European Medicines Agency

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SCIENTIFIC DISCUSSION
FOR
BONDRONAT

International non-proprietary name: ibandronic acid

Procedure No: EMEA/H/C/000101/II/0049

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

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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. Bondronat is intended for prevention of skeletal events in patients with breast cancer and bone metastases (concentrate for solution for infusion and film-coated tablets), as well as for the treatment of tumour-induced hypercalcaemia with or without metastases (concentrate for solution for infusion only).

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.

Further to the update on the risk of severe oesophageal irritation, the MAH proposes to revise the “contraindications” section of the Bondronat SPCs for vials and tablets to add hypocalcaemia in line with recent Bondronat CDS changes in order to reflect the recommendations already given in the “warnings and precautions” section, i.e. to treat hypocalcaemia before starting Bondronat therapy. This is also in accordance with the medical/clinical practice.

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 the 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 significant 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 BP therapy.

1.2.5 MAH's conclusions on oesophageal safety

This 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, Roche 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.

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.

1.2.6 Hypocalcaemia

The current SPC for Bondronat states in section 4.4 "Warnings and precautions" that hypocalcaemia needs to be effectively treated before starting Bondronat therapy. Hypocalcaemia is basically a contraindication, but this hasn't been reflected in section 4.3 Contraindications so far. The MAH therefore proposes to add hypocalcaemia as contraindication in the SPC for Bondronat tablets and vials. With this change Roche aims to correctly reflect the recommendations already given in the "warnings and precautions" section. Furthermore the proposed change is in alignment with the medical/clinical practice and the approved Bonviva label.

1.3. Update of the SPC, Labelling and Package Leaflet

The revisions to the Product Information pertain to an upgrade of the safety information on risk of severe oesophageal irritation from "Warnings and Precautions" to "Contraindication" with a strengthening of the "Warnings and Precautions" text.
In addition hypocalcaemia is added to the "Contraindications" section in the SPC for Bondronat tablets and vials in order to correctly reflect the already existing recommendations under "Warnings and Precautions" and the medical practice.
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
Bondronat – Vials 2 mg/2 ml and 6 mg/6 ml
Section 4.3 Contraindications
- Description of changes:

In line with the recent Bondronat CDS changes, the MAH proposes to include “hypocalcaemia” as a contraindication in section 4.3 in order to correctly reflect the recommendations already given in the “warnings and precautions” section and the medical practice.

- Proposed changes:

“Hypocalcaemia (see section 4.4).
Hypersensitivity to the active substance or to any of the excipients.”

Bondronat – 50 mg Film-coated tablets

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 and other factors 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.

Furthermore, the MAH proposes to include “hypocalcaemia” as a contraindication in section 4.3 in order to appropriately reflect the recommendations already given in the “warnings and precautions” section in line with the medical practice.

- 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
- 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 ibandronic acid risk minimization measure 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:

“

~~Oral bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore, patients should pay particular attention to the dosing instructions (see section 4.2).~~
~~Physicians should be alert to signs or symptoms signalling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue Bondronat and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.~~

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 Bondronat 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 hospitalization, 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. Patients should pay particular attention 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 and patients should be instructed to discontinue Bondronat and seek medical attention if they develop dysphagia, 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 NSAIDS are associated with gastrointestinal irritation, caution should be taken during concomitant oral medication with Bondronat."

EUPackage Leaflet
Bondronat – Vials 2 mg/2 ml and 6 mg/6 ml
Package Leaflet Section 2

- Description of changes:

Section 2 has been updated to reflect the new contraindication of hypocalcaemia in line with the SmPC and CDS change. The proposed wording is identical to the respective Bonviva text.

- Proposed changes:

"Do not use Bondronat:
- if you are allergic (hypersensitive) to the active substance or any of the other ingrediants of Bondronat.
- if you have, or had in the past low blood calcium. Please consult the doctor.
Bondronat should not be used in children.

