CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets Synthon B.V., the Netherlands

ibandronic acid (as sodium monohydrate)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1826/001- 002/DC
Registration number in the Netherlands: RVG 106000-1

17 March 2011

Pharmacotherapeutic group:	Drugs affecting bone structure and mineralization; bisphosphonates
ATC code:	M05BA06
Route of administration:	oral
Therapeutic indication:	*50 mg* - prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases. *150 mg* - osteoporosis in postmenopausal women at increased risk of fracture.
Prescription status:	prescription only
Date of authorisation in NL:	31 December 2010
Concerned Member States:	Decentralised procedure with EL, ES, IT (all strengths); FR and PT (only 150 mg strength)
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets, from Synthon B.V. The date of authorisation was on 31 December 2010 in the Netherlands.

The product is indicated for:

50 mg - prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.
150 mg - 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.

A comprehensive description of the indications and posology is given in the SPC.

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

This decentralised procedure concerns a generic application claiming essential similarity with Bondronat 50 mg (EU/1/96/012/009; EU/1/96/012/010) and Bondenza/Bonviva 150 mg film-coated tablets (EU/1/03/265/003; EU/1/03/265/004; EU/1/03/266/003; EU/1/03/266/004), which have been registered through a centralised procedure by Roche Registration Limited. The reference product is Bondronat 1 mg/ml concentrate for solution for infusion (EU/1/96/012/001) which also has been registered through a centralised procedure by Roche Registration Limited since 1996.

Legal basis
Bondronat film coated tablets and Bondenza/Bonviva 150 mg film-coated tablets belong to the same global marketing authorisation as Bondronat concentrate for infusion. Directive 2001/83/EC Article 6, paragraph 1. Art. 6 requires that "*when a medicinal product has been granted an initial marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same marketing authorisation, in particular for the purposes of Article 10(1)*". Bondronat concentrate for infusion was authorised on 25 June 1996, over 10 years ago, throughout Europe. Therefore, the applications for Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets meet the requirements of Article 6 and 10(1). The marketing authorisation is therefore granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference products Bondronat 50 mg film-coated tablets and Bonviva 150 mg film-coated tablets, both registered in the UK. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted, as this is not required for generic medicinal products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
Ibandronic acid is an established active substance. Ibandronic acid is present in the tablets as the sodium salt monohydrate. The active substance is soluble in water. No centre of chirality is present in the structure. The active substance is obtained in a crystalline form.

The Active Substance Master File (ASMF) procedure is used for the active substance from one supplier. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

For the other supplier full documentation was submitted by the MAH.

Manufacture
Sufficient information has been provided on the synthesis. For all raw materials sufficient specifications have been laid down to guarantee an adequate quality of the drug substance. The manufacturing process of the drug substance by both suppliers has been adequately described.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches of one supplier and for three full-scale batches from the other supplier.

Stability of drug substance
Supplier 1 - Stability data on the active substance have been provided for four full scaled batches stored at 25°C/60% RH (36 months) AND 40°C/75% RH (6 months). The batches were adequately stored. Based on the data provided, a retest period of 3 years is justified. No special storage condition is required.
Supplier 2 - Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (6 months) AND 40°C/75% RH (6 months). The batches were adequately stored. Based on the data provided, a retest period of 1 year is justified. No special storage condition is required is provided.

Medicinal Product

Composition
Ibandronic acid 50 mg are white to off-white, oblong, biconvex film-coated tablets, 9 mm in length and debossed with "*I9BE*" on one side and on the other side with "*50*".
Ibandronic acid 150 mg are white to off-white, oblong, biconvex film-coated tablets, 14 mm in length and debossed with "*I9BE*" on one side and on the other side with "*150*".
The 50 mg and 150 mg film-coated tablets are packed in OPA/Al/PVC:Al blisters.

The excipients are:
Tablet core - lactose monohydrate, crospovidone (E1202), microcrystalline cellulose (E460), colloidal anhydrous sylica (E551), sodium stearyl fumarate.
Tablet coating - poly (vinyl alcohol), macrogols/PEG 3350, talc (E553b), titanium dioxide (E171).

The tablets are fully dose proportional.
The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batches used in BA/BE studies is identical to the marketed product.
The pharmaceutical development of the product has been adequately performed.

