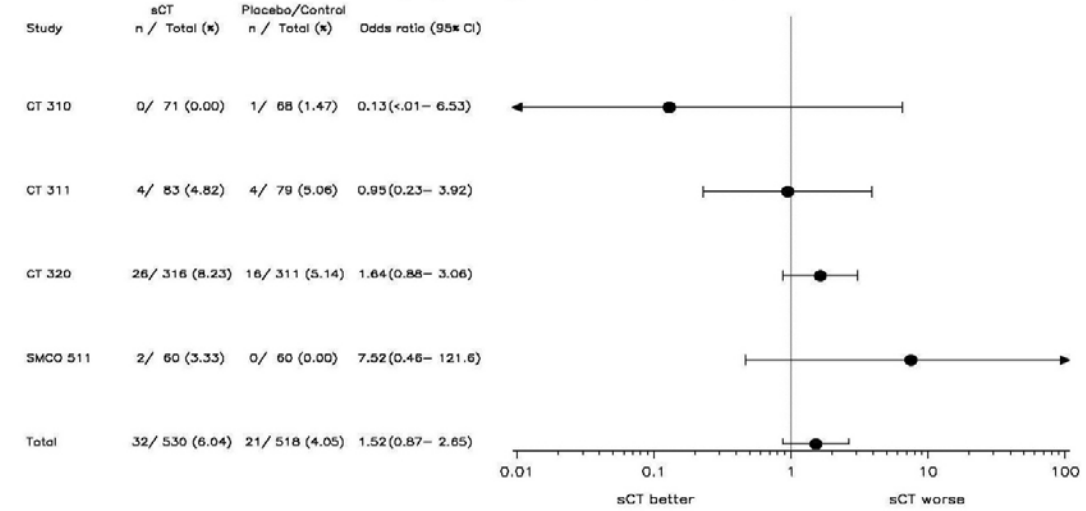
524	3.77	(0.0-356.4)	PMO	24 months	67/23	100, 200, 400IU daily		Current malignancy	
MIA-16	6.94	(0.1-350.5)	PMO	24 mo	63/60	400IU daily	Other (1)	Current malignancy	• Patients over age 60 enrolled. • AE assessment poorly documented
ORAL Studies									
C2301	3.2	1.5-6.8	Osteo-arithritis	24 mo	585/584	oral 0.8 mg 2x daily	Other (6)	Cancer within last 5-9 yr except BCC, cervical/breast in situ	Full study report not available.
C2302	1.5	0.8-2.9	PMO	24 mo	521/509	oral 0.8 mg 2x daily	Other (8)	Cancer within last 5 yr except basal cell or cervical, breast carcinoma in situ	Full study report not available
A2303	1.0	0.8-1.4	Osteo-arithritis	36 mo	2334/2331	oral 0.8 mg daily	US (9)	Cancer within last 5 yr except basal cell or cervical, breast carcinoma in situ	Full study report not available

* no malignancies were noted in these studies for either the treatment or control groups
** PMO=Post-Menopausal Osteoporosis

Appendix B – Forest Plots for Dose Meta-Analyses

CSMC021– Safety Analysis 2012

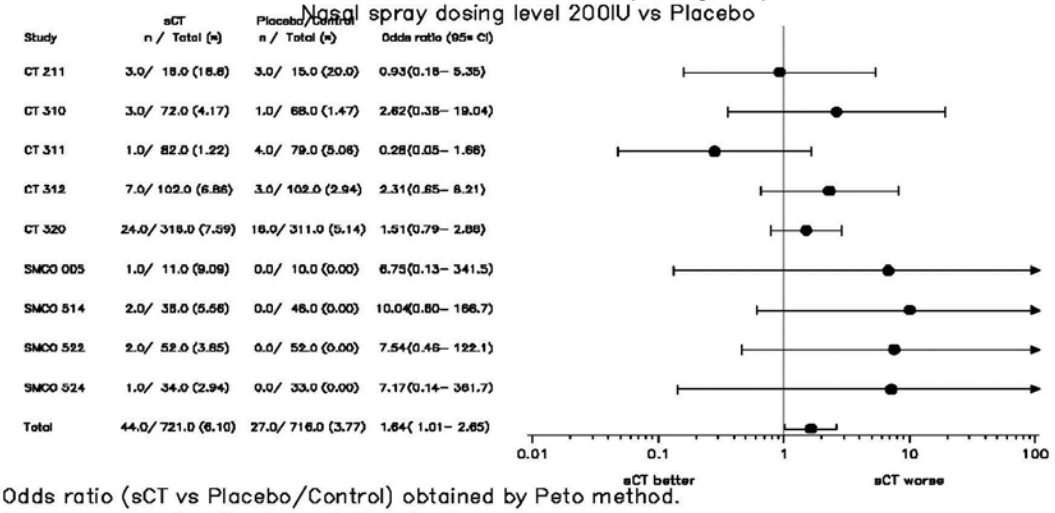
Figure 3.3a (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 100IU vs Placebo



