CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Perindopril Tosilaat Teva 2,5 mg, 5 mg and 10 mg film-coated tablets
Teva Nederland B.V., The Netherlands

perindopril tosilate

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/2468/001-003/DC
Registration number in the Netherlands: RVG 110703, 110718-110719

11 Februari 2014

Pharmacotherapeutic group:	ACE inhibitors, plain
ATC code:	C09AA04
Route of administration:	oral
Therapeutic indication:	hypertension, hearth failure (2,5 mg and 5 mg strengths), stable coronary artery disease.
Prescription status:	prescription only
Date of authorisation in NL:	12 June 2013
Concerned Member States:	Decentralised procedure with BG, EE, EL, 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 Teva 2,5 mg, 5 mg and 10 mg film-coated tablets, from Teva Nederland B.V. The date of authorisation was on 12 June 2013 in the Netherlands.

The product is indicated for:

- Hypertension:
  Treatment of hypertension.

- [2.5 mg and 5 mg strengths]
  Heart failure:
  Treatment of symptomatic heart failure.

- Stable coronary artery disease:
  Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

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

Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikrein-kinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Coversyl 2,5 mg, 5 mg and 10 mg film-coated tablets (NL License RVG 31957- 31959) which has been registered in France by les Laboratoires Servier since 2005 (original product). In addition, reference is made to Coversyl 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 Coversyl 10 mg film-coated tablets, registered in Italy. 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
The active substance is perindopril tosilate, is not described in the European Pharmacopoeia (Ph.Eur.*), but a different salt is, perindopril tert-butylamine. The active substance 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. Perindopril has five chiral centres.

The Active Substance Master File (ASMF) procedure is used for the active substance. 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 manufacturing process of the active substance Perindopril tosilate is described in sufficient detail. 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. The drug substance specifications of the ASMF holder and MAH are acceptable.
Batch analytical data demonstrating compliance with the drug substance specification were provided by the ASMF holder for three commercial scale batches and by the Applicant for five commercial scale batches.

Stability of drug substance
Stability data on the active substance were provided for three commercial scale batches stored at 2 to 8°C (12 months (two batches) and nine months (one batch)) and 25°C/60% RH (six months). On the basis of the provided stability data, a re-test period of 18 months can be approved. Storage conditions are "Store in a refrigerator (5°C ± 3°C)" and "Store in the original package in order to protect from light and moisture".

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
Perindopril Tosilaat Teva 2,5 mg are white, round, biconvex, film-coated tablets of approximately 5 mm diameter, debossed “T” on one side and plain on the other.
Perindopril Tosilaat Teva 5 mg are light green, capsule shape, biconvex film-coated tablets of approximately 4 mm width and 8 mm length, debossed “T” on one side, plain on the other side with breaklines on both edges. The tablet can be divided into equal halves.
Perindopril Tosilaat Teva 10 mg are green, round, biconvex, film-coated tablets of approximately 8 mm diameter, debossed “10” on one side and “T” on the other.

The drug product corresponds to immediate release tablets containing 1.704 mg, 3.408 mg, and 6.816 mg of perindopril, respectively. Apart from the film-coating, the three strengths are dose proportional.

The film-coated tablets are packed in white opaque PP containers with white opaque PE stopper with desiccant insert equipped with a tamper-evident (TE) polyethylene flow reducer containing 30, 60, 90, 90 (3x30) or 100 film-coated tablets..

The excipients are:
Core: lactose monohydrate, maize starch, sodium hydrogen carbonate, starch (maize) pregelatinized, povidone K30, magnesium stearate.
Film-coating: poly(vinyl alcohol) - part. hydrolysed, titanium dioxide E171, macrogol 3350, talc, indigo carmine E132, brillant blue FCF E133, iron oxide yellow E172, quinoline yellow E104.

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

With the exception of the colouring agents of the non-functional coating material, the three strengths are dose proportional.

Pharmaceutical development
The pharmaceutical development was sufficiently described. The choice of the drug substance perindopril tosilate was justified.
A bioequivalence study comparing the 10 mg strengths 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 media and at 3 different pHs. . The MAH requested a waiver for the 2.5 and 5 mg strengths. The three strengths are manufactured from a common blend according to the same manufacturing process. Dissolution profiles of the 2.5 and 5 mg strengths of the test product were similar to 10 mg strength used in the bioequivalence study. A waiver for the 2.5 and 5 mg strengths is acceptable from a chemical pharmaceutical point of view.

Manufacturing process
The manufacturing process is a standard process involving granulation, compression, and coating with a non-functional film-coat. The manufacturing process was adequately described.
The manufacturing process was qualified with one pilot scale batch of each strength. The manufacturing process will be validated post approval on commercial scale with three consecutive batches of each strength.