Excipients
The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Manufacturing process
The tablets have been developed to obtain essential similarity with the originator. The characteristics of the originator tablets were established. The main parameter studied in originator samples was the dissolution profile. The generic product should be an immediate release film coated tablet with a rapid and complete dissolution to ensure bioequivalence with the originator product. The ingredients are mixed and the powder mixture is compressed to tablet cores then the cores are film-coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 2 pilot scaled batches for the 50 mg strength and 3 pilot scaled batches for the 150 mg strength. Dissolution profiles of the Bondronat® and Bonviva® tablets in release media and at different pH were performed. The dissolution profile of Ibandronate proved to be pH independent. All samples dissolved faster that 85% in 15 minutes in all pH's. Process validation for full scaled batches will be performed post authorization.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, disintegration and uniformity of dosage units. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 2 pilot scaled batches for the 50 mg tablet strength and 3 pilot batches for the 150 mg tablet strength, demonstrating compliance with the release specification.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. Microbiological testing is performed on the finished product in accordance with Ph.Eur. Testing will be performed on the first 10 commercial batches and then on every 10th batch or once a year whichever is earlier.

Stability tests on the finished product
Stability data on the product has been provided 2 pilot scaled batches for the 50 mg tablet strength and 3 pilot scaled batches for the 150 mg tablet strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the intended blisters. At both conditions all parameters stay within specification; no trend is observed. A shelf-life of 2 year and no special storage conditions packed in PVC/PVDC:Al or OPA/Al/PVC: Al blister is acceptable.
The MAH has committed to continue the long term stability studies on the 5 pilot-scale batches through the proposed shelf-life.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Bondronat, Bondenza, and Bonviva tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of Ibandronic acid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ibandronic acid is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Ibandronic acid Synthon 50 mg and 150 mg film-coated tablets (Synthon B.V., the Netherlands) are compared with the pharmacokinetic profile of the reference products Bondronat 50 mg tablets (Roche Products Ltd. UK), and Bonviva 150 mg tablets (GlaxoSmithKline Ltd., UK)

The choice of the reference product
Bondronat and Bonviva tablets are registered via the centralised procedure and hence are presumed to be identical in all member states of the EEA.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study with 50 mg film-coated tablets
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 98 healthy (80 male / 18 female) volunteers, aged 19-43 years. One tablet (either test or reference product) containing 50 mg ibandronate sodium monohydrate was administered orally to each of the volunteers in the sitting posture, and with 240 mL water after an overnight fast of at least 10 hours. Subjects remained sitting in upright posture for the first 3 hours after the oral administration. Thereafter, the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. They refrained from drinking water 1 hour before until 2 hours after dosing in each period (except for the water given with the medicine administration). There was a wash-out period of 30 days between study periods.

Blood samples were collected predose and at 0.166, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Six subjects were withdrawn during the washout period, in which four subjects were dosed with reference drug and two subjects were dosed with test drug. One subject receiving the reference product was withdrawn in study period II. Ninety-one subjects completed both the periods and were included in statistical analysis. The safety issues were sufficiently addressed, and the result seems to be acceptable

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibandronic acid under fasted conditions.

Treatment N=91	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	134 ± 69.8	142 ± 74.7	31.7 ± 17.4	1 (0.33-6)	27.1 ± 8.7
Reference	134 ± 79.9	143 ± 85.9	33.3 ± 22.7	1 (0.33-6)	27.3 ± 8.5
***Ratio (90% CI)**	1.02 (0.93-1.13)	1.02 (0.92-1.12)	1.0 (0.89– 1.12)	-	-
CV (%)	46.7	39	57.2	-	-

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ibandronic acid under fasted conditions, it can be concluded that Ibandronic acid Synthon 50 mg film-coated tablets and the Bondronat 50 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study with 150 mg film-coated tablets
An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover bioequivalence study was carried out under fasted conditions in 98 healthy (72 male / 26 female) volunteerd, aged 19-43 years. One tablet (either test or reference product) containing Ibandronate sodium monohydrate 150 mg was administered orally to each of the volunteers in the sitting posture, and with 240 mL water after an overnight fast of at least 10 hours. Subjects remained sitting in upright posture for the first 3 hours after the oral administration. Thereafter, the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. They refrained from drinking water 1 hour before until 2 hours after dosing in each period (except for the water given with the medicine administration). There was a wash-out period of 28 days between study periods.

