EMA/598319/2010

Evaluation of Medicines for Human Use

Assessment report

Ibandronic Acid Teva

International Nonproprietary Name: ibandronic acid

Procedure No. EMEA/H/C/001195

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 1 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ibandronic Acid Teva, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to:

A - Centralised / Article 10(1) / Generic application.

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, 2 mg, Concentrate for solution for infusion
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 1996-06-25
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: EU/1/96/012/004

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: Bonviva, 150 mg, film-coated tablet
- Marketing authorisation holder: Roche Registration Limited
- Date of authorisation: 2004-02-23
- Marketing authorisation granted by: **Community**
- Community Marketing authorisation number: EU/1/03/265/003-004
- Bioavailability study number(s): IAT-P7-289

Medicinal Product which is or has been authorised in accordance with Community provisions in force used in other studies

- Not applicable

Scientific Advice:

The applicant did not seek scientific advice at the CHMP.

1.1.1. Licensing status:

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

The Rapporteur appointed by the CHMP was Robert James Hemmings.

1.2. Steps taken for the assessment of the product

- The application was received by the Agency on 1 July 2009.
- The procedure started on 22 July 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 October 2009
- During the meeting on 16-19 November 2009, 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 19 November 2009
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 February 2010
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 April 2010
- During the CHMP meeting on 19-22 April 2010 the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- During the meeting on 21-24 June 2010 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 Teva on 24 June 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 17 September 2010.

2. Scientific discussion

2.1. Introduction

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 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 products Bondronat and Bonviva, 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 Teva.

The indication proposed for Ibandronic Acid Teva 50 mg is the same as the authorised indication for the reference medicinal product Bondronat:

Ibandronic Acid Teva is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

Posology

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

The indication proposed for Ibandronic Acid Teva 150 mg is the same as the authorised indication for the reference medicinal product Bonviva:

Ibandronic Acid Teva is indicated 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.

Posology

The recommended dose is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

2.2. Quality aspects

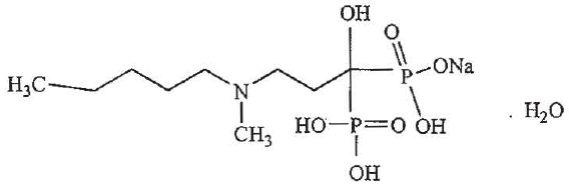
2.2.1. Introduction

Ibandronic Acid Teva is presented as film-coated tablets containing 50 mg and 150mg of ibandronic acid as active substance. The excipients used in the preparation of the film-coated tablets are well known excipients such as Cellulose microcrystalline, Povidone K-30, Crospovidone (type A),Silica colloidal anhydrous and Stearic acid. Other ingredients are defined in the SPC, section 6.1.

Ibandronic Acid Teva film-coated tablets are packaged in PVC/Aclar/PVC – Aluminium blisters in cardboard boxes.

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- diphosphonic acid, monosodium salt, monohydrate, and has the following structure:



Ibandronate sodium monohydrate is an off white to white coloured powder. It is sparingly soluble in water across the pH range or 3 to 8 and has a pKa of 6.0. Ibandronate sodium monohydrate is also slightly hygroscopic in nature.

Ibandronate sodium monohydrate has no chiral centres and is therefore not optically active. It has different polymorphic forms and the B polymorphic form is reported to be the form routinely manufactured by the ASMF holder, as determined by X-ray diffraction studies.

2.2.2.1. Manufacture

Information about manufacturing process has been provided using Active Substance Master File (ASMF) procedure. A three step synthesis has been well described. Controls of critical steps and intermediates are sufficient to ensure quality of the final compound.

The final structure of ibandronate sodium monohydrate is stated to be assured by the full characterisation of the starting material as well as the controls exercised during the synthetic route. The chemical structure of ibandronate sodium monohydrate has been confirmed by spectroscopy (IR, UV, ^{1}H-NMR and ^{13}C-NMR), elemental analysis and mass spectrometry. The physical characteristics have also been determined by X-ray diffraction (XRD) and DSC studies.

