CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril Tosilaat/Indapamide Teva 2,5 mg/0,625 mg and 5 mg/1.25 mg, film-coated tablets Teva Nederland B.V., the Netherlands

perindopril tosylate / indapamide

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/2467/001-002/DC
Registration number in the Netherlands: RVG 110897 - 110898

4 October 2013

Pharmacotherapeutic group:	perindopril and diuretics
ATC code:	C09BA04
Route of administration:	oral
Therapeutic indication:	2.5 mg/0.625 mg - essential hypertension; 5 mg/1.25 mg – essential hypertension in patients whose blood pressure is not adequately controlled on perindopril alone
Prescription status:	prescription only
Date of authorisation in NL:	6 August 2013
Concerned Member States:	Decentralised procedure with BG, CZ, EE, EL, ES, FR, HU, IE, IT, LT, LV, PL, PT, RO and SI
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 Perindopril Tosilaat/Indapamide Teva 2,5 mg/0,625 mg and 5mg/1.25 mg, film-coated tablets, from Teva Nederland B.V. The date of authorisation was on 6 August 2013 in the Netherlands.

The product is indicated for treatment of essential hypertension. The 5 mg/1.25 mg product is indicated in patients whose blood pressure is not adequately controlled on perindopril alone.

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

This product is a combination of perindopril tosylate salt, an angiotensin converting enzyme inhibitor, and indapamide, a chlorosulphamoyl diuretic. Its pharmacological properties are derived from those of each of the components taken separately, in addition to those due to the additive synergic action of the two products when combined.
Perindopril is an inhibitor of the angiotensin converting enzyme (ACE inhibitor) which converts angiotensin I to angiotensin II, a vasoconstricting substance; in addition the enzyme stimulates the secretion of aldosterone by the adrenal cortex and stimulates the degradation of bradykinin, a vasodilatory substance, into inactive heptapeptides.
Indapamide is a sulphonamide derivative with an indole ring, pharmacologically related to the thiazide group of diuretics. Indapamide inhibits the reabsorption of sodium in the cortical dilution segment. It increases the urinary excretion of sodium and chlorides and, to a lesser extent, the excretion of potassium and magnesium, thereby increasing urine output and having an antihypertensive action.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Preterax 2.5 mg/0.625 mg tablets and Bipreterax 5 mg/1.25 mg tablets which have been registered in France by Les Laboratoires Servier since 1997. In the Netherlands, Preterax 2 mg/0.625 mg and 4 mg/1.25 mg have been registered through MRP FR/H/0130/001-002. In addition, reference is made to Preterax/Bipreterax authorisations in the individual member states (reference product).

The marketing authorisation is 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Bipreterax 5 mg/1.25 mg tablets, registered in Germany. 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 a generic application.

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
Perindopril tosylate
The active substance perindopril tosylate, is not described in the European Pharmacopoeia (Ph.Eur.*), but a different salt is, perindopril tert-butylamine. Perindopril tosylate is a white to off-white powder, which is very soluble in water between pH 1.2 to 6.8, methanol, ethanol, acetonitrile, and dichloromethane, freely soluble in ethyl acetate and practically insoluble in n-hexane. The substance is present in amorphous form and is hygroscopic.

The Active Substance Master File (ASMF) procedure is used for perindopril tosylate. 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/EMA 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.

Manufacturing process
The active substance Perindopril tosylate is manufactured by a one step synthesis. Consistency of the polymorphic form of the active substance is demonstrated. .

Quality control of drug substance
The drug substance is controlled by an in-house specification. The drug substance specification of the ASMF holder contains tests for description, identification, specific optical rotation, water, sulphated ash, heavy metals, related substances, assay and tosylic acid content, stereochemical purity, residual solvents and sulfonate esters. The drug substance specification of the MAH contains additional requirements for particle size distribution, bulk and tapped density, and microbiological quality. Control of related substances and stereochemical purity is based on the Ph.Eur. monograph on perindopril tert-butylamine.
Batch analytical data demonstrating compliance with the drug substance specification were provided by the ASMF holder for three commercial scale batches and by the MAH for five commercial scale batches.

Stability of drug substance
Stability data on the active substance Perindopril Tosylate were provided for three commercial scale batches stored at 2 to 8°C (twelve months (two batches) and nine months (one batch)) and 25°C/60% RH (six months (three batches)). A re-test period of 18 months can be granted.
** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Indapamide
Indapamide is an established active substance described in the European Pharmacopoeia. It is a white or almost white powder, which is practically insoluble in water and soluble in ethanol. It is a chiral substance which is present as a racemate.

The CEP procedure is used for indapamide. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both.

