

Public Assessment Report

Scientific discussion

**Perindopril tosilaat/Amlodipine Teva
5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg
and 10 mg/10 mg, tablets**

(perindopril tosilate/amlodipine)

NL/H/2842/001-004/DC

Date: 25 August 2014

This module reflects the scientific discussion for the approval of Perindopril tosilaat/Amlodipine Teva tablets. The procedure was finalised on 4 February 2014. For information on changes after this date please refer to the module 'Update'.

A list of abbreviations is given on page 12. This report also includes a summary, on pages 14-16.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Perindopril tosylaat/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg, tablets from Teva Nederland B.V. Each tablet contains an amount equivalent to 5 mg or 10 mg of perindopril tosylate corresponding to 3.4 mg and 6.8 mg perindopril, and 5 or 10 mg amlodipine as besylate.

The product is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.

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

This decentralised procedure concerns an application for a fixed combination medicinal product where the individual active substances (monocomponents) have established clinical use as well as regulatory approval. For both perindopril and amlodipine a number of generic formulations are already available on the market in Europe. For this kind of application it is not necessary to provide pre-clinical and clinical data relating to each individual active substance. Reference is made to the innovator products described below.

Perindopril was first registered in the Netherlands as Coversyl 2 mg and 4 mg (NL License RVG 13635-13636) by Les Laboratoires Servier in July 1989. The tablets contain perindopril tertbutylamine corresponding to perindopril 1.669 mg and 3.338 mg and are involved in Mutual Recognition Procedure FR/H/0246.

Perindopril arginine is registered in the Netherlands by Les Laboratoires Servier under the name Coversyl arg 2.5 mg, 5 mg and 10 mg tablets (NL License RVG 31957-31959). The tablets contain perindopril arginine corresponding to perindopril 1.6975 mg, 3.395 mg and 6.790 mg, respectively. The product was approved through a Mutual Recognition Procedure in September 2005 (FR/H/0265/001-003).

The approved indications for Coversyl are treatment of hypertension, symptomatic heart failure, stable coronary artery disease (prophylaxis of cardiac events post myocardial infarction and/or revascularisation in stable coronary artery disease).

The Dutch amlodipine innovator product Norvasc 5 mg and 10 tablets (NL RVG 13348-13349) has been registered by Pfizer since June 1990 for the indications hypertension, chronic stable angina pectoris and vasospastic (Prinzmetal's) angina (UK/H/5127/001-002/MR).

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Finland, Greece, Ireland, Italy, Latvia, Poland, Portugal, Romania and Slovenia.

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

The MAH gave the following argumentation for this fixed dose combination:

In line with the requirements stated in the document CHMP/EWP/191583/2005 entitled *Questions and answers on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention*:

- perindopril and amlodipine are well known active substances
- the joint application of the components has proven to be efficacious and safe, and thus clinically useful
- the pharmacological rationale for the use of perindopril/amlodipine in combination is adequately justified in literature. The MAH presented a bibliographical data analysis.
- the present application is based on pharmacokinetic data, *i.e.* interaction and bioequivalence studies.

No dedicated studies in the target population have been performed with this product on blood pressure, or with respect to increased compliance in a target population with possible comorbid disease or using co-medication. This is however not necessary taking into account the substitution indication.

No new non-clinical studies were performed in support of this application.

Two pharmacokinetic studies have been performed; one study investigated bioequivalence and the other interaction potential. A comparison was made with one tablet of the proposed fixed dose combination to the reference products administered as two tablets of perindopril erbumine plus one tablet of amlodipine. The results from the bioequivalence study, which was conducted with the highest amlodipine/perindopril strength (10 mg/10 mg), are extrapolated to the lower strengths (10 mg/5 mg, 5 mg/10 mg, 5 mg/5 mg). For these strengths a biowaiver has been granted. The study results are briefly presented in this report under section IV 'Clinical aspects'.

The RMS checked Paediatric Investigation Plan (PIP) compliance. On 22 October 2012 the EMA adopted a product-specific waiver for all subsets of the paediatric population from birth to less than 18 years of age (EMA-001320-PIP01-012, waiver decision number P/0246/2012).

II. QUALITY ASPECTS

II.1 Introduction

Perindopril tosilat/Amlodipine Teva tablets are:

5/5 mg: White, oval, biconvex tablets, debossed "5/5" on one side and plain on the other side.

5/10 mg: White, square-shaped, biconvex tablets, debossed "5/10" on one side and plain on the other side.

10/5 mg: White, round, biconvex tablets, debossed "10/5" on one side and plain on the other side.

10/10 mg: White, round, biconvex tablets, debossed "10/10" on one side and plain on the other side.

The tablets are packed in white opaque PP tablet containers with white opaque PE stopper with desiccant (silica gel) insert equipped with a tamper-evident PE flow reducer.

The excipients are: sodium hydrogen carbonate, povidone K 30 (E1201), lactose monohydrate, maize starch, microcrystalline cellulose (E460), sodium starch glycolate (Type A), magnesium stearate (E572) and anhydrous calcium hydrogen phosphate.

The four strengths are quantitatively dose proportional.

II.2 Drug Substances

The active substances are perindopril tosilate and amlodipine besilate. Perindopril tosilate is not described in the European Pharmacopoeia (Ph.Eur.), but a different salt is described, perindopril tert-butylamine (INN perindopril erbumine). Perindopril tosilate is a white to off-white powder which is very soluble in water, methanol, ethanol, dichloromethane and acetonitrile, 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. Perindopril tosilate corresponds to the S, S, S, S, S enantiomer.

