



European Medicines Agency

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**SCIENTIFIC DISCUSSION
FOR
BONVIVA**

International non-proprietary name: ibandronic acid

Procedure No: EMEA/H/C/000501/II/0021

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

1.1. Introduction

Ibandronate, (INN: ibandronic acid) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. Through suppression of farnesyl pyrophosphate (FPP) synthase, an enzyme of the mevalonate pathway ibandronate reduces the synthesis of the isoprenoid geranylgeranyl pyrophosphate and, subsequently, the prenylation of small guanosine triphosphate (GTP)-binding proteins that are essential for the integrity of the cytoskeleton of the osteoclasts and for intracellular signalling, thus inducing early apoptosis. In long-term studies in relevant animal models, ibandronate was shown to reduce the rate of bone turnover, to increase bone mass, and to maintain or increase bone strength with no adverse effects on bone quality or biomechanical competence at doses much higher than those intended for human use. The total dose, rather than dose schedule, was shown to be the major determinant for efficacy.

Oesophageal irritation is known to be associated with the use of oral bisphosphonates, and oesophageal Adverse Events are already identified as a class effect.

In response to a recent safety review conducted by the FDA to assess the potential association between oesophageal cancer and oral bisphosphonate use, FDA requested in April 2009 a class label update to all MAHs of oral bisphosphonates, adding new contraindications and strengthening the Warnings and Precautions in relation to the risk of severe oesophageal irritation.

The MAH conducted a safety review in 2009 on reporting rate, clinical manifestations, and current scientific and medical knowledge of oesophageal cancer in patients receiving ibandronic acid or other bisphosphonates. In the light of the few publications around oesophageal cancer and the many questions still remaining unanswered, an association between ibandronic acid and oesophageal cancer is not established and seems unlikely given currently available data.

However, in order to mitigate the risk and in line with the FDA US class labeling request, the MAH decided to update its Core Data Sheet (CDS) for ibandronic acid oral formulations in the osteoporosis as well as oncology setting. The labeling revisions pertain to an upgrade of the safety information on risk of severe oesophageal irritation from “Special warnings and Precautions for use” to “Contraindication” with a strengthening of the “Special warnings and Precautions for use” text..

The MAH submitted this type II variation to update sections 4.3 and 4.4 of the SPC in line with the CDS. The Package Leaflet is proposed to be updated accordingly.

1.2. Oral ibandronic acid and oesophageal safety review

Oesophageal irritation has long been associated with use of oral bisphosphonates, and patients are advised to take oral ibandronic acid with a full glass of water and remain upright for at least 60 minutes after taking it (30 minutes for other oral bisphosphonates).

Recent publicity on case reports of oesophageal cancer in patients taking bisphosphonates has raised questions whether chronic oesophageal irritation in combination with known risk factors (e.g., gastroesophageal reflux disease, Barrett’s esophagus, esophageal strictures, achalasia or motility disorders) might exacerbate the risk of complications including dysplasia and neoplastic transformation. At this point these concerns are theoretical but biologically plausible and thus warrant further investigation and preventive clinical precautions.

The MAH recently conducted a safety review (with cut-off date 20 March 2009 and late breaking information through 24 June 2009) of ibandronic acid and oesophageal cancer. It includes pre-clinical, clinical and data from Roche’s global Safety database ADVENT, which contains serious adverse events from clinical trials as well as serious and non-serious spontaneous adverse events from post-marketing settings, supplemented with an epidemiology and literature review. The corresponding safety report was submitted to EMEA in August 2009 as part of ibandronic acid PSUR covering the period 25 June 2008 to 24 June 2009.

1.2.1. Pre-clinical

Three oral carcinogenicity studies in the rat and mouse were conducted during the preclinical development program. There was no evidence of any carcinogenic potential of ibandronic acid at daily doses of up to 6 fold (rat) and 20 fold (mouse) higher than the monthly dose of 150 mg in humans. Therefore, an increased risk of oesophagus cancer due to a systemic effect of ibandronic acid can be excluded.

Cases of local irritation of the upper GI-tract including the oesophagus were also observed in animal toxicity studies. However, in all preclinical oral studies, ibandronic acid was administered in formulations completely different to the film-coated tablet used in humans. Thus, they do not reflect the clinical situation adequately and are considered to be not relevant for the risk assessment of upper GI tract intolerability.

1.2.2. Clinical

Two cases of oesophageal cancer were reported during the clinical development program with ibandronic acid for the indication of postmenopausal osteoporosis. This represents an incidence rate of 2 cases in 6830 patients exposed to oral and IV ibandronic acid (> 15,000 patient years) in pivotal trials.

In one case oesophageal cancer was diagnosed about 500 days after study drug discontinuation in a patient with a medical history of dyspepsia. In the other case, the first symptoms of dysphagia occurred after 3 months of study drug and the diagnosis was made after 7.5 months. Both patients were smoking for about 50 years, which is known to be an important risk factor for esophageal cancer. Both these cases were considered by the investigators as not causally associated with ibandronic acid.