Blood samples were collected predose and at 0.166, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
There were 8 drop-outs and 90 subjects completed both study periods and passed all study procedures.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ibandronic acid under fasted conditions.

Treatment N=90	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** <x>g/ml	**t_{max}** h	**$t_{1/2}$** h
Test	572 ± 382	607 ± 397	119 ± 90.0	1.0 (0.33-6.0)	23.0 ± 8.4
Reference	634 ± 426	673±440	129 ± 86.6	1.75 (0.33-6.0)	24.6 ± 8.6
***Ratio (90% CI)**	0.90 (0.83-0.98)	0.90 (0.83 – 0.98)	0.91 (0.83-0.99)	-	-
CV (%)	34.6	33	45.9	-	-

$AUC_{0-\infty}$ 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*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of ibandronic acid under fasted conditions, it can be concluded that Ibandronic acid Synthon 150 mg film-coated tablets and the Bonviva 150 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety
37 post-dose adverse events (AEs) were reported by 27 of the 98 subjects, who received at least one dose of the study drug (safety population). The breakdown by treatment group is as follows: 21 AEs were reported by 16.49% (n=16) of the 97 subjects who received treatment A (reference) and 16 AEs were reported by 12.09% (n=11) of the 91 subjects who received treatment B (test). The causality relationship was judged as possible for 22 AEs, unlikely for 14 AEs and unrelated for 01 AE. Upon conclusion of the clinical portion of the study, the results from all subjects, who completed post-study procedures including laboratory tests and vital signs measurements, confirmed the absence of significant changes in the subjects' state of health. The safety issues were sufficiently addressed, and the result seems to be acceptable

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan
Ibandronic acid was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ibandronic acid can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation

which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The SPC has been adapted to the latest versions of Bondronat (25 January 2010) and Bonviva (05 May 2010).

Readability test
The package leaflets for the 50 mg and 150 mg strengths have been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

50 mg:
The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The target demographic group were potential users of Ibandronate acid 50 mg film-coated tablets between 18 and 70 years of age. As this medicine is indicated for use in woman the demographic reflects that by including only woman as they could be potential users of the medicine.
The 1st round of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly.
The 2nd round of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly.
Based on the above mentioned facts the Package Leaflet is qualified as acceptable.

150 mg:
The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The target demographic group were potential users of Ibandronic acid 150 mg film-coated tablets between 45 and 75 years of age. This medicine is indicated to treat osteoporosis which occurs most commonly in postmenopausal woman, therefore the demographic selected was woman between 45 and 75 years of age.
In the pilot test, the correct section was traced to answer the question 100% of the time, and a correct answer was given 100% of the time.
The 1st round of testing showed that, for each question, at least 90% of participants were able to find the correct information, and at least 90% of participants were able to answer the questions correctly.
The 2nd round of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly.
All of the participants offered positive remarks about the leaflet, some specifically stating "*the information in easy to locate*" and "*the language is understandable*" . Six participants mentioned that the leaflet is too long. The leaflet must accurately represent all of the key safety messages in its SmPC and therefore cannot be shorted. Based on this as well as the results from the first and second rounds of testing there are no suggestions for revisions to the leaflet.
The readability test has been sufficiently performed. Based on the above mentioned facts the Package Leaflet is qualified as acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Bondronat 50 mg and Bondenza/Bonviva 150 mg film-coated tablets. Bondronat and Bondenza/Bonviva are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 October 2010. Ibandroninezuur Synthon 50 mg and 150 mg film-coated tablets are authorised in the Netherlands on 31 December 2010.

The international birth date is known (IBD): 25 June 1996.The date for the first renewal will be 25 March 2015.
The PSUR submission cycle is 3-years, hence the first PSUR have a DLP of October 2013 based on approval date.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product
- The MAH has committed to continue the long term stability studies on the 5 pilot-scale batches through the proposed shelf-life.
- The MAH has committed to perform post authorisation the process validation for full scaled batches (maximum size range)

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached