



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
EMA/CHMP/90168/2011

Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Ibandronic Acid Hexal

International nonproprietary name: ibandronic acid

Procedure No. EMEA/H/C/002366

This Withdrawal Public Assessment Report is based on the CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjugation with the "Question and Answer" document on withdrawal of the application.



Table of contents

1. Background information on the procedure	3
1.1. Submission of the dossier.....	3
1.2. Steps taken for the assessment of the product	4
2. Scientific discussion	4
2.1. Introduction	4
Problem statement	4
2.2. Quality aspects	5
2.2.1. Introduction	5
2.2.2. Active Substance	5
2.2.3. Medicinal Product	6
2.2.4. Discussion on chemical, and pharmaceutical aspects	8
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects	8
2.3. Non-Clinical aspects	8
2.3.1. Introduction	8
2.4. Clinical Aspects.....	9
2.4.1. Introduction	9
2.4.2. Pharmacokinetics	9
2.4.3. Pharmacodynamics.....	12
2.4.4. Additional data.....	12
2.4.5. Post marketing experience.....	12
2.4.6. Discussion on Clinical aspects.....	13
2.4.7. Conclusions on clinical aspects	13
2.5. Pharmacovigilance.....	13
2.6. User consultation	14
2.7. Benefit/risk assessment and recommendation	14

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hexal submitted on 6 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ibandronic Acid Hexal, through the centralised procedure falling within the Article 3 (3) – ‘Generic of a Centrally authorised product’ of Regulation (EC) No. 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 June 2010.

Pursuant to Article 82(1) of Regulation (EC) No 726/2004, this application was submitted as a duplicate to Iasibon, 50 mg film-coated tablets, which was authorised on 21 January 2011.

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.

The legal basis for this application refers to:

Article 10(1) of Directive 2001/83/EC, as amended.

The application submitted is composed of administrative information, complete quality data and at least a bioequivalent study with the reference medicinal product **Bondronat**.

The legal basis for this application refers to Article 10(1) of Directive 2001/83/EC, as amended.

The chosen reference product is:

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

- Product name, strength, pharmaceutical form: Bondronat 50 mg Film-coated tablets.
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1996-06-25
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/96/012/009-010

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

- Product name, strength, pharmaceutical form: Bondronat 50 mg Film-coated tablets.
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1996-06-25
- Marketing authorisation granted by: Community
- Marketing authorisation number: EU/1/96/012/009-010

■ 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:

- Product name, strength, pharmaceutical form: Bondronat 50 mg Film-coated tablets.
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1996-06-25
- Marketing authorisation granted by: Community
- Marketing authorisation number(s): EU/1/96/012/009-010
- Bioavailability study number(s): Project No. IAT-P9-457

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 was:

Rapporteur: **Dr. Jens Ersbøll**

- The application was received by the Agency on 6 December 2010.
- The procedure started on 19 December 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 27 January 2011.
- During the meeting on 14-17 February 2011 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 Hexal on 17 February 2011.

2. Scientific discussion**2.1. Introduction****Problem statement**

Ibandronic acid is a 3rd generation 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 is 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 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, except a bioequivalence study, have been conducted with Ibandronic acid Hexal.

The indication and posology proposed for Ibandronic acid Hexal 50 mg (film coated tablets) is the same as the indication and posology authorised for the reference medicinal product Bondronat 50 mg (film-coated tablets):

Tablets:

Prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

The recommended dose is one 50 mg film-coated tablet daily.

For patients with mild renal impairment ($\text{CLcr} \geq 50$ and < 80 mL/min) no dosage adjustment is necessary. For patients with moderate renal impairment ($\text{CLcr} \geq 30$ and < 50 mL/min) or severe renal impairment ($\text{CLcr} < 30$ mL/min) being treated for the prevention of skeletal events in patients with breast cancer and metastatic bone disease the dosing recommendations as provided in the SmPC should be followed.

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

Ibandronic acid Hexal is not recommended for patients below age 18 years due to insufficient data on safety and efficacy.

Complete information on posology and administration times can be found in the SmPC.

The applicant did not apply for the other pharmaceutical form of the reference product (Bondronat concentrate for solution for infusion), which is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases and for the treatment of tumour-induced hypercalcaemia with or without metastases.

2.2. Quality aspects

2.2.1. Introduction

Ibandronic acid Hexal presented as film-coated tablets contain 50 mg of ibandronic acid as active substance (corresponding to 56.26 mg of ibandronic sodium monohydrate). The other ingredients are povidone K30, cellulose microcrystalline, starch pregelatinised, crospovidone, purified water, silica colloidal anhydrous and glycerol dibehenate. The film coating consists of titanium dioxide, lactose monohydrate, hypromellose, polyethylene glycol 400, ethanol and purified water. The film-coated tablets are marketed in Polyamide/Al/PVC - Aluminum (PA/ALL/PVC/alu) blisters packed in cartons.

2.2.2. Active Substance

The active substance in this product is ibandronate sodium monohydrate or 3-(N-methyl-N-pentyl) amino-1-hydropropane-1, 1- di phosphonic acid, monosodium salt, monohydrate, and has the following structure:

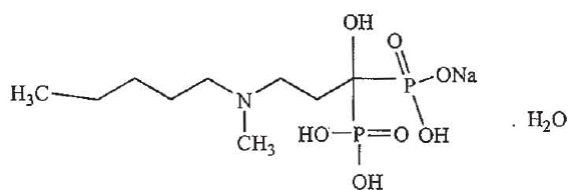


Figure 1: Chemical structure of Ibandronate sodium monohydrate

Ibandronate sodium monohydrate is an off white to white coloured powder. It is sparingly soluble in water. This active substance is also slightly hygroscopic.

Ibandronate sodium monohydrate has no chiral centres and is therefore not optically active.

2.2.2.1. Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure. A 2 step synthesis has been well described. Controls of critical steps and intermediates are sufficient to ensure quality of the active substance. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented. The purified active substance is packed in clear white polyethylene bag that is filled with nitrogen and tied. This bag is then put in a triple laminated black bag with a silica gel bag and is sealed before being put in a HDPE container with a HDPE lid.

The chemical structure of ibandronate sodium monohydrate has been confirmed by appropriate testing at release and during stability spectroscopy (IR, ¹H-NMR, UV, MS, and ¹³C-NMR). In addition the molecular weight was determined by elemental analysis. The X-ray diffraction studies demonstrated that polymorphic form B is indeed manufactured routinely by the defined synthetic route. For confirmation, an XRD polymorphic form test is included in the drug substance specification and is also monitored during stability.

2.2.2.2. Specification

The active substance specification includes tests for physical appearance, solubility, identification (IR and HPLC), solubility, loss on drying, heavy metals, impurities (HPLC), phosphate and phosphate content, assay (HPLC), residual solvents (GC), sodium content and physical form by XRD. It was noted that all specifications reflect the relevant quality attributes of the active substance.

A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable to control the quality of the active substance

Impurities have been evaluated and found to be acceptable from the point of view of safety.

Data on three production scale batches of ibandronate sodium monohydrate have been provided and the requirements in the drug substance specification were met.

2.2.2.3. Stability

The stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: description, identification, loss on drying, related substances, phosphate & phosphate content, XRD and assay. It was noticed that the test methods applied are those used for release of the active substance.

It can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3. Medicinal Product

2.2.3.1. Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified.

The main aim of the applicant was to develop a medicinal product essentially similar to the reference product and demonstrating acceptable stability in the proposed container closure systems. In this context, the characteristics of the reference product have been studied in terms of its qualitative composition along with its physico-chemical properties. The excipients for this particular formulation were selected carefully and are commonly used in pharmaceutical formulations. The comparative dissolution profiles were provided. The results demonstrated that the generic batches used for the bioequivalence studies and the EU brand leader batches are similar with respect to dissolution rate.