No cases were reported in the oncology setting.

Furthermore, no cases were reported in the three year long term extension osteoporosis trials (N=1500 (781 oral and 719 IV) patients).

1.2.3. Post-marketing experience

No cases of oesophageal cancer were reported in post-marketing studies (completed & validated analyses, and of at least 6 months duration) (N=3986 oral patients).

Four spontaneous case reports of oesophageal cancer were identified for an estimated more than 17 Million patients (Bonviva: 16 Million; Bondronat: 1 Million) exposed to ibandronic acid until 30 June 2009. This represents a crude reporting rate of less than 1 event in 1'000'000 patients exposed (0.2 per 1'000'000). No cases were reported for Bondronat.

In summary, when assessing these 4 spontaneous case reports, a contributory role of ibandronic acid in the occurrence of esophageal cancer could not be excluded in 3 patients (reporter causality possible (2) and unknown (1)). However, in 1 out of these three reports, previous bisphosphonate use was described. (No information on bisphosphonate use was provided in any of the other cases.) In one case, there was a medical history of cancer and hiatal hernia and reflux. And in one case, information on past medical history, relevant investigations and co-medications was lacking. In 3 patients the latency was short with the likeliness of the cancer pre-existing the bisphosphonate use and/or the drug exposure minimal (e.g. one dose only).

1.2.4. Epidemiology & literature

The review of epidemiology data revealed that women with osteoporosis have a non-statistically significantly higher risk of oesophagus cancer compared with those in the general population.

The crude odds ratio of oesophagus cancer with bisphosphonate use was non-statistically significant elevated to 2.0 (0.9-4.4). There were no cases reported in patients exposed to ibandronic acid, however total exposure to ibandronic acid was low (only 74 (0.5% of total bisphosphonate use)).

A literature search for ibandronic acid and oesophageal cancer in patients with benign disease (non-oncology indications) yielded only the NEJM 1 Jan 2009 Dr. Wysowski (FDA) letter to the editor, and publications cross referencing to this letter. In response to the Letter to the Editor (NEJM 23 Apr 2009), with data from other databases, other authors do not provide support for a suspected oesophageal cancer risk in patients on bisphosphonate therapy.

1.2.5. MAH's conclusions

The MAH's safety review provided a summary on the reporting rate, clinical manifestations, and current scientific and medical knowledge of oesophageal cancer in patients receiving ibandronic acid or other bisphosphonates in the osteoporosis and cancer setting.

In the light of the few publications around oesophageal cancer and the many questions still remaining unanswered, an association between ibandronic acid and oesophageal cancer is clearly not established and seems unlikely given currently available data.

However as an association cannot be fully excluded, it is important to mitigate the potential risk. In line with the recent FDA class labeling recommendation, the MAH has therefore decided to update the oral ibandronic acid CDS to include an emphasis on the adverse events related to the local irritation of the upper gastrointestinal mucosa, i.e. by adding appropriate new contraindications: (a) abnormalities of oesophagus that delay emptying such as stricture or achalasia; (b) inability to stand or sit upright for at least 60 minutes, and by strengthening the "Warnings and Precautions" wording related to severe oesophageal irritation.

During the last revision (version 2) of the ibandronic acid post-menopausal osteoporosis Risk Management Plan (RMP), which incorporated the oral ibandronic acid formulations to the existing intravenous formulation initial RMP, severe oesophageal irritation was added as an identified risk.

The benefit-risk assessment of ibandronic acid in the osteoporosis and oncology setting remains unchanged. As part of its routine Pharmacovigilance procedures, the MAH will continue to obtain as much information as possible on received reports suspicious for oesophageal cancer.

1.3. Update of the SPC and Package Leaflet

The labeling revisions pertain to an upgrade of the safety information on risk of severe oesophageal irritation from "Special warnings and Precautions for use" to "Contraindication" with a strengthening of the "Special warnings and Precautions for use" section text.

In line with the CDS updates, the MAH proposed the following changes for sections 4.3 and 4.4 of the SPC and the Package Leaflet.

SPC

Section 4.3 Contraindications:

- Description of changes:

In order to minimise the potential risk of oral bisphosphonates exacerbating oesophageal irritation complications, the MAH is proposing to contraindicate oral formulations of ibandronic acid in patients with history of abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia.

In addition, the MAH proposes to upgrade the current safety warnings regarding patients who cannot comply with the current dosing recommendations, by contraindicating oral ibandronic acid use in patients unable to stand or sit upright for at least 60 minutes.

- Proposed changes:

“

- Abnormalities of the oesophagus which delay oesophageal emptying such as stricture or achalasia
- Inability to stand or sit upright for at least 60 minutes
- Hypocalcaemia (see section 4.4)

- Hypersensitivity to ibandronic acid or to any of the excipients.
See also section 4.4. “

Section 4.4 Special Warnings and Precautions for Use:

- Description of changes:

As part of oral ibandronic acid risk minimisation measures related to the identified risk of severe oesophageal irritation with oral bisphosphonates, the MAH proposes to strengthen the existing “Warnings and Precautions” wording.

