22 January 2015
EMA/198447/2015
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Ibandronic acid Accord

### International non-proprietary name: ibandronic acid

### Procedure No. EMEA/H/C/002638/X/0006

## Note

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

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# List of abbreviations

**Ph. Eur.** - European pharmacopoeia

**PFS -** Pre-filled stringe

**API** – active pharmaceutical ingredient

**DMF** – Drug master File

**ASMF** – Active Substance Master File

**NfG** – Note for Guidance

**RMP** – Risk management Plan

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Accord Healthcare Ltd submitted on 03 February 2014 an application for an extension to the Marketing Authorisation to the European Medicines Agency (EMA) for Ibandronic acid Accord 3mg solution for injection, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 indents c and d) of the Commission Regulation (EC) No 1234/2008.

Accord Healthcare Ltd is already the Marketing Authorisation Holder for Ibandronic Acid 2mg concentrate for solution for infusion (EU/1/12/798/001) and 6mg concentrate for solution for infusion in packs of 1, 5 and 10 vials (EU/1/12/798/002-004)

The applicant applied for a line extension to include a new pharmaceutical form, solution for injection, in the following indication:

Ibandronic acid is indicated in adults for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

**The legal basis for this application refers to:**

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and at least literature data on essential similarity with the reference medicinal product Bonviva 3mg solution for injection instead of non-clinical and clinical unless justified otherwise.

***Information on Paediatric requirements***

Not applicable.

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

***Scientific advice***

The applicant did not seek scientific advice at the CHMP.

***Licensing status***

Ibandronic Acid Accord was given a Marketing Authorisation in the EU on 19 November 2012.

## *1.2. Manufacturers*

**Manufacturers responsible for batch release**

Accord Healthcare Ltd
Sage House
319 Pinner Road
North Harrow
HA1 4HF
UNITED KINGDOM

Cemelog-BRS Ltd.
Vasút u. 13
HU-2040 Budaörs
Hungary

## *1.3. Steps taken for the assessment of the product*

The Rapporteur appointed by the CHMP was:

Rapporteur: Alar Irs

- The application was received by the EMA on 03 February 2014.
- The procedure started on 26 February 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 May 2014.
- The PRAC assessment overview was adopted by PRAC on 13 June 2014.
- During the meeting on 23-26 June 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 August 2014.
- The Rapporteurs circulated the joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 24 October 2014.
- The PRAC assessment overview was adopted by PRAC on 6 November 2014.
- During the CHMP meeting on 17-20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 December 2014.
- The Rapporteurs circulated the joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 22 December 2014.
- During the meeting on 22 January 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension of the Marketing Authorisation for 3 mg Ibandronic acid Accord solution for injection in pre-filled syringe.

# 2. Scientific discussion

## *2.1. Introduction*

Ibandronic acid is a 3rd generation nitrogen-containing bisphosphonate which inhibits bone resorption. It is an analogue of pyrophosphate, the naturally occurring inhibitor of mineralization in bone. It is taken up by osteoclasts and inhibits their bone resorbing activity in a dose-dependent manner. It can be given orally or intravenously, and is used in the prevention of skeletal events in breast cancer patients with bone metastases, in the treatment of tumour-induced hypercalcaemia, and in the treatment of post-menopausal osteoporosis.

The already previously approved pharmaceutical form/strengths of Ibandronic acid Accord (i.e. 2mg and 6mg concentrate for solution for infusion) are indicated for:

> Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
>
> Treatment of tumour-induced hypercalcaemia with or without metastases.

The current application concerns a line extension for a generic version of ibandronic acid 3 mg solution for injection in pre-filled syringes (at a concentration of 1 mg/ml), under the trade name Ibandronic acid Accord. The reference product is Bonviva 3 mg solution for injection by Roche Registration Ltd.

The indication applied for Ibandronic Acid Accord 3mg is the same as the authorised indication for the reference medicinal product Bonviva:

> Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1). A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

The recommended dose in osteoporosis is 3 mg, administered as an intravenous injection over 15 – 30 seconds, every three months.

Patients must receive supplemental calcium and vitamin D.

## *2.2. Quality aspects*

### 2.2.1. Introduction

The present application is an extension to the existing Marketing Authorisation for Ibandronic acid Accord, 2 mg and 6 mg, concentrate for solution for infusion.

The finished product is presented as 3 mg (per 3 ml) solution for injection in pre-filled syringe containing ibandronic acid (as ibandronate sodium monohydrate) as active substance.