2.2.3.2. *Manufacture of the product*

The proposed commercial manufacturing process involves standard technology and it is divided into nine main steps: weighing of the raw materials, first mixing, wet granulation, drying, dry granulation, second mixing, compression, coating and packaging.

Furthermore, the equipment used is commonly available in the pharmaceutical industry. The critical steps in the manufacturing process have been identified and controlled.

It was noticed that the manufacturing process has been adequately validated for one pilot and two scale batches the results of the manufacturing validation reports were considered satisfactory.

2.2.3.3. *Product specification*

The product specification is standard for tablets and contains tests with suitable limits for appearance, average mass (Ph.Eur), loss on drying (Ph.Eur), disintegration (Ph.Eur), hardness (Ph.Eur), identification (HPLC and FTIR), assay impurities (HPLC), dissolution, residual solvents (GC), microbial contamination (Ph.Eur), identification of titanium dioxide, tightness of blister (Ph.Eur) and packaging.

Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. Their limits are justified by reference to stability studies.

All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.

The batch analysis data for three scale batches confirm that the tablets can be manufactured reproducibly according to the agreed finished product specifications.

2.2.3.4. *Stability of the product*

Three batches of each of the film-coated tablets packed in intended market containers were placed on stability under ICH conditions 25° C/60% RH, 30° C/65% RH and 40° C/75% RH. The following parameters were controlled: appearance, identification, average mass, loss on drying, assay, degradation products, dissolution, hardness, disintegration, tightness of blisters and microbial contamination

It was noted that a forced degradation study has also been conducted on a single batch of the drug product (heat, water hydrolysis, acid hydrolysis, base hydrolysis, photo degradation and hydrogen peroxide). No significant changes were observed in the finished product.

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. Dissolution results (film coated tablets) indicate comparability with the reference product (Bondronat) and this is confirmed by in-vivo bioequivalence results (see the clinical part of the report).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

At the time of the CHMP opinion, all quality issues have been resolved quality. In this context, it can be concluded that the quality characteristics of the finished product are adequate and should have a satisfactory and uniform performance in the clinic.

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.

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Ibandronic Acid Hexal manufactured by Hexal AG 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 ERA is expected to be similar and not increased.

2.4. Clinical Aspects

2.4.1. Introduction

This is an abridged application for film-coated tablets containing ibandronic acid.

To support the marketing authorisation application the applicant has submitted a single bioequivalence study, IAT-P9-457. This study was the pivotal study for the assessment.

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 for the pharmaceutical form applied for.

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

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Bioanalytical and PK inspections have been performed in October 2007 and July 2008.

2.4.2. Pharmacokinetics

Methods

Study design

Single dose, replicate, crossover, laboratory blinded, 4-period, 2 sequence, comparative bioavailability study of Ibandronate 50 mg film-coated tablets in healthy male and female volunteers under fasting conditions and a wash-out period of 21 days between each of the 4 administrations. 1x 50 mg was administered in each period.

Dosing period 1: 16/4-2009

Dosing period 2: 7/5-2009

Dosing period 3: 28/5-2009

Dosing period 4: 18/6-2009

	Period 1	Period 2	Period 3	Period 4
Sequence 1 (n= 20)	Test	Reference	Test	Reference
Sequence 2 (n= 20)	Reference	Test	Reference	Test

Test and reference products

The test formulation of ibandronic acid 50mg film-coated tablets manufactured by Pharmathen S.A. (batch No. 0900628, batch size 100.000 tablets, exp. date 08/2009) has been compared to Bondronat

manufactured by Roche Pharma AG (Batch No: B1014B71, from the UK=EU market, exp. date 07/2011).

Population(s) studied

40 healthy (black (33)/white (4)/other (3)) male/female subjects (19-51 years) participated in the study.

Analytical methods

The blood samples were analysed by HPLC MS/MS method for detection of ibandronate. The linear concentration range for the analysis of plasma samples is between 0.250 ng/ml (=LOQ) to 250.000 ng/ml.