- Proposed changes:

“Gastrointestinal disorders

~~Bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers.~~

Orally administered bisphosphonates may cause local irritation of the upper gastrointestinal mucosa. Because of these possible irritant effects and a potential for worsening of the underlying disease, caution should be used when Bonviva is given to patients with active upper gastrointestinal problems (e.g. known Barrett’s oesophagus, dysphagia, other oesophageal diseases, gastritis, duodenitis or ulcers).

Adverse experiences such as oesophagitis, oesophageal ulcers and oesophageal erosions, in some cases severe and requiring hospitalisation, rarely with bleeding or followed by oesophageal stricture or perforation, have been reported in patients receiving treatment with oral bisphosphonates. The risk of severe oesophageal adverse experiences appears to be greater in patients who do not comply with the dosing instruction and/or who continue to take oral bisphosphonates after developing symptoms suggestive of oesophageal irritation.

~~Therefore Patients, especially those with a history of prolonged oesophageal transit time,~~ should pay particular attention to and be able to comply with the dosing instructions (see section 4.2).

~~Physicians should be alert to any signs or symptoms signaling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue Bonviva and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, odynophagia, retrosternal pain or new or worsening heartburn.~~

While no increased risk was observed in controlled clinical trials there have been post-marketing reports of gastric and duodenal ulcers with oral bisphosphonate use, some severe and with complications.

Since Nonsteroidal Anti-Inflammatory Drugs and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

...”

Package Leaflet

Section 2

- Description of changes:

Section 2 of the Package Leaflet has been updated to reflect the new Contraindications and the strengthening of the “Warning and Precautions” wording related to the risk of severe oesophageal irritation as described in the proposed SPC.

- Proposed changes:

“Do not take Bonviva

- If you are allergic (hypersensitive) to ibandronic acid, or to any of the other ingredients of Bonviva.
- If you have certain problems with your oesophagus (the tube connecting your mouth with your stomach) such as narrowing or difficulty swallowing.
- If you can’t stand or sit upright for up to an hour at a time.
- **If you have, or had in the past low blood calcium. Please consult your doctor.**

Do not give Bonviva to children or adolescents.

Take special care with Bonviva

Some people need to be especially careful while they're taking Bonviva. Check with your doctor:

- *If you have any disturbances of mineral metabolism (such as vitamin D deficiency).*
- ~~- *If you can't stand or sit upright for up to an hour at a time.*~~
- *If your kidneys are not functioning normally.*
- *If you have any swallowing or digestive problems.*
- ~~- *If you have ever had problems with your oesophagus (the tube connecting your mouth to your stomach). Problems in your oesophagus might give you symptoms including: severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting. If you develop these symptoms, speak to your doctor straight away.*~~
- *If you are under dental treatment or will undergo dental surgery, tell your dentist that you are being treated with Bonviva.*

Irritation, inflammation or ulceration of the oesophagus (the tube connecting your mouth with your stomach) often with symptoms of severe pain in the chest, severe pain after swallowing food and/or drink, severe nausea, or vomiting may occur, especially if you do not drink a full glass of plain water and/or if you lie down within an hour of taking Bonviva. If you develop these symptoms, stop taking Bonviva and tell your doctor straight away.

...

Section 4

- Description of changes:

Under Section 4 of the Package Leaflet (Possible Side Effects), the current bolded text related to the oesophageal irritation side effects and its symptoms is being kept (even if redundant with the proposed Section 2 text), in order to emphasize the patient information on this common adverse event for all oral bisphosphonates. So that the actions to be taken by the patient in case of symptoms of severe oesophageal reflects the proposed strengthened "Warning and Precautions" SmPC text, "stop taking Bonviva" is being added to the current wording.

- Proposed changes:

"...

Common side effects are heartburn, indigestion, diarrhoea, stomach ache and nausea. Bonviva can also irritate the oesophagus, although you can usually avoid this by taking your dose as described in this leaflet. If you develop symptoms such as severe pain in the chest, severe pain after swallowing food or drink, severe nausea, or vomiting, stop taking Bonviva and tell your doctor straight away.

..."

The CHMP was in agreement with the proposed wording from the MAH however made a comment to the wording in section 2 of the Package Leaflet. The CHMP requested to change the sentence "- *If you can't stand or sit upright for up to an hour at a time.*" to "- *if you can't stand or sit upright for **at least up to an** one hour (60 minutes) at a time*".

This was acceptable for the MAH and implemented in the Package Leaflet.

The MAH also took to the opportunity to update the details of the Finnish local representative and to reflect the new web address of the European Medicines Agency.

OVERALL CONCLUSION

The CHMP is of the opinion that the changes introduced into the SPC and PL are acceptable to address this safety concern and will provide adequate information to the treating physician and the patient. The benefit-risk assessment of ibandronic acid film-coated tablets remains unchanged.