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.
/report/pgm_saf/new_metafigs.sas 30MAY12:19:10 Final Version

CSMC021– Safety Analysis 2012

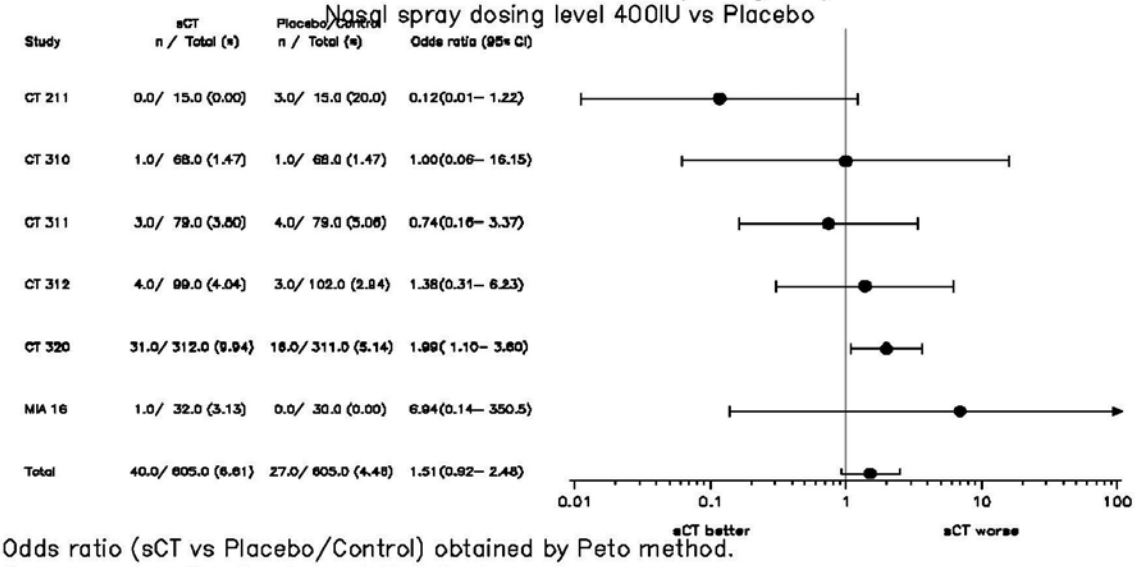
Figure 3.3b1 (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 200IU vs Placebo



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.
/report/pgm_saf/metafigs_dose.sas/main/1 17JAN13:19:49 Final Version

CSMC021– Safety Analysis 2012

Figure 3.3c1 (Page 1 of 1)
Incidences and odds ratio for any malignancy
Nasal spray dosing level 400IU vs Placebo



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.
/report/pgm=saf/metafigs_dose.sas99/main/1 17JAN13:19:49 Final Version

Appendix C – Completers and incidence for first malignancy by time period

Sponsor Table 3-2 Completers and incidence of first malignancy by time period

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

-For multiple malignancies within a patient, only the first occurred malignancy is considered.
-Eight missing time to event (5 for calcitonin group, 3 for placebo group) for nasal calcitonin trials.
-Two elevated PSA cases without time to event information (both in calcitonin group).
-Percentage is calculated based on the completers at each period.
* including two patients with time-to-event >36 months.
** including four patients with time-to-event >36 months.
(#) the data by time period is not available for study MIA16.
(^) the number of patients remaining in the study at 182 (6 months), 365 (12 months), 547 (18 months), 730 (24 months), 1095 (36 months) days is used.

Appendix D QUORUM checklist[5]

Heading	Subheading	Descriptor	Reported? (Y/N)	Page Number
Title		Identify the report as a systematic review		
Abstract		Use a structured format		
	Objectives	The clinical question explicitly		
	Data sources	The databases (ie, list) and other information sources		
	Review methods	The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses		
	Conclusion	The main results		
		Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review		
Methods	Searching	The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design		
	Validity assessment	The criteria and process used (eg, masked conditions, quality assessment, and their findings)		
	Data abstraction	The process or processes used (eg, completed independently, in duplicate)		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed		
	Quantitative data synthesis	The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias		
Results	Trial flow	Provide a meta-analysis profile summarising trial flow (see figure)		
	Study characteristics	Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)		
	Quantative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2X2 tables of counts, means and SDs, proportions)		
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda		

[5] Quality of reporting of meta-analyses, The Lancet, vol 354, November 27, 1999

Appendix D –Text Summaries of studies included in the meta-analysis

Nasal spray studies

Study 005-

Examined the effect of CS on bone density after 12 months treatment at doses of 50, 100 and 200 IU daily. The study was a DB-RCT with 4 parallel groups, enrolled July 1986 – 1987. The study duration was 12 months. 36 healthy, post-menopausal (>=12 months) women age 45-72 years with established osteoporosis as shown by previous Colles' fracture were enrolled and randomized to placebo (10 patients) and 4 treatment groups: 50 IU/day (11 patients), 100 IU/day (10 patients), 200 IU (11 patients).