This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification of Indapamide is in line with the Ph.Eur. and additional requirements of the CEP. Additional tests for particle size, bulk and tapped density and microbiological quality are included. The specification is acceptable in view of various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance
The active substance Indapamide is stable for 5 years. Assessment thereof was part of granting the CEP and the claimed storage conditions and re-test period has been granted by the EDQM.

Medicinal Product

Composition
Perindopril tosilaat/indapamide TEVA 2,5 mg/0,625 mg are white, capsule shaped biconvex film-coated tablets of approximately 4 mm width and 8 mm length, with debossed breakline on one side and plain on the other side.
Perindopril tosilaat/indapamide TEVA 5 mg/1,25 mg are white, capsule shaped biconvex film-coated tablets of approximately 5 mm width and 10 mm length, debossed with 'P', 'I' end a breakline on one side and plain on the other side.

The drug product corresponds to immediate release tablets containing 1.7 mg and 3.4 mg perindopril, respectively. The theoretical amount of perindopril tosylate is 2.5 or 5 mg, respectively

The tablets are packed in white opaque PP containers with white opaque stopper with desiccant insert equipped with a tamper-evident (TE) polyethylene flow reducer containing 30, 60, 90, 90 (3 x 30) or 100 film-coated tablets.

The excipients are:
Core: lactose monohydrate, maize starch, sodium hydrogen carbonate, starch pregelatinized (maize), povidone K30 and magnesium stearate (E572)
Film-coating: poly(vinyl alcohol) - part. hydrolized (E1203), titanium dioxide E171, macrogol/PEG 3350 (E1521) and talc (E553b).

The two strengths have dose proportional compositions.

The tablets contain a breakmark. A test on subdivision of tablets is included in the drug product specification for the function of the breakmark. Only the higher strength can be divided into equal doses, for the lower strength the score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The used excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The pharmaceutical development was sufficiently described. The choice of the amorphous drug substance perindopril tosylate was satisfactorily justified.
A bioequivalence study comparing the 5 mg/1.25 mg strength of the test and reference product was conducted. The biobatch of the test product was produced according to the composition and manufacturing process laid down in the dossier. Dissolution profiles of the biobatches were similar in the quality control medium and at 3 different pHs.. The MAH requested a waiver for the 2.5 mg / 0.625 mg

strength. The two strengths are manufactured according to the same manufacturing process. Dissolution profiles of the 2.5 mg/ 0.625 mg strength of the test product were similar to 5 mg / 1.25 mg strength used in the bioequivalence study. The waiver for the 2.5 mg / 0.625 mg strengths is acceptable from a chemical pharmaceutical point of view.

Manufacturing process
The manufacturing process is considered a non-standard process. The process involves blending, granulation, compression, and coating with a non-functional film-coat. The manufacturing process was validated with three commercial scale batches of each strength.

Control of excipients
All excipients and all ingredients of the coating agent comply with the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification of the active substance and colouring agent titanium dioxide, uniformity of dosage units, subdivision of tablets, dissolution, assay, impurities/degradation products, and microbiological quality. Friability, resistance to crushing, and core and tablet weight are tested in process. The release and shelf life specifications differ with regard to the limits for impurities/degradation products. The specification is acceptable.
The analytical methods were adequately described. Batch analytical data from the proposed production site were provided on three pilot scale batches of each strength. All batches complied with the release specification.

Stability of drug product
Stability data on the product were provided on three pilot scale batches of each strength stored at 25 °C/60% RH (two batches 16 months and one batch 9 months) and 40 °C/75% RH (three batches six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in white opaque polypropylene tablet containers with white opaque polyethylene tamper-evident stoppers with desiccant insert. No significant changes were observed. On the basis of the provided 16 months stability data, a shelf life of 28 months, when stored in the original container to protect from moisture can be granted.
An in use stability study was carried out with one batch of the 2.5 mg/0.625 mg strength which had been stored for six months previous to the study and for 30 days during the study at 25°C/60% RH. Based on calculations, an in-use period of 100 days can be granted. In use stability will be studied again close to the claimed shelf life of 28 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose is prepared in accordance with the requirements of the Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents in medicinal products; magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

This product is a generic formulation of Preterax/Bipreterax, which is available on the European market. 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. Therefore, the member states agreed that no further non-clinical studies are required.

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 perindopril tosylate or indapamide 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

Perindopril tosylate and indapamide are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Perindopril Tosilaat/Indapamide Teva 5 mg/1.25 mg, film-coated tablets is compared with the pharmacokinetic profile of the reference product Bipreterax 5 mg/1,25 mg tablets.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence test batch is identical to the formula proposed for marketing.

Design
A randomised, open-label, 2-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy (26 male and 8 female) subjects, aged 24-55 years. Both people of the White race and of the African American race were included. Each subject received a single dose (5 mg/1.25 mg) of one of the 2 perindopril /indapamide formulations. There were two dosing periods, separated by a washout period of 22 days.