Other ingredients are: sodium chloride, glacial acetic acid, Sodium acetate trihydrate and water for injections in the solvent, as described in section 6.1 of the SmPC.

The product is available in pre-filled syringes made of glass with an injection needle as described in section 6.5 of the SmPC.

## 2.2.2. Active substance

The information on the active substance has provided according to the Active Substance Master File (ASMF) procedure within the initial Marketing Authorisation Application. The information has been previously assessed at the time of the initial application and subsequently updated via appropriate variations. No changes in manufacturing sites, manufacturing process, control of raw materials, critical steps and intermediates or process validation report other than those already assessed previously have been implemented.

## 2.2.3. Finished medicinal product

### *Description of the product and pharmaceutical development*

The objective of the pharmaceutical development was to develop a generic product of Bonviva 3 mg (per 3 ml), solution for injection in a pre-filled syringe (PFS). The product has an equivalent composition to the reference product using the same commonly used for parenteral pharmaceutical forms excipients as in the reference product. No incompatibilities between them and the active substance are known. The choice and function of the excipients in the formulation have been justified. No preservative or antioxidant is included in the formulation. The polymorphic form and particle size distribution are not considered as critical quality parameters As the active substance is freely soluble in water and is used in the product in solution form.

Comparision of the impurity profile, description, pH, assay, and osmolality of the applicant`s product and Bonviva 3 mg (per 3 ml) has shown no significant differences. The applicant's product is considered equivalent to the reference product.

Osmolality study of both the new as well as reference product has been performed. The data showed that the osmolality does not change during the storage period at controlled room temperature or accelerated conditions. Based on the above data it can be concluded that the osmolality will remain within the normal serum range throughout the proposed shelf-life.

Ibandronic acid Accord 3 mg solution for injection in a pre-filled syringe is an aqueous intravenous solution containing the same active substance in the same concentration as the reference product, thus it is not required to submit a bioequivalence study.

The product presentation includes a CE-marked medical device, the BD Hypoint$^{TM}$ Needle. The CE mark has been attributed for the intended use and the details of the device have been provided. All the PFS components are provided by the Pre-filled Syringe manufacturer as ready to use sterile materials.

The manufacturing process includes terminal sterilisation in the final container under standard conditions described in Ph. Eur. In addition information on validation of the solution filtration and aseptic filling into PFS has also been provided although the product is terminally sterilised. The process has been optimised with regard to the solubilisation of the active substance, the sterilisation method, the selection of inert gas for sparging / flushing of the headspace of PFS, the pH, the manufacturing equipment and filters used. Holding times for the bulk solutions and bulk filled PFS before terminal sterilisation have been established and the integrity of the container closure system has been proven.

Repeated freeze-thaw study was undertaken to evaluate the adverse temperature conditions on the product when cycled through temperature conditions that simulate the short-term excursions outside of the proposed labelled storage conditions likely to be encountered by the drug product during distribution.

No significant effect was observed under the tested conditions in the following parameters: description, pH, assay, related substances and particulate matter. Hence it was concluded that the product is not affected when exposed to temperature variation which may to happen during transit.

## *Manufacture of the product and process controls*

The manufacturing process comprises preparation of bulk solution, filtration, aseptically filling into sterile syringe barrels, closing of syringe barrels and terminal sterilisation in the final container by heating in an autoclave under standard Ph. Eur. conditions. The critical process steps and intermediates have been identified and the proposed in-process controls are adequate for this type of manufacturing process.

The process has been validated with three batches at the smallest proposed batch size. The applicant has committed to perform the validation also on three larger size commercial scale batches. It has been confirmed that the manufacturing process and the equipment to be used for manufacturing of both the proposed batch sizes are the same. The manufacturing process is considered adequately validated.

## *Product specification*

The finished product release and end of shelf life specifications include appropriate tests and limits for appearance, (visual examination), clarity and colour of solution (Ph. Eur.), identification (HPLC and UV- at release only), pH of the solution (Ph. Eur.), extractable volume (Ph. Eur. - at release only), particulate contamination (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), assay (HPLC) and related substances (HPLC). Analytical methods are well described and validated according to ICH guidelines.