Assessment of malignancy

For the assessment of side effects, the patients underwent a full physical exam at entry and at months 3 and 12. All patients enrolled were subject to the safety analysis. Malignancy outcomes were assessed via investigator report of adverse events. At least one post treatment follow-up was attempted for patients discontinuing treatment. All patients randomized, with a baseline evaluation and who received a study drug were included in safety assessment.

Results

42 patients enrolled, 32 completed as planned, 10 patients left prematurely (2 from placebo, 50 IU, 100 IU groups, and 4 from the 200 IU) group. Calcitonin groups had a statistically higher baseline BMI, compared to placebo. They were similar with respect to age, and height. There was one case of malignant pancreatic neoplasm in the 200 IU arm in a patient who reported abdominal pain and had an enlarged liver noted at the baseline exam. The relative risk of neoplasm in the calcitonin group compared to the control group was 3.724 (95% CI 0.004-370.5).

DEPI Reviewer comments

This is a small, short term study. There was one malignancy in the treatment arm, and no malignancies in the placebo arm. Although there were differential dropout rates by treatment arm, the investigators obtained reasons for discontinuation and these reasons were included in the safety outcome assessment. BMI values were statistically different by treatment arm, indicating a potential randomization failure.

Study 504

Examined whether intranasal salmon calcitonin is effective compared to placebo in preventing bone loss in early post-menopausal women following 2 years of intranasal application of 100 IU/day CS (given as 50 IU twice daily); the secondary objective was to examine the long term safety of CS. The study was a DB-RCT, enrolling 58 post-menopausal women who had a last mense from 1-5 years

previously. The enrollment began Sept 1986 and ended March 1989. Exclusion Criteria included malignancy of any kind. Patients were randomized to 2 years of 100 IU/day of calcitonin or to placebo.

Assessment of malignancy

Subjects received a full physical exam at baseline, month 12 and month 24. Adverse events were assessed every 3 months. The investigators attempted to obtain at least one post discontinuation follow-up visit for patients who left the study early.

Results

At baseline, the calcitonin subjects were slightly younger (mean age was 53.7 years in placebo, 54.6 in calcitonin), the groups were similar with regard to BMI and smoking status. There were no statistically significant differences in baseline demographics. By study end, 11 placebo and 12 CS patients has withdrawn; 2 patients were lost to follow up in the placebo group, and 1 in the CS group. Withdrawals due to an adverse even were more common in the CS group (7 versus 4). There was one case of breast cancer in the CS group, and no cases in the placebo group. The relative risk of neoplasm in the calcitonin group compared to the control group was 7.39 (95% CI 0.15-372.4).

DEPI Reviewer comments

This is a relatively long term study (2 years). At baseline, the patients in this study were well matched for cancer risk factors. The investigators attempted to follow up with patients who left the study prematurely, minimizing the effect of differential loss to follow up. However, 2 placebo patients were lost, compared to one CS patient.

Study 506

A Prospective, randomized, open, controlled, parallel group study. Evaluating NS calcitonin 50 IU 5 times weekly is effective in preventing bone loss over a 3 year period. Enrollment of post-menopausal women with last menses <36 months prior occurred Dec 1985 – March 1991 and 147 CS, 141 controlls entered study. Exclusions included any clinically relevant neoplastic disease.

Assessment of malignancy

Subjects received a full physical examination at baseline, then every 6 months thereafter. Adverse events were assessed at each examination, and adverse events resulting in study discontinuation were recorded. For subjects lost to follow-up, no attempts were made at a safety assessment.

Results

51 controls and 53 CS subjects withdrew from the study. Withdrawals due to adverse events numbered 14 for control, 28 for CS. Total exposure years were similar (372 versus 372.3). The study groups were similar at baseline with respect to age, bmi, height, weight,

There was one case of breast cancer recurrence in the control arm after 3.5 months of study time. The CS group had 3 malignancy events (ovarian tumour at 24 months, intracranial tumor at 6.5 months, and breast cancer recurrence at 25.6 months). The

relative risk of neoplasm in the calcitonin group compared to the control group was 2.63 (95% CI 0.37-18.91).