Take special care with Bondronat:
If you know or believe that you may have:
- hypersensitivity to other bisphosphonates
- ~~low blood calcium~~
- other disturbances of mineral metabolism (such as vitamin D deficiency)
- severe kidney disease (renal insufficiency i.e. creatinine clearance <30 ml/min)"

Bondronat – 50 mg Film-coated tablets
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. In addition, "hypocalcaemia" is added in line with the SPC change.

- Proposed changes:

"Do not take Bondronat
- if you are allergic (hypersensitive) to ibandronic acid or any of the other ingredients
- 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 at least one hour (60 minutes) at a time
- if you have, or had in the past low blood calcium. Please consult your doctor.
Bondronat should not be used in children.

Take special care with Bondronat
if you know or believe that you may have:
- hypersensitivity to other bisphosphonates
- ~~low blood calcium~~
- other disturbances of mineral metabolism (such as vitamin D deficiency)
- severe kidney disease (renal insufficiency i.e. creatinine clearance <30 ml/min)
or when
~~- you have had problems in the past with your oesophagus (the tube that connects your mouth to your stomach)~~
~~- you become aware of any signs or symptoms suggesting a possible reaction of the oesophagus (this may include: pain in the chest, heartburn, pain after swallowing drink and / or food). If this is the case, you should speak to your doctor without delay.~~

- you have any swallowing or digestive problems.
- you are also taking non-steroidal anti-inflammatory drugs (NSAIDs), since both types of medicinal products (NSAIDs and bisphosphonates) may cause irritation to the stomach and intestine.
- you suffer from galactose intolerance, the Lapp lactase deficiency or have problems with glucose-galactose absorption

Irritation, inflammation or ulceration of the oesophagus (the tube that connects 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 Bondronat. If you develop these symptoms, stop taking Bondronat and tell your doctor straight away."

Package Leaflet Section 3

- Description of changes:

Under Section 3 of the Package Leaflet additional information is added to explain to the patient why it is necessary to remain in an upright position after taking Bondronat for an hour.

- Proposed changes:

"To reduce possible irritation, it is important that you follow the instructions below:
- BEFORE taking your first food, drink or other medicinal products of the day, take your Bondronat tablet with a full glass of plain water only (about 200 mL). Do not take your tablet with any drink other than plain water
- Do not chew, suck, crush or allow the tablet to dissolve in your mouth.
- After taking your Bondronat tablet, wait at least 30 minutes before taking your first food, beverage, or other medication of the day.
- You should remain in an upright (sitting or standing) position while taking Bondronat tablets and remain upright for the next hour (60 minutes) after taking your tablet. If you do not stay upright (standing or sitting), some of the medicine could leak back into your oesophagus.
- It is important to continue taking Bondronat for as long as your doctor prescribes the medicine. Bondronat can help with your condition only if you continue to take the tablets."

Package Leaflet Section 4

- Description of changes:

Additional text is added related to the oesophageal irritation side effects and its symptoms in line with the proposed Section 2 text in order to emphasize the patient information on this common adverse event for all oral bisphosphonates.

- Proposed changes:

"Common side effects include indigestion, nausea, abdominal pain, oesophagitis, tiredness, and low calcium levels in the blood.
Bondronat 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 Bondronat and tell your doctor straight away. "

The MAH also took the opportunity to update the details of the local representatives for minor address changes and to reflect the new webaddress of the European Medicines Agency in the Package Leaflet.

The CHMP was in agreement with the proposed wording from the MAH however made a comment to clarify the method of administration; this change has been reflected in section 4.2 of the SPC for Bondronat film-coated tablets, the labeling and package leaflet:

SPC section 4.2. Posology and method of administration: "…Patients should not chew, ~~or~~ suck or crush the tablet because of a potential for oropharyngeal ulceration…."

Labeling (outer carton) section 5. Methods of administration:

" …Do not suck, chew or crush tablets…"

Package leaflet section 3. How to take Bondronat :

"…Do not chew, suck, crush or allow the tablet to dissolve in your mouth….

OVERALL CONCLUSION

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