Direct Healthcare Professional Communication on calcitonin (Miacalcic) associated with malignancy – new restrictions on use and withdrawal of the nasal spray from the market.

Please cascade as appropriate

Dear Healthcare Professional,

Summary

The European Medicines Agency has recently completed a review of the benefits and risks of calcitonin concluding that there was evidence from randomised controlled clinical trials of an increased risk of malignancies with the long term use of calcitonin compared with placebo treated patients.

Due to the higher incidence of malignancies, the following is concluded:

- **Calcitonin should no longer be used in the treatment of established post-menopausal osteoporosis, since the risks associated with calcitonin outweigh the benefits in this indication.**

  Patients being treated for osteoporosis with calcitonin should be switched to alternative treatment during the next scheduled (or routine) appointment.

The benefits of calcitonin continue to outweigh the risks in the short term treatment of:

- **Paget's disease only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, e.g. in patients with severe renal impairment. Treatment in this indication should be limited in most cases to 3 months (Please see below, further information on recommendations to healthcare professionals).**
- **Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures, with treatment limited to two to four weeks.**
- **Hypercalcaemia of malignancy.**

This letter is sent in agreement with the Medicines & Healthcare products Regulatory Agency.

Further information on the safety concern

The review by the European Medicine Agency's Committee for Medicinal Products for human use (CHMP) considered information on the risk of all types of malignancies from randomised controlled trials in patients with osteoporosis or osteoarthritis receiving calcitonin nasal spray or an unlicensed oral calcitonin formulation.

Patients treated with calcitonin in these trials had a higher incidence of malignancies. The increased rate of malignancies varied between 0.7% in the oral calcitonin trials and 2.4% for the calcitonin nasal spray trials. Taking into account the increased risk of cancer with long-term use, the CHMP concluded that the risks of calcitonin outweighed the benefits for the treatment of established post-menopausal osteoporosis in order to reduce the risk of vertebral fractures.

As a result of these findings, calcitonin nasal spray, which is authorized only for treatment of post-menopausal osteoporosis, will be withdrawn from the market, and calcitonin will only be available as a solution for injection and infusion.

Further information on recommendations to healthcare professionals

Due to the increased risk of malignancies, duration of treatment with calcitonin should be limited to the shortest period of time possible and using the minimum effective dose.

For the treatment of Paget's disease in particular, treatment should not exceed 3 months unless under exceptional circumstances – for example, in patients with impending pathologic fractures, where treatment can be extended up to 6 months. Repeated (intermittent) treatment may be considered taking into account the benefits and risks.

The product information for Miacalcic Solution for Infusion and Injection will be updated with information on the risk of malignancy and the new restrictions (see Annex).

Call for Reporting

Healthcare professionals should report any suspected adverse reactions associated with use of calcitonin.

Suspected adverse drug reactions should be reported to the MHRA via the Yellow Card Scheme. Reporting forms and information can be found at http://yellowcard.mhra.gov.uk

Alternatively, prepaid Yellow Cards for reporting are available:

- **upon request by mail: "FREEPOST YELLOW CARD"**
- **at the back of the British National Formulary (BNF)**
- **by telephoning the Commission of Human Medicines (CHM) free phone line: 0800-731-6789**
- **or by electronic download through the MHRA website (http://yellowcard.mhra.gov.uk/downloads)**

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Adverse reactions should also be reported to Novartis Pharmaceuticals UK Ltd; please call 01276 698370 or e-mail: adecseuk.phgbfr@Novartis.com

For additional questions regarding this issue, please call the Medical Information Department at Novartis Pharmaceuticals UK Ltd on 01276 698370.

Yours faithfully,

Dr. Mark Bechter
Medical Director – Chief Scientific Officer UK.
13th August 2012
See overleaf for the referenced Annex.

Annex – Product Information Changes for Calcitonin-Containing Medicines as Approved by the CHMP on 19 July 2012, Pending Endorsement by the European Commission

A. Summary of Product Characteristics

4.1 Therapeutic indication

[the currently approved indications should be deleted and replaced by the following]

- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures
- For the treatment of Paget's disease, only in patients who do not respond to alternative treatments or for whom such treatments are not suitable, for example those with severe renal impairment
- Treatment of hypercalcaemia of malignancy

4.2 Posology and method of administration

[the wording below should be inserted]

[…]

Due to the association of the increased risk of malignancies and long term calcitonin use (see section 4.4), the treatment duration in all indications should be limited to the shortest period of time possible and using the minimum effective dose.