DEPI Reviewer comments

This is a relatively large, long-term study with an imbalance of malignancy events in the CS group (3 vs 1). There was a small level of differential discontinuation. In contrast to other studies, no specific attempt was made to assess patients lost to follow-up. Higher rates of discontinuation occurred earlier in the control group, but by the end of the study, 69% of CS subjects and 67% of control subjects remained. The study group comparability, longer study duration of exposure and clear imbalance make this a compelling study. It is limited by the fact that exposure was not blinded. However, given that cancer is not a suspected outcome and not one of the primary outcomes of interest, the lack of blinding may be of minimal impact.

Study: 511

This 36 month, single center DB-RCT was undertaken to evaluate the safety and efficacy of calcitonin NS in the early treatment of bone loss during the peri-menopausal period. Starting in 1987, the investigators enrolled 120 Caucasian peri-menopausal women aged >40 years and randomized them to calcitonin NS 100 IU daily or to placebo (60 per group).

Assessment of malignancy

The sponsor cover page for this study notes that the investigators conducted the study in poor compliance to good clinical practice. The deficiencies noted were documentation missing for sample case report form (CRF) pages, CRFs for deaths, severe adverse events, adverse event withdrawals, and safety narratives. Physical exams were given at baseline, 12 months, 24 months, and 36 months, the patients reported side effects every 3 months. For patients who discontinued or dropped out prior to study end, the date and circumstance of the dropout were to be noted in the patient's CRF. The investigators attempted to obtain at least one post discontinuation follow-up visit for patients discontinuing between visits.

Results

At baseline, the placebo and calcitonin groups were similar with respect to the mean age (45.0 and 45.5 years, respectively), smoking status. The placebo group had a larger proportion of patients withdrawing early (37%), compared to the calcitonin group (32%). There were 2 neoplasms reported in the calcitonin group (hepatic neoplasm, colon carcinoma) and no neoplasms reported in the placebo group.

The relative risk of neoplasm in the calcitonin group compared to the placebo group was 2.63 (95% CI 0.37-18.91).

DEPI Reviewer comments

While this one of the longer duration studies included in the meta-analysis, the poor GCP compliance compromises the study strength, making it one of the weakest studies in the analysis. In addition, the small sample size limits the precision and the lack of diversity among participants limits the generalizability.

Study 2402

A prospective DB-RCT examining the effect of 200 IU NS daily on muscle strength and pain after distal forearm fracture, over a 6-month period. Postmenopausal women age >=60 with distal forearm fracture were enrolled; there were no malignancy associated exclusions. The investigators enrolled 149 CS subjects, 119 placebo patients were enrolled. The study enrollment period was 13-Mar-2002 Last patient completed: 11-Feb-2005.

Assessment of malignancy

Physical exam at study start and end. No attempt was made to follow-up on patients who discontinued early.

Results

The arms were similar with regard to baseline demographics for CS and controls; the median weight was 67kg and 68.5 kg and the median age was 71 and 69 years. Of note, 7.4% of patients in the CS group reported a prior neoplasm (benign, malignant or unspecified), compared to 4.1% of the placebo group. The dropout rate for CS was 10.7%, and for controls was 19.6% (133/149 and 119/148). Four patients in the placebo group (2.7%) and 1 patient in CS (0.7%) were lost to followup. There was one patient from each arm which had a reported malignancy (lymphatic neoplasm in CS and lung metastases in placebo).

DEPI Reviewer comments

The sponsor does not include this among the studies in which a malignancy is reported, although the adverse event tables list 1 malignancy for each arm. The discrepancy may be due to the classification of these malignancies as prevalent instead of incident. The lack of dropout follow-up and short duration (6 months) limit the utility of this study. Of note, previous malignancy was not an exclusion criteria, and the CS group had a higher proportion of subjects reporting a history of any neoplasm.

Study: 211

This single center DB-RCT evaluated the safety and efficacy of 2 years of intranasal calcitonin plus oral calcium in the treatment of osteoporosis in postmenopausal females. The investigators enrolled post-menopausal non-black females less than 75 years of age beginning Aug-89 through Nov-92. Exclusion criteria included history of malignant disease within five years or evidence of recurrence except squamous or basal cell carcinomas. 46 postmenopausal female patients were randomized (16 in 200 IU daily, 15 in 400 IU daily and 15 in placebo). An additional optional 1 year open label treatment period was available.

Assessment of malignancy

Reasons for premature withdrawal were to be ascertained, and the patient reassessed for efficacy and safety immediately after withdrawal. A physical exam was given at baseline and at 24 months with clinical and patient assessment forms every 3 months.