Control of excipients
With the exception of the colouring agents of the coating material, all excipients 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 agents, uniformity of dosage units, subdivision of tablets (5 mg strength only), dissolution, assay, impurities/degradation products, and microbiological quality. Friability, resistance to crushing, and core and tablet weight are tested in process. Uniformity of dosage units and subdivision of tablets of the 5 mg strength are tested in accordance with the Ph.Eur. 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 two pilot and one production scale batch of each strength. All batches complied with the release specification.

Stability of drug product
Stability data on the product were provided on two pilot and one commercial scale batch of each strength stored at 25°C/60% RH (17 months (two pilot scale batches) and nine months (commercial scale batch)) and 40°C/75% RH (six months (two pilot scale batches) and three months (commercial scale batch)). 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 stability data and statistical evaluation of the long term data for assay and impurities, the claimed shelf life of 28 months is justified. The drug product was shown to be sensitive to light. The proposed storage condition “Keep the container tightly closed in order to protect from light and moisture” is justified.
An in use stability study was carried out with one batch of the 2.5 mg strength which had been stored for five months at 25°C/60% RH prior to the study and one batch of the 10 mg strength which had been stored for eleven months at 25°C/60% RH prior to the study. The drug product remained stable during 30 days in use. In use stability will be studied again with one batch of the 2.5 mg strength close to shelf life.

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 Coversyl, 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 tosilate 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

Generic applications
Perindopril tosilate is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted three bioequivalence studies in which the pharmacokinetic profile of the test product Perindopril Tosilaat Teva 10 mg film-coated tablets was compared with the pharmacokinetic profile of the reference product Coversyl 10 mg film-coated tablets.
The first study failed to show bioequivalence between the test and the reference product with respect to Cmax.

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 batch is identical to the formula proposed for marketing.

Bioequivalence study I

Design

A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 28 healthy adult, 23 male and 5 surgically sterile or postmenopausal female subjects, aged 20-54 years. Each subject received a single dose (10 mg) of one of the 2 perindopril formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.883, 1.0, 1.25, 1.5, 2, 3, 4, 5, 6, 8 and 12 hours after administration of the products.

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

Twenty-five subjects received both doses of the study medication and were included in the pharmacokinetic analysis.

Three subjects received only one dose of the study medication and were only included in the safety evaluation. One subject withdrew prior to period 2 of the study for personal reasons, another subject was dismissed due to bradycardia prior to period 2, a third subject was dismissed from the study prior to period 2 due to a positive drug screen.

A protocol deviation (Consumption of poppy-seed containing product) was observed in one subject, this deviation was assessed to have no effect on the study data as the quantity of the restricted item was considered to be minimal. The subject continued participation.

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

Treatment N=25	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	175.8 ± 40.7	177.4 ± 40.9	118.1 ± 33.9	0.83	1.14 ±0.31
Reference	161.3 ± 43.7	163.0 ± 44.0	103.6 ± 31.9	0.67 (0.33- 1.50)	1.16 ±0.27
***Ratio (90% CI)**	1.10 (1.01 -1.20)	-	1.16 (1.02 – 1.33)	-	-
CV (%)	18	-	28	-	-

$AUC_{0-\infty}$ 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*

This bioequivalence study failed to show bioequivalence between the test and the reference product with respect to Cmax. This high variability appears to be due to a single tablet of reference product giving a lower value. The MAH has chosen to repeat the study with a larger number of subjects, together with the measurement of perindoprilat levels, which is considered acceptable.

Safety results
There were 19 adverse events involving 12 subjects in the study. All adverse events were judged to be mild in severity. Both test and reference products were well tolerated in this study.

Bioequivalence study II
Design
A single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 64 healthy adult, 61 male and 3 surgically sterile or post-menopausal female subjects aged between 18 and 55 years. Each subject received a single dose (10 mg) of one of the 2 perindopril formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 21 days.

In this study the subject safety was also monitored. The design of the study was almost identical to the initial study, test and reference products were identical. The conditions during administration of the tablets, the washout period were identical as well.
Blood samples were collected predose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after administration of the products and for Perindoprilat: predose and at 0, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours after administration.

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
Fifty-nine subjects received both doses of the study medication and were included in the pharmacokinetic analysis. Two subjects were dismissed due to non-compliance, one withdrew to personal reasons, another subject withdrew due to adverse events an a last subject was dismissed due to out of range vital signs.