Ibandronate sodium monohydrate is a not a chiral molecule and therefore has no optical isomers. XRD and DSC data have demonstrated that polymorphic form B is indeed manufactured routinely by the defined synthetic route. For confirmation, an XRD polymophic form test is included in the drug substance specification and is also monitored during stability.

2.2.2.2. Specification

The drug substance specification includes tests for physical appearance, solubility, identification (IR and HPLC), loss of drying, heavy metals, related substances (HPLC), assay (HPLC), residual solvents (GC),sodium content and physical form by XRD.

A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods (HPLC and GC).In general analytical methods proposed are suitable to control the quality of the drug 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 by the ASMF Holder and the requirements in the drug substance specification were met.

2.2.2.3. Stability

Stability data has been provided from four batches of material stored at ICH long term conditions
Four commercial batches have been stored under ICH long term conditions (up to 24 months at 25°C/65%RH and 6 months at 40°C/ 75% RH). The data demonstrates that the active substance is stable. No adverse stability trends are observed.

The parameters investigated during stability included parameters such as description, identification, loss on drying, XRD, assay and related substances. This is acceptable as the other parameters are not considered to be stability-indicating. The primary packaging for the stability batches is stated to be the commercial packaging

The stability studies confirmed the proposed re-test period with no specific storage conditions.

2.2.3. Medicinal Product

2.2.3.1. Pharmaceutical Development

The proposed product was developed to be an immediate release film-coated tablet for oral administration, identical to the innovator product in terms of quantitative amount of ibandronic acid.

The excipients selected for the formulation are commonly used in pharmaceutical formulations. The major excipient, microcrystalline cellulose, was selected as filler with stearic acid as a lubricant. Colloidal anhydrous silica was selected to act as glidant, povidone as a binder and crospovidone as disintegrant.

A comparison was made of the compositions of the Teva product and the innovator 50mg and 150mg products sourced from the UK; the main difference in compositions is the lack of lactose monohydrate in the Ibandronic Acid Teva formulations. This difference in formulation has no clinical significance – the two products have been shown to be bioequivalent.

Comparative dissolution profiles between the proposed 50mg and 150mg product and the respective Bonviva and Bondronat innovator products showed that the dissolution of the proposed and innovator products for both strengths including the clinical batches is considered to be similar.

The primary container closure system being utilized for ibandronic acid 50mg and 150mg film-coated tablets is stated to be PVC/Aclar/PVC-Aluminium blisters.

2.2.3.2. Manufacture of the product

The manufacturing process is divided into eight main steps: Preheating, Granulation, Intermediate blending I, Intermediate blending II, Final blending, Compression, Coating and Packaging.

The critical steps in the manufacturing process to be monitored were identified as final blending, compression and coating.

A process validation protocol has been provided for the validation of the manufacturing process for three consecutive production batches of 50mg and 150mg ibandronic acid tablets. The protocol includes information on additional testing to be carried out during process validation. Reference has been made to validated procedures for the finished product for the assay and blend uniformity tests during process validation. The validation protocol is considered to be acceptable.

2.2.3.3. Product specification

The product specification is standard for tablets and contains tests with suitable limits for appearance, identification (HPLC and IR), dissolution, uniformity of dosage units (by mass variation), assay, impurities and degradation products (HPLC) and microbial limits (PhEur).

Analytical procedures have been described for routine testing of the ibandronic acid tablets to the proposed specifications. Validation data has been provided for HPLC procedures for the assay, impurities and for dissolution of the ibandronic acid finished product. In addition, the specificity of the IR identification procedure has been validated to demonstrate that there is no interference on the IR spectrum with the formulation excipients.

Batch analysis data have been provided for two pilot scale batches of each strength of ibandronic acid tablets. The provided batch analyses data demonstrated that the batches manufactured comply with the currently proposed specification. Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety.

2.2.3.4. Stability of the product

Stability studies were carried out in two batches of each strength under ICH conditions of 25ºC/60%RH (long term, 12 months) and 40ºC/75%RH (accelerated, 6 months) packed in the proposed primary blister packaging. The data shows no adverse stability trends and all specifications are met.