Results

Eight patients discontinued from the study; the discontinue rate for placebo/200/400 was 27%, 19% and 7%; 1 placebo patient was lost to follow-up. All of the discontinuations occurred during the first 12 months of the study. Age, weight and BMI at baseline was similar in all 3 study arms. One patient in the placebo group developed ovarian cancer after 6 months of treatment (7%), one 200 IU calcitonin patient developed cancer during the open label phase (6%). The odds ratio for any neoplasm was 0.41 (95% CI 0.07-2.51).

DEPI Reviewer comments

This study had apparent successful randomization and follow up for adverse events was sufficient. A disproportionally high rate of placebo dropout occurred, resulting in lower person time being accrued in this group (and a resulting lower possibility of outcome occurrence).

Study: 310

This 24 month, multicenter placebo controlled DB-RCT examined the maximal efficacy and safety of diverse doses of calcitonin nasal spray in the prevention of postmenopausal bone loss at axial and appendicular skeletal sites. The investigators enrolled 279 patients and assigned them to 4 study arms (71-100 IU, 72-200 IU, 68-400 IU, 68-Placebo), starting in September 1988 and ending in November 1993. The study population consisted of recently postmenopausal non-black females. There were no exclusions for a history of previous malignancy. An open label phase enrolling 53 continuing placebo patients and 142 continuing calcitonin patients was after the blinded phase.

Assessment of malignancy

Physical exam at baseline, 12 and 24 months, or upon early discontinuation; adverse event form were completed every 3 months and upon early discontinuation

Results

The placebo group was slightly older (53.5 versus approx. 52.5), and had a slightly lower BMI (24.7 versus ~25.3). The CS groups were more likely report a history of smoking (8%, 10% and 18%), compared to 0% in placebo. Alcohol history was similar. Patients on placebo were more likely to complete the study (68%) compared to the calcitonin groups (55%, 65%, 56%, respectively) .

Occurrence of neoplasm was reported in 1 placebo patient (7 wk treatment), in three 200 IU patients (at 12-26 weeks, 22 weeks, 26 weeks) and one 400 IU patient (at 15 weeks). The cancers reported were basal cell carcinoma (nose, shoulder, nose, arm, lip) and breast cancer (200 IU and placebo). The odds ratio for any neoplasm was 1.27(95% CI 0.16-9.95). No malignancies occurred during the open label phase.

DEPI Reviewer comments

The study arms were fairly well balanced, although there were slight differences in age and bmi. A significant limitation to this study is the high dropout rate in all study arms, potentially decreasing the precision of the estimate. The somewhat higher dropout rate among the calcitonin groups may have resulted in a decreased risk estimate.

Study 311

This two year, multicenter trial was undertaken to compare the efficacy and safety of three dose levels compared to placebo in the treatment of bone loss at axial and appendicular skeletal sites in patients with steroid induced osteoporosis.

Males or postmenopausal (at least 1 year) females, 35 years of age or older with rheumatoid arthritis or an underlying pulmonary disease who were being treated with oral corticosteroids. Enrollment began January 1992 and continued through September 2005. 323 patients were randomized to 100, 200, or 400 IU CS or placebo, followed by an open label phase in which all patients were offered 400 IU CS daily (195 patients entered the open phase). Patients with prior malignancy were not specifically excluded.

Assessment of malignancy

A complete final evaluation (efficacy and safety) was to be performed for patients discontinuing early. Physical exams at baseline, 1, 3, 6, 12, 18, 24, 30 and 36 months, adverse event reports at 1,3,6,9,12,18,24,30,36. Patients or the examining physician reported AEs.

Results

Placebo users were slightly older 63.4 vs ~62.1 years of age, and had a lower bmi (26 vs ~ 27.2). One hundred ninety-seven patients completed the double-blind phase of the study (143 [59%] Miacalcin and 54 [68%] placebo). The loss to follow-up was higher in the CS groups (45% 100 IU, 35% 200 IU, 44% 400 IU, 32% placebo). Discontinuations were earliest in the 400 IU group. Three malignancies were were reported in the 100 IU arm (prostate, cecal carcinoma, renal cell carcinoma), 4 in the 400 IU arm (colon cancer, colon cancer resection due to cancer, lung cancer, breast cancer) and 3 in the placebo arm (lung cancer, merkel's cell tumor, prostate cancer). In the open label portion, there were 3 malignancies in the patients which entered from the CS group, and none from those who entered from the placebo group. The odds ratio for neoplasm among calcitonin versus placebo patients was 0.61 (95% CI 0.16-2.32).

DEPI Reviewer comments

While this was a longer term study, the rate of cancer in each group was very similar. The imbalance in the treatment (2 cases) vs placebo (0 cases) in the open label phase is of note. A substantially higher rate of discontinuations among the CS groups may have lead to a decrease in the event rate for the CS groups, and a resultant lower odds of cancer development. This was one of the few studies which included men.