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

The recommended dosage is 100 IU daily or 50 IU twice daily administered subcutaneously or intramuscularly. The dose may be reduced to 50 IU daily at the start of remobilisation. The recommended treatment duration is 2 weeks and should not exceed 4 weeks in any case due to the association of the increased risk of malignancies and long term calcitonin use.

Paget's disease

The recommended dosage is 100 IU per day administered subcutaneously or intramuscularly, however a minimum dosage regimen of 50 IU three times a week has achieved clinical and biochemical improvement. Dosage is to be adjusted to the individual patient's needs. Treatment should be discontinued once the patient has responded and symptoms have resolved. Duration of treatment should not normally exceed 3 months due to the association of the increased risk of malignancies with long term calcitonin use. Under exceptional circumstances, e.g. in patients with impending pathologic fracture, treatment duration may be extended up to a recommended maximum of 6 months.

Periodic re-treatment may be considered in these patients, and should take into account the potential benefits and the association of the increased risk of malignancies and long term calcitonin use (see section 4.4)

The effect of calcitonin may be monitored by measurement of suitable markers of bone remodelling, such as serum alkaline phosphatase or urinary hydroxyproline or deoxypyridinoline.

4.4 Special warnings and precautions for use

[the wording below should be inserted]

[…]

Analyses of randomised controlled trials conducted in patients with osteoarthritis and osteoporosis have shown that calcitonin is associated with a statistically significant increase in the risk of cancer compared to patients treated with placebo. These trials demonstrated an increase in the absolute risk of cancer occurrence for patients treated with calcitonin compared to placebo which varied between 0.7% and 2.4% with long term therapy. Although based on small numbers, cancer mortality was also higher in patients treated with calcitonin in these trials, which may indicate a treatment dependent increased risk of tumour promotion. Patients in these trials were treated with oral or intra-nasal formulations however it is likely that an increased risk also applies when calcitonin is administered subcutaneously, intramuscularly or intravenously especially for long-term use, as systemic exposure to calcitonin in such patients is expected to be higher than for other formulations.

[…]

4.8 Undesirable effects

[the wording below should be inserted]

[…]

Malignancy (with long term use), frequency: common

[…]

B. Patient Information Leaflet

[the wording below should be inserted in the relevant sections]

1. What <invented name> is and what it is used for:

<invented name> can be given for the following conditions:

- Prevention of bone loss in patients who have suddenly become immobile. For example, patients who are bed-bound because of a fracture.
- Paget's disease of bone in patients who cannot take other treatments for this condition, for example patients with serious kidney problems. Paget's disease is a slowly progressing illness which can cause a change in the size and shape of certain bones.
- Treatment of high calcium levels in the blood (hypercalcaemia) due to cancer.

2. Before you take <invented name>

[…]

Take special care with <invented name>

Please tell your doctor if you have been diagnosed with cancer. In clinical trials, patients treated with calcitonin for osteoporosis and osteoarthritis have shown an increase in the risk of cancer following long term treatment. Your doctor will decide if calcitonin is a suitable treatment for you and for how long you can be treated.

3. How to take <invented name>

Your doctor will decide the correct dose and how long you should receive calcitonin treatment depending on your condition.

The usual doses are:

- **For prevention of bone loss:** 100 IU per day or 50 IU twice daily for 2 to 4 weeks, given into the muscle or the tissue just under the skin.
- **For Paget's disease:** 100 IU daily injected into a muscle or into the tissue just under the skin, normally for up to 3 months. In some cases, you doctor might decide to extend your treatment up to 6 months.
- **For the treatment of high calcium levels:** 100 IU every 6 to 8 hours, given into a muscle or into the tissue just under the skin. In some cases, it may be given by injection into a vein.

4. Possible side effects

[…]

Common side effects:

Cancer (following long term treatment)

[…]