In addition, two stability studies have been completed on Ibandronic Acid Teva (one in 50mg and one in 150mg) in the proposed bulk packaging at 15-25ºC/max 70%RH for 6 months. No significant change in assay, impurities or dissolution was observed after bulk storage for 6 months. A holding period of 6 months for bulk tablets was therefore accepted.

Photostability studies have been conducted for one batch of 50mg in accordance with ICH requirements. The drug product was found not be light sensitive.

Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

2.3. Non-clinical aspects

Ibandronic acid is a well known active substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. No further non-clinical studies are therefore required.

Ibandronic Acid Teva is a generic product that will be prescribed interchangeably with other similar products already marketed in Europe. The introduction of this product into the market is unlikely to result in any significant increase in the combined sales of ibandronic acid containing products and thus an increased exposure to the environment is unlikely. For this reason, an environmental risk assessment is not considered necessary.

2.4. Clinical aspects

The CHMP assessment addressed pharmacokinetic data in respect of a single bioequivalence study which investigates the 150 mg strength only.

Exemption

The applicant has provided a justification for a biowaiver for Ibandronic Acid Teva 50 mg film-coated tablets on the basis that the following criteria are satisfied (CPMP/EWP/QWP/1401/98):

- The pharmaceutical products are manufactured by the same manufacturer and process.

Ibandronate 50 mg film-coated tablet and Ibandronate 150 mg film-coated tablet are both manufactured by Teva Pharmaceutical Works Private Limited Company by the same manufacturing process.

- The qualitative composition of the different strengths is the same.

Ibandronate 50 mg film-coated tablet and Ibandronate 150 mg film-coated tablet have the same qualitative composition.

- The ratio between amounts of active substance and excipients is the same, or, in the case of preparations containing a low concentration of the active substance (less than 5%), the ratio between the amounts of excipients is similar.

The ratio between amounts of active substance and excipients is the same for both strengths of the product.

- The dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Ibandronate 50 mg film-coated tablet and Ibandronate 150 mg film-coated tablet show similar dissolution profiles.

- The drug input has been shown to be linear over the therapeutic dose range (if this is not the case the strengths where the sensitivity is largest to identify differences in the two products should be used)

As stated in section 5.2 of the proposed SPC for the 150 mg strength:

"The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose." (This wording is identical to that found in the Bonviva SPC).

According to the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev.1 - Jan 2010), in case of non-linear pharmacokinetics there may be a difference between different strengths in the sensitivity to detect potential differences between formulations. If bioequivalence has been demonstrated at the strength(s) that are most sensitive to detect a potential difference between products, in vivo bioequivalence studies for the other strength(s) can be waived.

Since, according to Bonviva SmPC: "... plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose", the results of the provided bioequivalence study, which was conducted with the higher (and thus most sensitive) dose, using the higher strength (150mg), can also be extrapolated to the 50mg strength.

2.4.1. GCP

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

The applicant has provided a statement confirming that clinical trials conducted outside the European Community were carried out in accordance with the ethical standards of Directive 2001/20/EC and in compliance with Good Clinical Practice (GCP).

2.4.2. Clinical Studies

2.4.2.1. Pharmacokinetics

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration. Maximum observed plasma concentrations are reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability is about 0.6%. The extent of absorption is impaired when taken together with food or beverages (other than plain water). After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. There is no evidence that ibandronic acid is metabolized in animals or humans. The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (estimated to be 40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces. The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours.

A bioequivalence study was conducted to compare the bioavailability of Ibandronic acid 150 mg film-coated tablets (batch no. 0180908) and Bonviva 150 mg film-coated tablets (batch no.B1053) in healthy male and female volunteers under fasting conditions.

Methods

This was a single centre, single dose, randomised, laboratory-blinded, 4-period, 2-sequence, replicate design in healthy male and female subjects under fasting conditions.

A total of 70 healthy adult male and female subjects were randomised. 68 were included in the statistical analysis. After a supervised overnight fast of 10 hours, subjects received a single oral dose of the assigned formulation with 240 mL water. The washout period was at least 21 days, corresponding to more than 10 times the expected half-life of ibandronic acid.