Study 312

This 2 year, multicenter DB-RCT compared the efficacy and safety of two dose levels of calcitonin NS compared to placebo in the treatment of bone loss at axial and appendicular skeletal sites in patients with steroid induced osteoporosis. Males or postmenopausal (by at least 1 year) females, 35 years of age or older were recruited and assigned to 200 or 400 IU CS daily or to placebo. Recruitment began February 1992 and ended September 1993. Exclusion of malignancy not specified.

Assessment of malignancy

A complete final evaluation (efficacy and safety) was to be performed for patients discontinuing early. Physical exams at baseline, 1, 3, 6, 12, 18, 24, 30 and 36 months,

adverse events reports at 1, 3, 6, 9, 12, 18, 24, 30, and 36 months. Adverse events were reported by the patient or by examining physician

Results

Patient demographics were similar at baseline, although the median age in the placebo group was 64 years compared to the 400 IU group median of 62 years. The median patient weight was lowest in the 200 IU group (160.6 lbs), compared to 167.3 for placebo and 169 for the 400 IU groups. Early discontinuation occurred at a rate of 33% in placebo, and 36% in treatment groups (39.2% for the 200 IU group and 33.3% for the 400 IU group). Malignancies occurred for 1% of the 200 IU (1 case breast cancer)and 400 IU arm (1 case adenocarcinoma). There were no events in the placebo group. In the open label phase, 1 case of Hodgkin's lymphoma was diagnosed. The odds ratio for neoplasm among calcitonin versus placebo patients was 1.77 (95% CI 0.57-5.51).

DEPI Reviewer comments

This was a longer term study (2 years, plus 1 year open) which had an imbalance in the discontinuation rates between the arms; the 200 IU had a higher discontinuation rate, and while the overall rate was the same as placebo; the 400 IU group discontinuations occurred earlier. The study allowed the use of other medications, but these were not reported. The higher rate of discontinuation among the CS groups may have resulted in lower rates of cancers in these groups, decreasing the odds ratio.

Study MIA16

This is a 2 year DB-RCT with an additional 1 year open label period. The first subject enrolled August 1988 and the last subject completed in June 1993. The investigators enrolled postmenopausal women over 60 years of age in good general health but who had osteopenia or had suffered osteoporotic vertebral or forearm fractures, with at least 2 non-compressed lumbar vertebrae. Subjects were randomized to placebo (30 patients), CS 400 IU daily (32 patients), nandrolone (30 patients), or CS 400 IU daily +nandrolone (31 patients).

Assessment of malignancy

The sponsor provided a cover page for the published article noting that the study was done in poor compliance to good clinical practices (GCP), that there were no case report forms for deaths, serious adverse events, adverse event withdrawals, or safety narratives. The published report does not specify the method of adverse event assessment, or whether they attempted to evaluate subjects who left early.

Results

The groups were similar with respect to age, and height. The CS 400 IU arm was approximately 3 pounds heavier, on average, than the other 3 cohorts. The CS containing cohorts had higher rates of dropouts (cd=19%, ND+CS 26%) compared to 10% and 7% in placebo and nalandrone. The investigators noted 1 case of lung cancer in the 400 IU treatment group (per the cover page/sponsor review), 1 case of breast carcinoma and 1 case of lung cancer in the published study (in an unknown group). The odds ratio, as reported by the sponsor, for neoplasm among calcitonin versus placebo patients was 5.94 (95% CI 0.14-350.5).

DEPI Reviewer comments

This is a small, but relatively long study. However, the undocumented methods for assessment of AEs which may have resulted in early discontinuation is not provided. The sponsor's cover and the report disagree on the number of malignancy cases, and the report states that two cases occurred, but did not provide information about which treatment group they occurred in.

Due to issues with study quality, the results from this study should be interpreted with caution.

Study 503

This is a 24 month DB-RCT to evaluate the ability of calcitonin to maintain bone mineralization in early post-menopausal women. The study enrolled healthy 52 women aged 45 to 56 with recent menopause (last menses 2.5 to 5 years previously) and randomized them to calcitonin NS 50 IU daily or to placebo. Patients with any kind of malignancy were excluded.

Assessment of malignancy

To assess efficacy and adverse events, full physicals were conducted at baseline, 12 months and 24 months. Physicals included the reporting of possible drug related adverse events.
Whenever possible the investigators determined the reason for premature withdrawal and the patient followed up for efficacy and safety evaluations at the scheduled visit dates.

Results

The calcitonin group was slightly younger (mean of 52.3 years versus 53 years for placebo). Compared to placebo, the calcitonin patients were more likely to be smokers (16 vs. 10), and had a lower BMI (mean 23.7 vs. 24.7). An equal number of patients withdrew from each study group (6 each), although the placebo patients withdrew earlier (mean withdrawal month of 4.9 vs 6.2). No malignancies were reported in either study arm.