Batch analysis data have been presented on three commercial size batches at the lower end of the batch size range. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

## *Stability of the product*

Stability data were provided for three commercial scale batches stored in inverted position under long term conditions at 25 ± 2 °C/ 60 ± 5 % RH for up to 12 months and under accelerated conditions at 40 ±2 °C / 75 ± 5 % RH for six months according to the ICH guidelines. The following parameters have been tested: description, pH, related substances, assay, clarity and colour of solution. Particulate contamination (sub visible particles), sterility and bacterial endotoxins are tested periodically as per the protocol. The methods used are validated and shown to be stability indicating and are the same as those used for release. All parameters remained well within the specification limits. The results of Bacterial endotoxin were always below the specified limit indicating that the product remains sterile throughout the presented stability studies

Photostability testing was conducted in line with the current “Note for Guidance on the Photostability Testing of New Active Substances and Medicinal Products (CPMP/ICH/279/95)”. The study results indicated that the product is light sensitive when exposed to light condition (UV & Visible) as per ICH conditions. However, an additional photostability study was performed under normal room light showed that the product is not significantly sensitive towards normal daylight. Thus it was concluded that no additional storage restriction is necessary. Forced degradation study was performed under UV light, heat, water hydrolysis, acid hydrolysis, base hydrolysis and oxidation confirming the analytical methods are stability indicating.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

### *Adventitious agents*

None of the materials or excipients used in the manufacture of Ibandronic acid Accord 3 mg solution for injection in a pre-filled syringe are of animal origin.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The development of the product has been described well and the choice of excipients is justified. The excipients included in the formulation are well known and commonly used in the parenteral formulations. The container closure system is suitable for this type of formulation and the intended use of the product. The manufacturing process is described in sufficient detail. It is considered to be a standard process and has been properly validated. Sufficient reassurance is provided regarding the sterility of the product during the proposed shelf life. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendation(s) for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

## 2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

## 2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Ibandronic acid Accord 3m solution for injection manufactured by Accord Healthcare Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all IBANDRONIC ACID containing products and the exposure of the environment to the active substance. Thus, the risk to the environment is expected to be similar and not increased.

### 2.3.3. Conclusion on the non-clinical aspects

No new non-clinical studies have been performed and none are required for this type of applications. There are no non-clinical issues to be addressed.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This application is an extension of marketing authorisation to include an additional pharmaceutical form: Solution for injection.

Ibandronic acid Accord was granted marketing authorisation in 2012 for Ibandronic acid Accord, 2mg and 6 mg concentrate for solution for infusion.

The current extension of the marketing authorisation is for a generic version of ibandronic acid 3 mg solution for injection in pre-filled syringe. It is the same concentration as that prepared by dilution of the currently approved/marketed product. The applied product is to be administered as an aqueous intravenous solution containing the same active substance as the reference product. The applied product also contains the same excipients as the reference product (Bonviva).

Due to the parenteral administration mode, bioequivalence can be concluded without further studies and as the composition is the same, no differences in non-clinical or clinical effects are expected.

The safety and efficacy profile of ibandronic acid has been demonstrated in several clinical trials, details of which can be found in the EPAR for Bonviva and Bondronat. In addition, there is a long-term post-marketing experience contributing to the knowledge of the clinical use of this product. Since this application is a generic application referring to the reference medicinal product Bonviva, summary of the clinical literature of ibandronic acid has been submitted and no new clinical studies have been conducted with Ibandronic Acid Accord.

The indication applied for is in accordance with that of the reference medicinal product.

### *Exemption*

The product concerned by the present application contains the same active ingredient in the same concentration and pharmaceutical formulation as the reference product. It has an identical qualitative and quantitative composition in terms of the active substance as its reference medicinal product; also the same excipients are used.

For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) and the applicant has submitted none. Due to the parenteral administration mode, bioequivalence can be concluded without further studies.

### 2.4.2. Post marketing experience

No post-marketing data are available for Ibandronic acid Accord 3mg solution for injection. The medicinal product has not been marketed in any country.

## 2.5. Pharmacovigilance

### Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 5 with the following content:

***Safety concerns***

| | |
|---|---|
| Important identified risk (s) | Osteonecrosis of Jaw<br>Acute Phase reaction<br>Anaphylactic reaction/shock<br>Hypocalcemia |
| Important potential risk (s) | Renal function impairment<br>Atypical femoral fracture<br>Atrial fibrillation |
| Missing information | |