Blood samples were collected at baseline, and at 10, 20, 30, 40, 50 minutes, 1 hour, 1 hour 15mins, 1hour 30mins, 1hour 45minutes, 2 hours, 2 hours 30 mins, and then 3, 4, 6, 8, 10, 12, 16 and 24 hours after drug administration. Plasma was analysed for ibandronate by means of a validated HPLC method using MS/MS detection.

The study design is considered acceptable by the CHMP. A fasting study is appropriate, as Ibandronic Acid Teva is to be taken in the fasting state, according to the SmPC. The washout period was sufficiently long.

The applicant stated that the study was performed in compliance with GCP. The final protocol (amendment 02) and the final informed consent forms were approved by an institutional review board (ETHIPRO) on 19 November 2008. Informed consent was obtained from all study subjects.

Test and reference products

Ibandronic Acid 150 mg tablet by Teva Pharm. Works Private Ltd. Co. (batch No.0180908, exp. date 03/2009) was compared to Bonviva 150 mg film-coated tablet by Roche Pharma AG, Germany (Batch No: B1053., from the UK, exp. date 03/2010).

Population(s) studied

Standard inclusion and exclusion criteria were applied. Inclusion criteria included male and female, non- and ex-smokers, aged 18-55 inclusive, BMI 19-29 kg/m2 inclusive, and in good health (as assessed by medical history and examination, ECG, standard haematological and biochemical parameters, urinalysis, pregnancy test).

The study population of 70 included 31 women. Ethnicity for the majority of participants was reported as white. Two subjects were black and three were Asian. The age range was 18-55 and the BMI range was 19.4 to 29.6 kg/m2.

Of the 70 randomised patients, 68 were included in the statistical analysis. One patient was excluded at the end of period 1, due to a positive amphetamines test; another patient withdrew from the study at the end of period 1 due to adverse events (insomnia, injury). All other patients had measurements for at least 2 periods and were included in the analysis, and 59 of the 68 patients provided data for all 4 periods.

Due to errors in the collection of blood samples around the time of Cmax in period 3, the applicant considered that 8 patients did not have their concentration-time curve adequately characterised for this period. These patients had their period 3 data excluded from the main analysis, although all other periods were included. A sensitivity analysis including this data was provided by the applicant. This approach was considered by the CHMP.

There were 140 blood sampling time deviations. Time deviations greater than or equal to 2 minutes were adjusted to reflect actual sampling times. Other protocol deviations reported were minor and not considered likely to affect the pharmacokinetic conclusion.

Analytical methods

Ibandronate in human plasma was analysed by means of a validated HPLC method using MS/MS detection.

Pharmacokinetic Variables

Statistical and pharmacokinetic analyses were generated using a software developed by the CRO, and SAS® version 9.1.

The primary pharmacokinetic parameters of interest for this study were Cmax and AUC0-t. The secondary pharmacokinetic parameters Tmax, AUC∞, AUCt/∞, Kel and T½el were also calculated. Parameters were estimated using a non-compartmental approach with a log-linear terminal phase assumption.

Statistical methods

The data were analysed using a random Analysis of Variance model with repeated measures. The fixed factors included in this model were treatment, period, and sequence. A random factor was added for the subject effect where the heterogeneity of the variances was assumed. A repeated factor was also added to model the replicates made on each treatment and heterogeneity of the variances across treatment groups was assumed.

Acceptance criteria

In order to demonstrate bioequivalence, the 90% confidence interval ratio of geometric means for Cmax was to be within the acceptance range 75 - 133%. The applicant justified this widening because data from a previous study indicated that the intra-subject coefficient of variation for plasma ibandronate Cmax was about 42% - ibandronate exhibited a high intra-individual variability with a CV greater than 30%. The applicant also stated that pharmacokinetic parameters did not significantly affect the clinical response. AUCt was to be analysed using the standard 80 – 125% acceptance range.

Results

The results for the 68 patients included are shown below, excluding the period 3 data for 8 patients.