DEPI Reviewer comments

This is a small, moderate duration study with no malignancies reported. Follow up for adverse events was adequate and randomization appears acceptable, although there was an imbalance of smokers and bmi.

Study 514

This 24 month single center DB-RCT was undertaken to determine the safety and efficacy of calcitonin NS in the treatment of women with mild to moderate degrees of bone loss. The investigators recruited 118 post-menopausal women and randomized them into 4 treatment groups: 200 IU calcitonin daily, 200 IU Monday, Wednesday, Friday (MWF), placebo daily, or placebo MWF. There were 71 calcitonin and 46 placebo patients. Recruitment began in 1987. No exclusion for previous malignancy was required.

Assessment of malignancy

Adverse events were recorded at months 6, 12, 18 and 24 and the reason for early discontinuation was recorded on the patient's case report form.

Results

The odds ratio for neoplasm among calcitonin versus placebo patients was 5.27 (95% CI .031 – 91.9). The baseline demographics between the groups was similar for age, body weight, height, BMI, and use of tobacco. The proportion of patients

who discontinued the study early for the 200 IU daily, 200 IU MWF, and placebo groups was 6%, 17%, and 13% respectively. There were 2 cases of breast cancer in the 200 IU MWF group; one patient discontinued early. The odds ratio for neoplasm among calcitonin versus placebo patients was 5.27 (95% CI 0.31-91.09).

DEPI Reviewer comments

A baseline physical was required, but no interim or exit physicals were conducted and adverse events were reported by an unknown mechanism, making the completeness of adverse events identification in this study difficult to determine.

Study 517

A 24 month, single center DB-RCT examining whether CS NS (50 or 200 IU/day given for 5 days every week) is effective in preventing bone loss in early post-menopausal women over a 2 year period. The investigators began enrollment in 1987 and enrolled 251 recently post-menopausal Caucasian women, randomizing them to placebo (n=83), calcitonin 50 IU daily (n=84), and calcitonin 200 IU daily (n=84). Patients with neoplastic disease were excluded, but past-history of neoplasm was not an exclusion criteria.

Assessment of malignancy

Full physical examinations were conducted at all visits and adverse effects reported spontaneously by the patients. For patients discontinuing between visits, the investigators attempted to obtain at least one post discontinuation follow-up visit.

Results

The groups were similar at baseline with respect to age, BMI and smoking status. The calcitonin patients were more likely to report regular exercise (31.0% vs. 21.7%). Discontinuations occurred at a higher proportion in the placebo group (49.4%) compared to the 50 IU (46.3) and 200 IU (34.5%) groups. There were no malignancies reported in the three study groups.

DEPI Reviewer comments

This is a study in which the baseline demographics were comparable, and randomization appeared to be sufficient. Early discontinuation occurred at a higher rate in the placebo group compared to the calcitonin group, which is reassuring as time on calcitonin should have been longer and the time to develop cancers was longer in the calcitonin group. The lack of an exclusion for past cancer history increases the generalizability of this study.

Study 320 (PROOF)

This 5 year, multi-center study was undertaken to evaluate whether salmon CS NS reduced the risk of new vertebral fractures in postmenopausal women with osteoporosis. The investigators enrolled 1,255 white, Asian or Hispanic post-menopausal women to 3 treatment groups (100 IU, 200 IU, or 400 IU daily) or to placebo. Malignancy was not an exclusion criterion.

Assessment of malignancy

Evaluations were performed at months 1, 3, 6, 9, 12, and every 6 months thereafter. The investigators attempted a post discontinuation exam for patients discontinuing early.

Results

The baseline demographics for the study groups were similar with respect to age, race, BMI and smoking status. The proportion of patients discontinuing early during the study was similar in all 4 groups (between 58% for the 200 IU group and 61%% for the 200 IU group). There were 82 cases of neoplasm in the calcitonin group (8.58%) compared to 18 cases in the placebo group (5.79%). The odds ratio for neoplasm among calcitonin versus placebo patients was 1.62 (95% CI 1.00-2.61).

DEPI Reviewer comments

This is the largest study in the meta-analysis, with more ethnic and age variation, potentially increasing the generalizability of the study. There was a high rate of early discontinuation over the course of the study, decreasing the risk estimate precision and the ability of the study to evaluate long term safety.

Study 522

This single center, DB-RCT was undertaken to determine the safety and efficacy of 3 different doses of calcitonin NS to treat osteoporosis in postmenopausal, Caucasian, elderly women. The investigators recruited 208 women between the ages of 68 and 72, randomizing them to four treatment groups containing 52 participants each: 50, 100, 200 IU of daily calcitonin NS, or to placebo. Current malignancy was an exclusion criterion, but previous malignancy was not.

