EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/711044/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ibandronic acid Accord

ibandronic acid

Procedure No. **EMEA/H/C/002638**

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

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Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd. submitted on 30 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ibandronic acid Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 September 2011.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, and treatment of tumour-induced hypercalcaemia with or without metastases.

The legal basis for this application refers to:

The application submitted is composed of administrative information and complete quality data with the reference medicinal product Bondronat instead of non-clinical and clinical data unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Bondronat 2 mg and 6 mg, concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 22-06-1996
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/96/012/004, EU/1/012/012/011, EU/1/012/012/012, EU/1/012/012/013

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Bondronat 2 mg and 6 mg, concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 22-06-1996
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/96/012/004, EU/1/012/012/011, EU/1/012/012/012, EU/1/012/012/013

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Not applicable.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP and the evaluation team was:

Rapporteur: Alar Irs

- The application was received by the EMA on 30 December 2011.
- The procedure started on 25 January 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2012.
- During the meeting on 21 to 24 May 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 May 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 July 2012.
- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 31 August 2012.
- During the meeting on 17 to 20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ibandronic acid Accord on 20 September 2012.

2. Scientific discussion

2.1. Introduction

Ibandronic acid Accord 2 mg and 6 mg concentrate for solution for infusion is a generic medicinal product of Bondronat, which has been authorised in the EU since 22 June 1996.

The active substance of Ibandronic acid Accord is ibandronic acid a third generation bisphosphonate (ATC Code: M05BA06) which inhibits bone resorption, it is an analogue of pyrophosphate, the naturally occurring inhibitor of mineralization in bone.

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 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 Bondronat, summary of the clinical data of ibandronic acid is available and no new clinical studies regarding pharmacology, pharmacokinetics and efficacy and safety have been conducted.

Ibandronic acid Accord is administered intravenously and is 100% bioavailable, therefore, a bioequivalence study versus the reference product Bondronat was not required.

The approved indication is: prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, and treatment of tumour-induced hypercalcaemia with or without metastases.

The indication and posology proposed for Ibandronic acid Accord is the same as authorised for the corresponding pharmaceutical form of the Reference medicinal product.

The recommended posology is as follows:

Prevention of skeletal events in patients with breast cancer and bone metastases :
The recommended dose is 6 mg intravenous injection given every 3-4 weeks. The dose should be infused over at least 15 minutes.

Treatment of tumour-induced hypercalcaemia :
Prior to treatment with ibandronic acid the patient should be adequately rehydrated with 9 mg/ml (0.9%) sodium chloride. Consideration should be given to the severity of the hypercalcaemia as well as the tumour type. In general patients with osteolytic bone metastases require lower doses than patients with the humoral type of hypercalcaemia. In most patients with severe hypercalcaemia (albumin-corrected serum calcium* ≥3 mmol/l or ≥12 mg/dl) 4 mg is an adequate single dosage. In patients with moderate hypercalcaemia (albumin-corrected serum calcium <3 mmol/l or <12 mg/dl) 2 mg is an effective dose. The highest dose used in clinical trials was 6 mg but this dose does not add any further benefit in terms of efficacy.

In most cases a raised serum calcium level can be reduced to the normal range within 7 days.

A limited number of patients (50 patients) have received a second infusion for hypercalcaemia. Repeated treatment may be considered in case of recurrent hypercalcaemia or insufficient efficacy.

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 dosing recommendations should be followed (see Section 5.2).

No dosage adjustment is required for patients with hepatic impairment, nor the elderly.

The safety and efficacy of ibandronic acid in children and adolescents below age 18 years have not been established; no data are available.

Complete information on posology, calculation of albumin-corrected serum calcium, preparation and administration times can be found in the SmPC.

The applicant did not apply for the other pharmaceutical form of the reference product (Bondronat - tablets).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion containing 2 mg and 6 mg of ibandronic acid, as ibandronate sodium monohydrate, as active substance. The full composition is described in section 6.1. of the SmPC.

The product is available in glass vial (type I) with fluorotec plus rubber stopper and aluminium seals with flip-off cap.

2.2.2. Active substance

Ibandronate sodium monohydrate is a white to almost white crystalline slightly hygroscopic powder, freely soluble in water and 0.1N Sodium Hydroxide solution, practically insoluble in ethanol and diethyl ether. The chemical name is 3-(N-methyl-N-pentyl) amino-1-hydroxypropane 1,1-diphosphonic acid, monosodium salt, monohydrate and has the following structural formula: $C_9H_{22}NNaO_7P_2 \cdot H_2O$.

Ibandronate sodium monohydrate is a non-chiral molecular structure.

Polymorphism is not relevant since the active substance is marketed as a solution.

The structure of ibandronate sodium monohydrate was confirmed by means of elemental analysis, mass spectrometry, IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy. XRDP analysis shows a characteristic fingerprint for polymorphic form A. Thermal gravimetric analysis confirm water content between 4.5 %w/w and 6.5 %w/w, which is established for the monohydrate form.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure within the current Marketing Authorisation Application.

Manufacture

The active substance is sourced from one active substance manufacturer.

The active substance is manufactured in 3 steps of chemical synthesis, one salt formation and one purification stage starting from well defined starting materials.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for identification (IR, HPLC), pH, related substances (HPLC), assay (HPLC), residual solvents (GC), water content (KF), heavy metals (PhEur), and bacterial endotoxins.