***Pharmacovigilance plan***

Only routine Pharmacovigilance activities will be carried out

***Risk minimisation measures***

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Important Identified Risk: Osteonecrosis of Jaw | Accord product information for ibandronic acid has the following information on this safety concern:<br>**Section 4.4:**<br>Osteonecrosis of the jaw generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.<br>A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).<br>While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the | Currently available data does not support the need for additional risk minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | jaw. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.<br><br>**Section 4.8:**<br><br>The most serious reported adverse reaction is osteonecrosis for the jaw.<br><br>Musculoskeletal and connective tissue disorders: Very rare: Osteonecrosis of jaw<br><br><u>Osteonecrosis of jaw</u><br><br>Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors. | |
| Important identified risk: Acute phase reaction | Accord product information for ibandronic acid has the following information on this safety concern:<br><br>**Section 4.8:**<br><br>General disorders and administration site conditions: Common: Influenza-like illness<br><br><u>Influenza-like illness</u><br><br>A flu-like syndrome consisting of fever, chills, bone | Currently available data does not support the need for additional risk minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | and/or muscle ache-like pain has occurred. In most cases no specific treatment was required and the symptoms subsided after a couple of hours/days. | |
| Important identified risk: Anaphylactic reaction/shock | Accord product information for ibandronic acid has the following information on this safety concern:<br>**Section 4.4:**<br>Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with IV ibandronic acid.<br>Appropriate medical support and monitoring measures should be readily available when ibandronic acid intravenous injection is administered. If anaphylactic or other severe hypersensitivity/allergic reactions occur, immediately discontinue the injection and initiate appropriate treatment.<br>**Section 4.8:**<br>The most serious reported adverse reactions are anaphylactic reaction/shock.<br>Immune system disorders:<br>Very rare: anaphylactic reaction/shock<br>Cases of anaphylactic reaction/shock, including fatal events, have been reported in patients treated with intravenous ibandronic acid. | Currently available data does not support the need for additional risk minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| Important identified risk: Hypocalcaemia | Accord product information for ibandronic acid has the following information on this safety concern:<br>**Section 4.3:**<br>Contraindicated in hypocalcaemia<br>**Section 4.4:**<br>**3 mg SmPC mentions**: Ibandronic acid, like other bisphosphonates administered intravenously, may cause a transient decrease in serum calcium values.<br>Existing hypocalcaemia must be corrected before starting Ibandronic acid injection therapy. Other disturbances of bone and mineral metabolism should also be effectively treated before starting Ibandronic acid injection therapy.<br>All patients must receive adequate supplemental calcium and vitamin D.<br>**2 mg and 6 mg mentions**: Hypocalcaemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ibandronic acid therapy for metastatic bone disease.<br>Adequate intake of calcium and vitamin D is important in all patients. Patients should receive supplemental calcium and/or vitamin D if dietary intake is inadequate.<br>**2 mg and 6 mg SmPC:**<br>**Section 4.8:**<br>Metabolism and nutrition disorders: Common: | Currently available data does not support the need for additional risk minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Hypocalcaemia<br><br>Hypocalcaemia<br><br>Decreased renal calcium excretion may be accompanied by a fall in serum phosphate levels not requiring therapeutic measures. The serum calcium level may fall to hypocalcaemic values.<br><br>**Section 4.9:** Clinically relevant hypocalcaemia should be corrected by intravenous administration of calcium gluconate.<br><br>**3 mg SmPC**<br><br>**Section 4.9:** Based on knowledge of this class of compounds, intravenous overdosage may result in hypocalcaemia, hypophosphataemia, and hypomagnesaemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively. | |
| Important potential risk: Renal function impairment | Accord product information for ibandronic acid has the following information on this safety concern:<br><br>**Section 4.2:**<br><br>**2 mg and 6 mg SmPC:**<br><br>For patients with mild renal impairment (CLcr ≥50 and <80 ml/min) no dose adjustment is necessary. For patients with moderate renal impairment (CLcr | Currently available data does not support the need for additional risk minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | ≥30 and <50 ml/min) or severe renal impairment (CLcr <30 ml/min) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease the following dosing recommendations should be followed: | |

| Creatinine Clearance (ml/min) | Dosage / Infusion time [1] | Infusion Volume [2] |
|---|---|---|
| ≥50 CLcr <80 | 6 mg / 15 minutes | 100 ml |
| ≥30 CLcr <50 | 4 mg / 1 hour | 500 ml |
| <30 | 2 mg / 1 hour | 500 ml |

[1] Administration every 3 to 4 week

[2] 0.9% sodium chloride solution or 5% glucose solution

A 15 minute infusion time has not been studied in cancer patients with CLcr <50 ml/min.

**3 mg SmPC**

**Patients with renal impairment**

Ibandronic acid injection is not recommended for use in patients who have a serum creatinine above 200 µmol/l (2.3 mg/dl) or who have a creatinine clearance (measured or estimated) below 30 ml/min, because of limited clinical data available from studies including such patients.