For analysis of the parent compound perindopril, blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose. For analysis of indapamide, blood samples were collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods
The analytical method has been adequately validated and is 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
Two subjects withdrew their consent after the 1st period and one subject was withdrawn before the start of the 2nd period because of a positive cotinine test (marker for tobacco smoke exposure). Therefore, a total of 33 subjects were included in the pharmacokinetic and statistical analysis.

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

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	46.4 ± 7.7	47.1 ± 7.7	42.4 ± 9.0	0.75 (0.25 – 1.25)	0.72 ± 0.12
Reference	44.5 ± 8.6	45.2 ± 8.6	40.7 ± 10.0	0.75 (0.5 – 1.0)	0.74 ± 0.11
***Ratio (90% CI)**	1.05 (1.01-1.09)	1.05 (1.01-1.09)	1.05 (0.98-1.12)	-	-

CV (%)	9.0	9.0	16.3	-	-

$AUC_{0-\infty}$ 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*

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

Treatment N=33	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	974 ± 186	1006 ± 201	60 ± 11	1.0 (0.75 – 4.0)	14.2 ± 1.8
Reference	933 ± 173	964 ± 186	54 ± 10	1.5 (1.0 – 4.0)	14.2 ± 2.0
***Ratio (90% CI)**	1.04 (1.02-1.07)	1.04 (1.02-1.07)	1.11 (1.07-1.15)	-	-
CV (%)	5.5	5.8	9.5	-	-

$AUC_{0-\infty}$ 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 perindopril and indapamide under fasted conditions, it can be concluded that Perindopril Tosilaat/Indapamide Teva 5 mg/1.25 mg, film-coated tablets and Bipreterax® 5 mg/1.25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A total of 24 adverse events were reported by 15 subjects of the 36 subjects who received at least 1 tablet of the study drug. Of those, 9 were reported by subjects who received the test treatment, and 14 by subjects who received the reference product. None of the adverse events were severe of nature.

Perindopril and indapamide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of perindopril and indapamide. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 2.5 mg/0.625 mg strength
The results of the bioequivalence study with the 5 mg/1.25 mg strength can be extrapolated to the 2.5/0.625 mg strength. All criteria for this biowaiver have been met, as both strengths have the same manufacturer, same qualitative composition and same ratio between active substance and excipients. Furthermore, comparable in vitro dissolution has been demonstrated both by rapid dissolution and similarity factor calculations.

Risk management plan

The combination of perindopril and indapamide was first approved in 1997, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of perindopril and indapamide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Preterax 2.5 mg/0.625 mg tablets and Bipreterax 5 mg/1.25 mg tablets marketed by Les Laboratoires Servier.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 20 questions and 3 additional questions to give an opinion of the leaflet. In formulating the questions, firstly all the key safety messages in the package leaflet were identified and then questions were designed around those issues that would ensure a patient's comprehension and ability to act upon. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The objective was to test the readability of the PL according to the following criteria:

• 90% of participants tested should be able to find the information in the leaflet
• 90% of participants who found the information should also be able to understand the information in the leaflet.

There were no changes made to the PL based on pilot testing. The data show all 20 questions met the passing criteria in the first and second round. So, there were no revisions to the PL after the first and second round of testing. The results of the test were satisfactory. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril tosilaat/indapamide Teva 2,5 mg/0,625 mg and 5 mg/1.25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms, containing the same amount of active substance perindopril, of Preterax 2 mg/0.625 mg tablets / Preterax 2.5 mg/0.625 mg tablets and Bipreterax 5 mg/1.25 mg tablets / Preterax 4 mg/1.25 mg tablets respectively . Preterax and Bipreterax 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 and are in agreement with other perindopril/indapamide containing products.

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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Perindopril tosilaat/indapamide Teva 2,5 mg/0,625 mg and 5 mg/1.25 mg, film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 October 2012. Perindopril tosilaat/indapamide Teva 2,5 mg/0,625 mg and 5 mg/1.25 mg, film-coated tablets is authorised in the Netherlands on 6 August 2013.

The date for the first renewal will be: 17 October 2017.

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

Quality - medicinal product

- The ongoing stability studies of the drug product will be continued up to the registered shelf-life
- Stability studies will be carried out on the first three commercial scale batches.
- The results of the in-use stability study of the additional batch at the end of shelf-life will be provided when they become available.
- The MAH commits to perform confirmatory testing at the end of shelf-life for indapamide impurity A
- The MAH commits to perform stability studies, as well as in-use stability studies on the new proposed pack size (100 tablets).

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
Name change Romania	NL/H/2467/001/IB/001	IB	21-02-2013	10-04-2013	Approval	No
change in the manufacturing process of the finished product	NL/H/2467/001/IB/002	IB	21-03-2013	02-05-2013	approval	No