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

Treatment N=59	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	193.6 ± 69.7	124.1 ± 33.3	0.83 (0.50- 2.00)
Reference	180.6 ±65.2	113.8 ± 30.4	0.83 (0.50- 1.50)
***Ratio (90% CI)**	1.07 (1.04 – 1.11)	1.08 (0.99 – 1.17)	-
CV (%)	8	19	-

$AUC_{0-\infty}$ 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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindoprilat under fasted conditions.

Treatment N=59	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	282.0 ± 69.9	26.8 ± 8.2	2.00 (0.83- 4.00)
Reference	275.2 ± 74.1	25.6 ± 7.9	2.00 (1.00- 4.00)
***Ratio (90% CI)**	1.01 (0.99 – 1.04)	1.02 (0.97 – 1.07)	
CV (%)	8	11	-

$AUC_{0-\infty}$ 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 tosilate under fasted conditions, supported by the data of perindoprilat, it can be concluded that Perindopril Tosilaat Teva 10 mg film-coated tablets and the Coversyl 10 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety results

Safety was assessed based on vital signs measurements and on the severity and causality of adverse events experienced by subjects who underwent drug administration. There were 82 adverse events involving 32 subjects in the study. All adverse events were judged to be mild in severity. Both test and reference products were well tolerated in this study.

Bioequivalence study III

Design

A single centre, randomised, single-dose, open-label, two-way crossover bioequivalence study was carried out under fasted conditions in 64 healthy adult, 49 male and 15 female subjects aged between 18 and 55 years. Each subject received a single dose (10 mg) of one of the 2 perindopril formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of at least 21 days.

Blood samples were collected predose and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 2.00, 3.00, 4.00, 5.00, 6.00, 8.00, 12.0, 24.0, 48.0, and 72.0 hours after administration of the products.

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

One subject withdrew consent and 63 completed the study and were included in the pharmacokinetic analysis.

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindopril under fasted conditions.

Treatment N=63	**AUC_{0-t}** pg.h/ml	**$AUC_{0-\infty}$** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	82739 ± 16730	83496 ± 16870	71534 ± 19465	0.667 (0.500 - 1.25)	0.79 ± 0.15
Reference	79380 ± 16634	80120 ± 16705	70359 ± 18160	0.667 (0.500 - 1.50)	0.80 ± 0.15
***Ratio (90% CI)**	1.04 (1.02- 1.07)	1.04 (1.02- 1.07)	1.02 (0.97-1.07)	-	-
CV (%)	18.19	18.13	22.70	-	-

$AUC_{0-\infty}$ 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 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of perindoprilat under fasted conditions.

Treatment N=63	**AUC_{0-72}** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	213485± 69476	15843 ± 8755	4.00 (2.00 - 8.00)
Reference	194875 ± 53213	13647 ± 6195	4.00 (3.00 - 12.0)
***Ratio (90% CI)**	1.08 (1.06-1.11)	1.12 (1.08- 1.17)	-
CV (%)	7.39	13.91	-

$AUC_{0-\infty}$ 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 tosilate) under fasted conditions, it can be concluded that Perindopril Tosilaat Teva 10 mg film-coated tablets and the Coversyl 10 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Safety results

A total of 22 treatment-emergent adverse events (TEAEs) were reported by 14 of the 64 subjects who received at least one dose of the study medication (safety population).

Perindopril tosilate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of perindopril. 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 and 5 mg strengths
The results of the bioequivalence studies with the 10 mg strength can be extrapolated to the 2,5 mg and 5 mg strengths. 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 also been demonstrated.

Risk management plan
Perindopril was first approved in 1998, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of perindopril tosilate 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 Coversyl marketed by les Laboratoires Servier.

Readability test
A package leaflet combined for all strengths 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. They were spread on age, sex and education quotas. The test was performed in English.
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 PL were identified and then questions were designed around those issues that would ensure a patient's comprehension and ability to act upon. There were sufficient questions about the critical sections and the areas traceability, comprehensibility and applicability were sufficiently covered. Participants were interviewed individually.
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.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Perindopril Tosilaat Teva 2,5 mg, 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Coversyl 2,5 mg, 5 mg and 10 mg film-coated tablets. Coversyl is a well-known medicinal product 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 tosilaat containing products.

The Board followed the advice of the assessors. Perindopril Tosilaat Teva 2,5 mg, 5 mg and 10 mg film-coated tablets is authorised in the Netherlands on 12 June 2013.

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 Teva 2,5 mg, 5 mg and 10 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 31 October 2012. Perindopril Tosilaat Teva 2,5 mg, 5 mg and 10 mg film-coated tablets is authorised in the Netherlands on 12 June 2013.

The date for the first renewal will be: 21 October 2017.

There were no post-approval commitments made during the procedure.

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