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

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	303.048	321.602	78.214	1.25	9.92
Reference	306.040	325.711	83.151	1.03	10.28
***Ratio (90% CI)**	97.95 **(90.40-106.12)**	97.63 **(90.17-105.72)**	95.27 **(86.77-104.60)**		
CV (%)	38.9 (test) 40.8 (ref)	38.6 (test) 40.5 (ref)	48.0 (test) 45.3 (ref)		

$AUC_{0-\infty}$ 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*

When the 8 subjects who did not contribute period 3, data were included in the analysis, the 90% confidence intervals for AUCt, AUC∞ and Cmax were 90.57 – 105.83%, 90.35 – 105.44% and 87.40 – 104.83% respectively. These are all within the range 80 – 125%.

All subjects had an AUCt value that was at least 80% of the AUC∞ value. All subjects have a value below the limit of quantification at the start of each period. Tmax was not observed in any subject for the first sample time of any period.

Cmax was above the validated range in 9 concentration-time curves. However the dilution step was validated up to 500ng/ml, which was greater than the maximum Cmax value.

Although the reference compound did in fact exhibit high variability, the decision to widen the confidence intervals is not relevant, as Cmax was in fact within 80 – 125%. There are no concerns regarding the extrapolation of the data, or any potential carryover effects.

The model is robust to both the inclusion and exclusion of data where the concentration-time curve may not have been properly characterised. It can be concluded that bioequivalence has been reliably demonstrated for the 150 mg strength tablet.

Safety results

Adverse event monitoring was carried out during all 4 admissions (day 0, 1 and 2 of each period), and up to 17 days following the collection of the last blood sample if spontaneously reported. Haematology screening was carried out before and after period 4, and biochemistry screening at the end of period 4.

There were reports of 131 adverse events by 46 out of 70 subjects. Eighty-seven reports followed administration of the test product and sixty reports followed administration of the reference product. All adverse events resolved spontaneously. Two subjects were withdrawn due to adverse events (one for anaemia, one for injury and insomnia). There were no deaths or serious adverse events during the study.

The adverse events reported were consistent with the known safety profile of the active substance ibandronic acid. No new safety concerns were raised.

Pharmacokinetic Conclusion

Based on the presented bioequivalence study Ibandronic Acid Teva 150 mg film-coated tablet is considered bioequivalent with Bonviva 150 mg Film-coated tablet.

The results of study with 150 mg formulation can be extrapolated to the other strength 50 mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

2.4.2.2. Pharmacodynamics

No studies were submitted.

2.4.2.3. Post marketing experience

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

2.5. Pharmacovigilance

2.5.1. PSUR

The proposed generic product Ibandronic Acid Teva 150 mg film-coated tablets should follow an annual PSUR submission scheme, in line with that of Bonviva.

The proposed generic product Ibandronic Acid Teva 50 mg film-coated tablet should follow a 3-yearly PSUR submission scheme, in line with that of Bondronat.

2.5.2. Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.5.3. 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. This was considered acceptable by the CHMP.

User consultation

The user testing of the PIL for Ibandronic Acid Teva 150 mg film-coated tablet was conducted between October 26th, 2009 and November 6th, 2009.

The methodology was considered acceptable. Overall 90% of participants were able to find the required information, of which 90% could understand and use the information.

The PIL for Ibandronic Acid Teva 150 mg film-coated tablet (Parent PIL for Content) is considered to be the parent PIL for Ibandronic Acid Teva 50 mg film-coated tablet (Daughter PIL).

TEVA has reviewed both the Parent and daughter PILs and decided that a bridging study would suffice as the content of both PILs is identical. This was considered acceptable by the CHMP.

2.5.4. Benefit-risk balance

The application contains adequate quality, non clinical and clinical data and the bioequivalence has been shown. A benefit/Risk ratio comparable to the reference product can therefore be concluded.

2.5.5. Recommendation

2.5.5.1. Normal opinion

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Ibandronic Acid Teva in the indication as mentioned below was favourable and therefore recommended the granting of the marketing authorisation.

Ibandronic Acid Teva 50mg is indicated for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

Ibandronic Acid Teva 150mg is indicated 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.