Date of start and finish of the bio-analytical phase: 30/6-2009 to 22/7-2009.

Time from first blood sample collection to last sample analysis was 97 days (16/4-2009 to 22/7-2009). The long-term stability of Ibandronate in human plasma covers 158 days at a temperature of -20°C.

Reanalysis of samples: There were no samples retested for pharmacokinetic reasons in this study. The criteria for determining which sample values were to be re-assayed for pharmacokinetic reasons are described in SOP of the study sponsor.

Drop-out subjects were not analysed.

A validated HPLC method using MS/MS detection was employed in determining the concentrations of ibandronate in human plasma. Of 2352 analysable subject samples received, 2349 samples were successfully assayed at the CRO's Lab. The method has met acceptance criteria with respect to specificity, sensitivity, precision, accuracy, matrix effect, linearity and dilution integrity. Stability evaluations in matrix and solutions have also met acceptance criteria, demonstrating insignificant degradation of ibandronate and ibandronate-d3 (IS) over the specified storage durations and conditions.

Pharmacokinetic Variables

Bioequivalence was determined based on AUC_{0-t}, AUC_{0-∞} and C_{max} as primary variables with 90% confidence intervals of 0.80 to 1.25 for each parameter.

The parameters calculated were AUC_{0-t}, AUC_{0-∞}, C_{max}, t_{max}, Kel and t_{1/2} el.

The pharmacokinetic parameters assessed are considered adequate.

Statistical methods

ANOVA was performed on the ln-transformed C_{max}, AUC_{0-t} and AUC_{0-∞}. The ANOVA model included sequence, subject nested within sequence, period and treatment. Nonparametric test was carried out on t_{max}. Statistical and pharmacokinetic analysis were generated using Kinetic, version 9.00, an application developed at the CRO and SAS® version 9.1 (Mixed procedure).

Criteria for conclusion of bioequivalence:

Statistical Analysis based on a parametric ANOVA model was performed on two sided 90% confidence interval of the ratio of geometric means for the C_{max}, AUC_t, AUC_∞, based on ln-transformed data, rank transformed test for T_{max}. Level of significance was assessed at the two-sided 5% level. For the C_{max}, the observed intra-subject variation for the reference product (Bondronat 50 mg film-coated tablets) was greater than 30%. As per protocol, a widened acceptance range of 75 to 133% was therefore considered in the assessment of bioequivalence for the C_{max} parameter. The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} were within the acceptance range of 75 to 133%. In fact, they were also within the conventional bioequivalence range of 80-125%.

For the AUC_t and AUC_∞, the Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval were all within the acceptance range of 80 to 125%.

Ibandronate exhibits a high intra-individual variability with a CV greater than 30%. Furthermore, pharmacokinetic parameters do not significantly affect the clinical response. In fact, ibandronate bone concentration has more influence on the efficacy parameters than the plasma concentration. In addition, ibandronate is well tolerated in humans without any adverse effects on hepatic and renal function and has a wide therapeutic index. No relation between adverse events frequency and oral dose has been observed. Thus, according to this justification, the bioequivalence range for C_{max} criterion may be widened to 75-133%.

Results

Pharmacokinetic parameters for the 35 subjects who completed the study are presented in table 1. The terminal phases of ibandronate could not be adequately estimated for one subject. Therefore the parameters AUC, T_{1/2} and K_{el} were not calculated for this subject.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

N=35

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	42.936 (30.658)	45.852 (32.673)	13.923 (14.570)	0.67 (0.23-2.13)	6.40 (4.69)
Reference	39.686 (23.013)	42.217 (24.522)	11.114 (5.530)	1.00 (0.50-3.00)	6.01 (4.31)
*Ratio (90% CI)	96.51 (85.81-108.55)	97.01 (86.08-109.34)	99.21 (87.33-112.71)	-	-
CV (%)	44.34%	40.22%	40.81%	-	-
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration T _{max} time for maximum concentration T _{1/2} half-life					

*ln-transformed values

No statistically significant between-treatment differences were observed for any of the pharmacokinetic parameters under study. The 90% confidence intervals for each primary parameter were within the predefined limits and therefore bioequivalence with the reference product is established.

