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Reproductive Drugs and Drug Safety and Risk Management Advisory Committees

Calcitonin: March 5, 2013

(I have no financial conflict of interest)

Conclusion of EMA in July, 19, 2012
(based on the same data being reviewed today)

"…concluding that there was evidence of a small increased risk of cancer with long-term use of these medicines. …The Committee also concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in the treatment of osteoporosis and that they should no longer be used for this condition."

U.S. nasal calcitonin Rxs since 7/19/12

(data from 8/1/12 through December, 2012)

- Total Rxs: approximately 500,000/ five mos.

- Using FDA data to convert from Rxs to users, approximately 125,000 people, mainly women, were exposed to nasal calcitonin since the EMA announcement

IMS Data for retail prescriptions, FDA Rx user conversions from FDA briefing documents, page 114

Novartis response to EMA action

"EMA's Committee for Medicinal Products for Human Use (CHMP) recommended on November 15, 2012 that benefits of calcitonin-containing medicines did not outweigh their risks in the treatment of osteoporosis and that they should no longer be used for this condition. Given the fact that the NS formulation is solely approved for the treatment of PMO, this formulation is being suspended in the EU."

Novartis Briefing Document, p. 15

Warnings on current Novartis label

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).

Warnings on current Novartis Label (continued)

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.

Current Information on EMA Web site

Taking into account the limited benefit of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin did not outweigh the risks in this condition. As the nasal spray is only used in osteoporosis, the CHMP recommended that this formulation should no longer be used.

EMA Web site (continued)

- What are the recommendations for patients ?
- Calcitonin will no longer be used for the treatment of osteoporosis. Patients being treated for osteoporosis with calcitonin nasal sprays or other formulations are advised to speak to their doctor at a routine appointment, who will recommend suitable alternative treatment.
- Patients receiving injectable calcitonin who have any questions should speak to their doctor or pharmacist.

EMA Web site (continued)

- What are the recommendations for prescribers ?
- Prescribers should note that calcitonin should no longer be used for the treatment of osteoporosis.
- Calcitonin will only be available as a solution for injection and infusion, and should only be used for:
  - prevention of acute bone loss due to sudden immobilisation, with a recommended treatment period of two weeks and a maximum treatment period of four weeks;
  - Paget's disease, restricted to patients who do not respond to alternative treatments or for whom such treatments are not suitable….
  - hypercalcaemia caused by cancer.

Comments from FDA Brief Documents

- Novartis OR= 1.6, 95% CI (1.1, 2.3)
- FDA Risk Diff- 1.6%, 95% CI (0.5, 2.8)

"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. 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."

Comments from FDA Brief Documents

FDA Review of three fracture reduction trials

"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…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."

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Comments from FDA Brief Documents

"The second, Study CT320 or the PROOF trial, was …..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). …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. The biologic plausibility of such a result is unclear… 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."

Comments from FDA Brief Documents

"Finally, Study SMCO21A-2303 is a 3-year randomized, double-blind, placebo-controlled… study evaluating oral calcitonin salmon-CNAC therapy in postmenopausal women with osteoporosis and vertebral fractures at baseline. but the trial did not demonstrate a significant reduction in [new] vertebral fractures. Intervention to reduce the risk of fracture is the standard for treatment of postmenopausal osteoporosis."

FDA, 2/13, based on analysis of same data EMA used for 7/19/12 conclusions

"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."

FDA briefing document page 62, March 2013

History of Calcitonin

In the December 1995 issue of *Worst Pills, Best Pills News*, we listed calcitonin nasal spray as a **Do Not Use** drug because there was no credible evidence that the drug reduced the risk of fractures in postmenopausal women with osteoporosis.

History of Calcitonin

FDA guidelines issued in 1994 emphasized documenting the efficacy of a drug in reducing fractures before it is approved for the treatment of osteoporosis. Since 1995, the FDA has approved three drugs under these guidelines—alendronate (FOSAMAX), raloxifene (EVISTA), and risedronate (ACTONEL)—for the treatment of osteoporosis. Note that conjugated estrogens (PREMARIN) are no longer approved for the treatment of postmenopausal osteoporosis.

History of Calcitonin
(from an article in our newsletter in 2002)

A National Institutes of Health osteoporosis consensus panel summarized the results of the PROOF trial in the following manner: “The absence of dose response, a 60 percent dropout rate, and the lack of strong supporting data from BMD [bone mineral density] and markers decrease confidence in the fracture risk data.”

The FDA staffers who prepared the recently published calcitonin history concluded diplomatically that:

...after 30 [now 40] years of clinical experience, calcitonin's effect on fracture risk is uncertain. As the 40th [now 50th]anniversary of calcitonin's discovery approaches, perhaps it is time for all interested parties to reassess this drug's role in treatment of patients with osteoporosis.