Assessment of malignancy

Physical exams were conducted at baseline, 12 months and 24 months, adverse events were reported at 24 months. For patients that discontinued, the investigators attempted to determine the primary reason for discontinuation, but did not attempt an exit physical examination.

Results

The patients enrolled were similar at baseline with respect to age and BMI; placebo patients were more likely to be smokers (52%), compared to the calcitonin groups (50 IU-42%, 100 IU-44%, 200 IU-46%). The 50 IU study group had the highest proportion of early discontinuations (21%), compared to the 100, 200 IU, or placebo groups (12%, 15%, 15%, respectively). There were 4 malignancies in the calcitonin groups, and none in the placebo group. The malignancies were: 50 IU (breast cancer, basal cell carcinoma), 200 IU (pulmonary carcinoma, basal cell carcinoma).
The odds ratio for neoplasm among calcitonin versus placebo patients was 3.87 (95% CI 0.4-37.81).

DEPI Reviewer comments

Patients in this study were older than in other studies included in the meta-analysis (enrolled women between ages 68 and 72 years).

Study 524

This is a 24 month, single center, DB-RCT examining the safety and efficacy of 3 doses of calcitonin NS for the early treatment of postmenopausal osteoporosis. The investigators enrolled 134 Caucasian women who were 1-5 years post-menopause and randomized them to calcitonin NS 100, 200 or 400 IU daily or to placebo. Current malignancy was an exclusion criterion, but a history of malignancy was not.

Assessment of malignancy

A baseline physical examination was administered, but no inter-study physical examinations were required. Adverse events were reported every 3 months. The investigators attempted to determine reasons for early withdrawal.

Results

The baseline demographics were similar with respect to age (approximately 52 years in all groups, while the mean BMI differed between groups with the placebo group being the highest (100IU-25.6, 200IU-23.95, 400IU-24.85, placebo-26.00). Tobacco use was similar, though slightly higher in the low dose groups (100IU-42%, 200 IU-41%, 400 IU-35%, placebo-39%.) The proportion of patients who discontinued early was highest in the 100 IU group (27.7%), compared to the 200 IU, 400 IU, or placebo groups (11.76%, 11.76%, 12.12%, respectively.) There was one case of malignancy; a vaginal neoplasm in the 200 IU group, diagnosed at 22 months of treatment.

The odds ratio for neoplasm among calcitonin versus placebo patients was 3.77 (95% CI 0.04-356.4).

DEPI Reviewer comments

This is a study with an imbalance of malignancy in the calcitonin treatment groups. Baseline demographics were similar, indicating randomization was adequate. Follow-up for malignancies was acceptable, although physicals at discharge may have resulted in more complete ascertainment.

Oral Studies

Study 2301

This 24 month, multi-center, DB-RCT was undertaken to evaluate the safety and efficacy of oral calcitonin in the treatment of knee osteoaritiritis. Approximately 1150 men and women were randomized to receive calcitonin or placebo. The calcitonin dose was 0.8mg twice daily.

Assessment of malignancy
Prostate cancers were examined using follow-up outside the original scope of the study. Male study subjects invited to undergo prostate specific antigen testing.

Results

An imbalance in neoplasm between study groups was observed. The incidence rate ratio for neoplasm among calcitonin versus placebo patients was 4.13 (95% CI 1.676-10.197). The most common cancers with an imbalance were basal cell carcinoma (3 in CS, 0 in placebo) and prostate cancer (4 in CS, 0 in placebo).

DEPI Reviewer comments
A full study report is not provided; Baseline characteristic comparability and methods for malignancy assessment cannot be determined.

Study 2302

This 24 month, multi-center, DB-RCT study enrolled osteoarithritic men and women who were randomized to calcitonin (n=520) and placebo (n=508). The calcitonin dose was 0.8mg twice daily. The study has completed the treatment period, but a final study report is not available.

Assessment of malignancy

Results

The incidence rate ratio for neoplasm among calcitonin versus placebo patients was 1.61 (95% CI 0.818-3.163).

DEPI Reviewer comments
A full study report is not provided; Baseline characteristic comparability and methods for malignancy assessment cannot be determined.

Study 2303

This 36 month, multi-center, DB-RCT, enrolled post-menopausal women and randomized 2334 to calcitonin and 2331 to placebo. The calcitonin dose is 0.8mg once daily. The primary endpoint is the proportion of new vertebral fractures. The study has completed the treatment period, but a final study report is not available.

Assessment of malignancy

Results

The incidence rate ratio for neoplasm among calcitonin versus placebo patients was 1.1 (95% CI 0.820-1.481).

DEPI Reviewer comments
A full study report is not provided; Baseline characteristic comparability and methods for malignancy assessment cannot be determined.

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