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | No dose adjustment is necessary for patients with mild or moderate renal impairment where serum creatinine is equal or below 200 µmol/l (2.3 mg/dl) or where creatinine clearance (measured or estimated) is equal or greater than 30 ml/min.<br><br>**Section 4.4:**<br><br>**2 mg and 6 mg SmPC:**<br><br>Clinical studies have not shown any evidence of deterioration in renal function with long term ibandronic acid therapy. Nevertheless, according to clinical assessment of the individual patient, it is recommended that renal function, serum calcium, phosphate and magnesium should be monitored in patients treated with ibandronic acid.<br><br>**3 mg SmPC:**<br><br>Patients with concomitant diseases, or who use medicinal products which have potential for undesirable effects on the kidney, should be reviewed regularly in line with good medical practice during treatment.<br><br>Due to limited clinical experience, Ibandronic acid injection is not recommended for patients with a serum creatinine above 200 µmol/l (2.3 mg/dl) or with a creatinine clearance below 30 ml/min.<br><br>**Section 5.2:**<br><br>**2 mg and 6 mg SmPC:** | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | Exposure to ibandronic acid in patients with various degrees of renal impairment is related to creatinine clearance (CLcr). In subjects with severe renal impairment (mean estimated CLcr=21.2 ml/min), dose-adjusted mean $AUC_{0-24h}$ was increased by 110% compared to healthy volunteers. In clinical pharmacology trial WP18551, after a single dose intravenous administration of 6 mg (15 minutes infusion), mean $AUC_{0-24}$ increased by 14% and 86%, respectively, in subjects with mild (mean estimated CLcr=68.1 ml/min) and moderate (mean estimated CLcr= 41.2 ml/min) renal impairment compared to healthy volunteers (mean estimated CLcr=120 ml/min). Mean Cmax was not increased in patients with mild renal impairment and increased by 12% in patients with moderate renal impairment. For patients with mild renal impairment (CLcr ≥50 and <80 ml/min) no dosage adjustment is necessary. For patients with moderate renal impairment (CLcr ≥30 and <50 ml/min) or severe renal impairment (CLcr <30 ml/min) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease an adjustment in the dose is recommended.<br><br>**3 mg SmPC:**<br><br>Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance (CLcr). | |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | No dose adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or above 30 ml/min).<br><br>Subjects with severe renal impairment (CLcr less than 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2 - 3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg of ibandronic acid, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure, but there was no reduction in tolerability associated with the increase in exposure. Due to the limited clinical experience, Ibandronic acid is not recommended in patients with severe renal impairment. The pharmacokinetics of ibandronic acid in patients with end-stage renal disease was only assessed in a small number of patients managed by haemodialysis, therefore, the pharmacokinetics of ibandronic acid in the patients not undergoing haemodialysis is unknown. Due to the limited data available, ibandronic acid should not be used in all patients with end-stage renal disease. | |
| Important potential risk: Atypical femoral | Accord product information for ibandronic acid has the following information on this safety concern:<br><br>**Section 4.4:**<br><br>Atypical subtrochanteric and diaphyseal femoral | Currently available data does not support the need for additional risk |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| fractures | fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.<br><br>**Section 4.8:**<br><br>The most serious reported adverse reaction is atypical fractures of the femur.<br><br>Musculoskeletal and connective tissue disorders: Rare: Atypical subtrochanteric and diaphyseal | minimization activities. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | femoral fractures | |
| Important potential risk: Atrial fibrillation | None | Currently available data does not support the need for additional risk minimization activities. |

### *2.6. Product information*

The Product Information has been revised as per current version of QRD template (QRD version 9, 03/2013) and as in-line with the last approved version of innovator's (Bonviva) product information.

### 2.6.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Bonviva and Ibandronic acid Accord. The justification has been found acceptable.

## 3. Benefit-risk balance

This application concerns a generic version of ibandronic acid solution for injection. The reference product Bonviva is indicated for:

Treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference

medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

# 4. Recommendations

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ibandronic Acid Accord in the approved indication:

Treatment of osteoporosis in postmenopausal women at increased risk of fracture. A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established

is favourable and therefore recommends the granting positive opinion for granting an extension of the Marketing Authorisation for Ibandronic acid Accord 3 mg solution for injection in pre-filled syringe subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Ibandronic acid Accord 3 mg (for osteoporosos indications):Medicinal product subject to medical prescription.

***Conditions and requirements of the Marketing Authorisation***

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.***

Not applicable.