Safety data

The bioequivalence study showed no difference in safety profile between the test and the innovator product.

Twenty (20) of the forty (40) subjects experienced a total of forty-three (43) adverse events during the study. Eighteen (18) adverse events (11 different types) were reported after the single dose administration of the test product and twenty-seven (27) adverse events (18 different types) were reported after the single dose administration of the reference product. Two (2) adverse events (blood potassium increased and platelet count increased) associated with the post-study laboratory test results were imputed to both formulations. Fifteen (15) adverse events judged to be possibly related to the investigational products (ear pain, fatigue, oedema peripheral, platelet count increased, dizziness, headache (4 episodes) and somnolence (6 episodes) were unexpected. No serious adverse events (SAEs) were recorded in this study.

All reported adverse events, for subjects that were included in the statistical analysis, were considered to have negligible impact or no impact on the pharmacokinetic profiles of the drugs and the assessment of bioequivalence.

Conclusions

Based on the presented bioequivalence study, Ibandronic acid Hexal (duplicate of Iasibon) is considered bioequivalent with Bondronat.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Additional data

Not applicable.

2.4.5. Post marketing experience

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

2.4.6. Discussion on Clinical aspects

The CHMP assessment addressed pharmacokinetic data in respect of a single bioequivalence study (IAT-P9-457). The study design is considered adequate with regard to wash-out period, sampling period and sampling scheme according to expected T_{max} and T_{1/2}. The study was conducted in line with GCP.

The CHMP had requested justification of the chosen population as the majority of study subjects in study IAT-P9-457 are black, while the SmPC of the reference product states that there are only very few data available on patients with African origin. Clarification and justification had also been requested for exclusion from the statistical analyses of plasma concentrations for a number of samples. Additional analyses had been provided and based on the justifications and clarifications provided, the CHMP considered that these aspects did not impact on the validity of the study results.

The results of the bio-equivalence study show that the 90% confidence intervals for each primary parameter fall within the normal acceptance limits of 80-125% and therefore bioequivalence with the reference product is established.

2.4.7. Conclusions on clinical aspects

Based on the presented bioequivalence study the test formulation of ibandronic acid 50mg film-coated tablets is considered bioequivalent with Bondronat 50mg film-coated tablets.

2.5. Pharmacovigilance

PSUR

The next data lock point for the reference medicinal product is 24 June 2011.

The PSUR of the reference medicinal product is on a 1-yearly cycle. The PSUR submission schedule should follow the PSUR schedule for the reference product.

The PSUR submission schedule for Ibandronic acid Hexal film-coated tablets should follow the PSUR submission schedule for the reference medicinal product.

Description of the 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 Plan

The applicant has submitted a justification for the absence of a risk management plan, on the basis that the active ingredient has been in use for many years and has a well established safety profile.

Routine pharmacovigilance activities according to volume 9A/ICH will be undertaken whilst the product is in the market, including careful review of individual case safety reports, literature review, signal detection procedures and generation of the required safety reports.

The risk minimisation measures agreed for the reference product should be followed.

2.6. User consultation

The results of user consultation provided indicate that the Package leaflet is well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflet is readable and users are able to act upon the information that it contains.

2.7. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application for Ibandronic acid Hexal concerns a generic version of ibandronic acid 50 mg tablets. The reference product Bondronat 50mg tablets is indicated for prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

No nonclinical studies have been provided for this generic 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.

The pivotal basis forms a bioequivalence study with a single dose, replicate, crossover, laboratory blinded, 4-period, 2 sequence design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points and overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of ibandronic acid 50mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the reference product Bondronat 50 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} , $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

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.

Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Ibandronic acid Hexal in prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases, was favourable and therefore recommended the granting of the marketing authorisation.