CBG MEB

# Public Assessment Report

# Scientific discussion

# Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg, film-coated tablets

# (perindopril tosilate/indapamide)

## NL/H/3522/001/DC

## Date: 2 November 2017

**This module reflects the scientific discussion for the approval of Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg, film-coated tablets. The procedure was finalised on 12 October 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

## List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ICH | International Conference of Harmonisation |
| MAH | Marketing Authorisation Holder |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| RH | Relative Humidity |
| RMP | Risk Management Plan |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# 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 10 mg/2.5 mg, film-coated tablets from Teva Nederland B.V.

The product is indicated as substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril and indapamide given concurrently at the same dose level.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Perindopril tert-butylamine/indapamide Servier 4 mg/1.25 mg tablets (FR/H/0130/002) registered by Les Laboratoires Servier in France since 25 November 1997. Reference is made to perindopril/indapamide authorisations in the individual member states. Perindopril arginine/Indapamide Servier 10 mg/2.5 mg, film-coated tablets (FR/H/0346/001) is registered by Les Laboratoires Servier in the Netherlands since 8 April 2009.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Estonia, France, Croatia, Ireland, Italy, Lithuania, Latvia, Malta, Poland, Portugal, Romania and Slovenia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Perindopril Tosilaat/Indapamide Teva is a white, round and biconvex film-coated tablet, plain on both sides.

Each film-coated tablet contains 10 mg perindopril tosilate corresponding to 6.816 mg perindopril, converted in situ to perindopril sodium, and 2.5 mg indapamide.

The film-coated tablets are packed in white opaque polypropylene (PP) containers with white opaque polyethylene (PE) stopper with desiccant insert equipped with a tamper evident (TE) polyethylene flow reducer.

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

## II.2 Drug Substances

**Perindopril tosilate**
One of the two active substances is perindopril tosilate, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). A different salt is described in the Ph.Eur.; perindopril tert-butylamine (erbumine). Perindopril tosilate is a white to off-white powder. It is very soluble in water between pH 1.2 to 6.8, methanol, ethanol, acetonitrile and dichloromethane, freely soluble in ethyl acetate; soluble in water, and practically insoluble in n-hexane. Perindopril tosilate is hygroscopic and corresponds to the S, S, S, S, S enantiomer. The substance is present in the amorphous form and does not crystallise if stressed. A test for the polymorphic form of the drug substance is therefore not required.

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 active substance perindopril tosilate is manufactured by a one-step synthesis. The specifications are acceptable.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the in-house specification. In addition to the specification of the ASMF holder, it 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 this 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 perindopril tosilate were provided for three commercial scale batches stored at 2-8°C (48 months (three batches), 24 months (three batches), 18 months (one batch), and nine months (one batch)) and 25°C/60% RH (six months (three batches)). Apart from a slight decrease in water content, no specific trends or significant changes have been observed in the provided stability data. A retest period of 48 months can be granted. The substance should be stored at 2-8°C protected from light and moisture.

**Indapamide**
Indapamide is an established active substance described in the Ph.Eur. It is a white or almost white powder. Indapamide is practically insoluble in water, and soluble in ethanol. It is shown that indapamide has no polymorphic forms and is a chiral substance which is present as a racemate.

The CEP procedure is used for the active substance. 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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

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 five years when stored in double polyethylene bag inside a fibre drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The use of a less stable drug substance compared to the reference product, which needs to be stabilised in the drug product is not favourable from a chemical-pharmaceutical point of view, however was appropriately justified. Pharmaceutical development has been adequately performed.

A bioequivalence study was conducted for the strength at issue. In addition, dissolution profiles of the batches were compared *in vitro* in three conditions (0.1 M HCl, phosphate buffer pH 4.5, and phosphate buffer pH 6.8) as well as under routine dissolution testing conditions in water. The dissolution is fast for perindopril in water, 0.1 M HCl and pH 4.5 phosphate buffer (>85% within 15 min). For indapamide $f_2$ calculations demonstrated that the dissolution profiles are similar in water, 0.1 M HCl, and pH 4.5 phosphate buffer ($f_2$ >50). At pH 6.8 phosphate buffer dissolution is not similar for both perindopril tosilate and indapamide. However, the MAH has provided an adequate discussion on these differences.

Manufacturing process
The manufacturing process is considered a non-standard process and involves blending, granulation, compression, and coating with a non-functional film-coat. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three commercial scale batches of two lower, already approved strengths and by a qualification process comparable to validation, with three full scale batches of the proposed strength batches.

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

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of the active substance and colouring agent titanium dioxide, uniformity of dosage units, 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. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided on three full scale batches stored for 12 months at 25°C/60% RH and 40°C/75% RH. Supportive stability data has been provided on the three pilot-scale and three full scale batches of the two lower strengths, stored up to 28 months at 25°C/60% RH and 6 months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. No significant changes were observed. The product is not sensitive to light. On the basis of the provided 12 months stability data and supportive 28 months stability data of the lower strengths, a shelf-life was granted of 28 months. The labelled storage conditions are “store in the original container to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg, film-coated tablets is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

### III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Perindopril arginine/Indapamide 10 mg/2.5 mg Servier film-coated tablets which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Perindopril tosilate 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 member states agreed that no further clinical studies are required.

The MAH initially submitted one bioequivalence study comparing Perindopril Tosilaat/Indapamide Teva 5 mg/1.25 mg, film-coated tablets (NL/H/2467/002) to the originator product Coversyl Plus arg 5 mg/1.25 mg, film-coated tablets (FR/H/0130/004). Subsequently a biowaiver for Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg was requested. However the request for a biowaiver was made obsolete, after an additional bioequivalence with the perindopril/indapamide 10 mg/2.5 mg strength was submitted. The reference product for this study is Coversyl Plus 10 arg mg/2.5 mg film-coated tablets, registered in France through procedure FR/H/0345/001. The study with higher strength will be discussed below.

### IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg film-coated tablets (Teva Nederland B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Coversyl Plus arg 10 mg/2.5 mg film-coated tablets (Les Laboratoires Servier, France).

*The choice of the reference product*
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

*Design*
A randomised, open-label, two-way crossover bioequivalence study was carried out under fasted conditions in 32 healthy male (n=24) and female (n=8) subjects, aged 22-54 years. Each subject received a single dose (10 mg/2.5 mg) of one of the two perindopril/indapamide formulations. The tablet was orally administered after a fasting period. There were two dosing periods, separated by a washout period of 21 days.

The following blood samples were collected over the course of the study:
- For perindopril and perindoprilat, blood samples were collected prior to study drug administration and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours post-dose, in each period;
- For perindopril only, additional blood samples were collected: 0.17, 0.33, 0.67, 0.83, and 1.25 hours post-dose, in each period;
- For perindoprilat only, additional blood samples were collected: 3.5, 4.5, 5, 12, 24, 48, and 72 hours post-dose, in each period;
- For indapamide, blood samples were collected prior to study drug administration and 0.33, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8.00, 12, 24, 48, and 72 hours post-dose, in each period.

The design of the study is acceptable. The wash-out of 21 days is long enough and the sampling period and sampling scheme are adequate to estimate pharmacokinetic parameters. For the assessment of perindopril only data of the parent compound is considered. The perindoprilat data were presented by the MAH as supportive data and will not be discussed here.

*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 was withdrawn before the start of the second period because of a due to significant adverse event (Urticaria). Therefore, a total of 31 subjects were eligible for pharmacokinetic analysis.

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

| Treatment N=31 | $AUC_{0-t}$ pg.h/ml | $AUC_{0-\infty}$ pg.h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | 89740 ± 18654 | 90810 ± 18487 | 72955 ± 19186 | 0.8 (0.5 - 1.3) |
| **Reference** | 85066 ± 16483 | 86059 ± 16470 | 76524 ± 21598 | 0.7 (0.5 - 2.0) |
| ***Ratio (90% CI)** | 1.06 (1.02 - 1.09) | 1.06 (1.03 - 1.09) | 0.96 (0.88 - 1.04) | -- |
| **CV (%)** | 6.72 | 6.58 | 21.06 | -- |

| | |
|---|---|
| $AUC_{0-\infty}$ | 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 |
| CV | coefficient of variation |

**ln-transformed values*

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

| Treatment N=31 | $AUC_{0-t}$ pg.h/ml | $AUC_{0-\infty}$ pg.h/ml | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test** | 2010 ± 434 | 2074 ± 471 | 118 ± 23 | 1.5 (0.7 - 6.0) |

| | | | | |
|---|---|---|---|---|
| **Reference** | 1886 ± 458 | 1949 ± 504 | 104 ± 23 | 1.6<br>(0.7 - 6.0) |
| ***Ratio<br>(90% CI)** | 1.08<br>(1.06 - 1.09) | 1.07<br>(1.06 - 1.09) | 1.14<br>(1.09 - 1.20) | -- |
| **CV (%)** | 3.72 | 3.98 | 10.97 | -- |

**$AUC_{0-\infty}$** 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
**CV** coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg film-coated tablets is considered bioequivalent with Coversyl Plus arg 10 mg/2.5 mg film-coated tablets.

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).

### IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Perindopril Tosilaat/Indapamide Teva.

Summary table of safety concerns as approved in RMP:

| | |
|---|---|
| Important identified risks | • Electrolyte abnormalities including hypo- and hyperkalaemia<br>• (symptomatic) hypotension<br>• Hypersensitivity reaction incl. angioedema and intestinal angioedema, photosensitivity, anaphylactoid reactions<br>• Foetotoxicity/use during second and third trimesters of pregnancy<br>• Renal impairment (including renal failure)<br>• Hepatitis (incl. fulminant hepatic failure and hepatic encephalopathy)<br>• Decreases in blood counts (in particular neutropenia/agranulocytosis, thrombocytopenia)<br>• Dual blockade of the renin-angiotensin-aldosterone system (RAAS) |
| Important potential risks | • Use during first trimester of pregnancy |
| Missing information | • Exposure during breast feeding<br>• Exposure in children and adolescents<br>• Exposure in patients with severe hepatic impairment<br>• Exposure in patients with severe renal impairment<br>• Exposure in patients with other relevant morbidity (e.g. patients with cardiovascular disease and diabetes mellitus)<br>• Sub-populations carrying known and relevant polymorphisms<br>• Ethnic differences |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Perindopril arginine/Indapamide Servier 10 mg/2.5 mg, film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet (PL) 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 two participants, followed by three rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Perindopril Tosilaat/Indapamide Teva 10 mg/2.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Perindopril arginine/Indapamide Servier 10 mg/2.5 mg, film-coated tablets. The reference product 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 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 10 mg/2.5 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 October 2016.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

| Procedure number* | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
|---|---|---|---|---|---|
| NL/H/3522/1/IA/001 | Change within the range of the currently approved pack sizes | -- | 31-5-2017 | Approval | -- |
| NL/H/3522/IA/003/G | Addition of secondary packaging site | -- | 4-5-2017 | Approval | -- |
| NL/H/3522/001/IB/002 | Other variation | -- | 7-6-2017 | Approval | -- |