Batch analysis data is provided on 3 commercial scale batches produced with the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly.

All compendial and in-house test methods are adequately validated.

Stability

Three production scale batches of the active substance packed in the intended commercial package from the proposed manufacturer were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 48 months, and accelerated (40°C/75%RH) for up 6 months. Satisfactory results on stress conditions (photostability, acid, hydrolysis and oxidation) were also provided.

The following parameters were tested: description, identification, water content, related substances and assay.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 5 years in the proposed container tightly closed in order to protect from light and moisture.

2.2.3. Finished medicinal product

The medicinal product consists of a clear colourless solution in a clear glass vial (type I) with flip-off seal (fluorotec rubber stopper). This medicinal product is supplied in vials as a sterile concentrate for solution for infusion containing 2 mg/2 ml & 6 mg/6 ml of ibandronic acid.

Pharmaceutical development

The formulation is qualitatively identical to that of the originator.
All excipients are commonly used for parenteral pharmaceutical forms and are of compendial quality. The list of excipients is included in section 6.1 of the SmPC.

The primary packaging proposed is described in the SmPC. The material complies with PhEur requirements and it is adequate to support the stability and use of the product.

Ibandronic acid Accord is administered intravenously and is 100% bioavailable, therefore, a bioequivalence study versus the reference product Bondronat was not required.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The product is manufactured by a standard manufacturing process with a standard terminal sterilisation in the final container.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly

produce finished product of the intended quality. The in process controls are adequate for this pharmaceutical form.

The batch analysis data on 3 pilot scale and 3 production scale batches shows that the medicinal product can be manufactured reproducibly according to the agreed finished product specification.

Product specification

The finished product release specifications include appropriate tests for description, identification (HPLC and UV), pH, extractable volume, particulate contamination, bacterial endotoxins, sterility, related substances (HPLC), assay (HPLC) and clarity of solution.

Batch analysis results in 3 pilot scale and 3 production scale batches confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

Stability of the product

Stability data of three commercial scale batches stored under long term conditions for 12 months at 25ºC/60%RH and for up to 6 months under accelerate conditions at 40ºC/75%RH according to ICH guidelines were provided. The container closure system was similar to that proposed for marketing.

Samples were tested for description, pH, related substances, assay, clarity and colour of solution, particulate contamination, sterility and bacterial endotoxins.

Photostability studies were conducted and indicate that drug product is not sensitive to light.

In-use stability studies in 0.9 % NaCl and 5 % glucose solution for infusion have been presented.

All investigated parameters remain within specified limits. The stability studies provided support the shelf-life and in-use shelf life under the storage conditions declared in the SmPC.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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 the clinic.

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 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 environmental risk is expected to be similar and not increased.

2.3.3. Conclusion on the non-clinical aspects

There are no objections to approval of Ibandronic acid Accord concentrate for solution for infusion from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for concentrate for solution for infusion containing ibandronic acid.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of ibandronic acid based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product.

For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

N/A

Exemption

There are no bioequivalence studies submitted with this application. Bioequivalence testing with the reference product is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1):

"Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product".

The product 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.

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.

2.4.2. Post marketing experience

No post-marketing data are available for this generic medicinal product; it has not been marketed in any country.

2.4.3. Conclusions on clinical aspects

There are no objections to approval of Ibandronic acid Accord concentrate for solution for infusion from a clinical point of view.

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 applicant submitted a risk management plan.

Table 1. Summary of the risk management plan

Safety concern	Pharmacovigilance activities (routine and additional)	Risk minimisation activities (routine and additional)
Identified Risks: Osteonecrosis of the jaw	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal detection.	Covered under following sections of the SPC: 4.4 and 4.8. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference product.
Identified Risks: Acute phase reaction	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal detection.	Covered under following sections of the SPC: 4.8. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference product.
Identified Risks: Hypocalcaemia	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal	Covered under following sections of the SPC: 4.2, 4.4, 4.8 and 5.1. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference

Safety concern	Pharmacovigilance activities (routine and additional)	Risk minimisation activities (routine and additional)
	detection.	product.
Potential Risks: Renal function impairment	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal detection.	Covered under following sections of the SPC: 4.2, 4.4, 4.5 and 4.8. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference product.
Potential Risks: Atypical femoral fractures	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal detection.	Covered under following sections of the SPC: 4.4 and 4.8. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference product.
Potential Risks: Atrial fibrillation	Routine pharmacovigilance including close monitoring of the safety concerns by doing enhanced follow up Cumulative analysis in signal detection.	Covered under following sections of the SPC: 4.8. Periodic comparison of safety-related sections of the Accord SPC will be done to update Accord SPC in line with the SPC of the innovator/reference product.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

Not applicable

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of ibandronic acid concentrate for solution for infusion. The reference product Bondronat is indicated for prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases and for treatment of tumour-induced hypercalcaemia with or without metastases. 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.

There are no bioequivalence studies submitted with this application, and this is not required under the provisions of the "Guideline on the Investigation of Bioequivalence" (CPMP/QWP/EWP/1401/98 Rev.1), as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

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. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ibandronic acid Accord in the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, and treatment of tumour-induced hypercalcaemia with or without metastases is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the Guideline on good pharmacovigilance practices on Risk Management Systems for medicinal products for human use, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

PSUR cycle

Not applicable

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

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states.

Not applicable.