Amlodipine besilate is an established active substance described in the Ph.Eur. It is a white or almost white powder, which is slightly soluble in water and 2-propanol, freely soluble in methanol and sparingly soluble in anhydrous ethanol. It does not exhibit polymorphism.

For perindopril tosilate the Active Substance Master File (ASMF) procedure is used. 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.

For amlodipine besilate the CEP procedure is used. 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 European Pharmacopoeia.

Manufacturing process

The active substance perindopril tosilate is manufactured by a one step synthesis with the pharmacopoeial perindopril tert-butylamine as starting material. The amorphous form of the active substance is obtained.

For amlodipine besilate a CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substances

The drug substance perindopril tosilate is controlled by an in-house specification. Control of related substances and stereochemical purity is based on the Ph.Eur. monograph on perindopril tert-butylamine. The active substance specification is considered adequate to control the quality.

Batch analytical data demonstrating compliance with the drug substance specification were provided for three commercial-scale batches.

The drug substance specification of amlodipine besilate is in line with the Ph.Eur. and additional requirements of the CEP. 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 commercial-scale batches.

Stability of drug substances

Stability data on the active substance perindopril tosilate were provided for three commercial-scale batches stored at 2-8°C (twelve months for two batches and nine months for one batch) and 25°C/60% RH (six months for all 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 re-test period of 18 months can be granted. The substance should be stored at 2-8°C in the original storage package in order to protect from light and moisture.

The active substance amlodipine besilate is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known. A number of experiments were carried out in order to optimize the productions process. It turned out that bilayer tablets were more suitable for this product than monolithic tablets. The choice of the package and manufacturing process is justified. The manufacture and composition of the bio-batches used in bioequivalence and bioavailability studies is identical to the product for marketing. The reference products used were Coversum® 4 mg (which contains 4 mg perindopril erbumine which corresponds to 3.4 mg perindopril) tablets marketed in Germany by Servier Deutschland GmbH and Istin 10 mg tablets marketed in the UK by Pfizer Limited. Biobatch and reference batches have comparable dissolution profiles in 0.01N HCL, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The bioequivalence study was conducted with the highest amlodipine/perindopril strength (10 mg/10 mg). Similarity of dissolution profiles for the biobatch with the additional 5 mg/5 mg, 5 mg/10 mg and 10 mg/5 mg strengths was demonstrated in 0.01N HCL, pH 6.8 phosphate buffer and pH 4.5 acetate buffer. As similarity of the dissolution profiles in the three dissolution media for the 10 mg/10 mg biobatch with the additional strengths was demonstrated, a biowaiver can be granted from a pharmaceutical point of view.

Manufacturing process

The manufacturing process can be regarded as a standard process. The process involves blending, granulation, and compression and has been validated on one pilot-scale batch of each strength. Process validation for full-scale batches will be performed during the manufacture of the first three production batches conform to the provided validation protocol.

Control of excipients

The excipients comply with their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification of the active substances, uniformity of dosage units, dissolution, assay, impurities/degradation products, and microbiological quality. Hardness and friability are tested in-process. The release and shelf-life specifications differ with regard to the limits for impurities/degradation products. All specifications are acceptable.

The analytical methods were adequately described and validated. Batch analytical data from the

proposed production site were provided on three pilot-scale batch 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 (9 or 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 white opaque PP tablet containers with white opaque PE stopper with desiccant insert equipped with a tamper-evident (TE) PE flow reducer. No significant changes were observed. An increase in the content of one amlodipine impurity was seen under accelerated and long-term conditions. Also a decrease in dissolution for amlodipine was seen. No trends were observed for the other parameters. The results of a photostability study show that the tablets are sensitive to light.

On the basis of the provided stability data, a shelf life of 24 months can be granted for the tablets packed in PP container with silica gel. The storage condition "This product does not require any special temperature storage conditions. Store in the original package in order to protect from light and moisture" is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Magnesium stearate is of vegetable origin. Lactose is the only excipient of animal origin. It 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Perindopril tosilat/Amlodipine Teva tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH committed to revise the limits for impurities after the manufacture of production-scale batches, when more stability data are available.
- The MAH committed to perform process validation studies for full-scale batches during the manufacture of the first three production batches.
- The MAH committed to continue all on-going stability studies. The results at least up to the proposed shelf life will be submitted.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology and pharmacokinetics

For this fixed dose application, the MAH provided an overview summarising the relevant literature on the pharmacology of amlodipine, perindopril tosilate and the combination of these two active substances. The pharmacokinetics of amlodipine and perindopril tosilate were also reviewed. No new studies have been performed. This is acceptable, as both active substances are well known.

III.2 Toxicology

The MAH reviewed the available non-clinical data on the toxicology of amlodipine and perindopril. In addition potential toxicity of the counter ion tosilate was considered. As amlodipine and perindopril are compounds with a long-term clinical experience, both separately and in combination, there is no need for any additional combination toxicology studies.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Since Perindopril tosilat/Amlodipine Teva is intended for substitution of both active ingredients used in separate tablets, its use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.4 Discussion on the non-clinical aspects

This product is a fixed-dose formulation of established active substances, which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. The Member States agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Amlodipine and perindopril tosylate are well-known active substances with established efficacy and tolerability.

The clinical development program was designed to assess the potential pharmacokinetic interaction between perindopril tosylate and amlodipine besilate and to evaluate the comparative bioavailability between amlodipine besilate/perindopril tosylate 10 mg/10 mg by Teva compared to Istin™ (amlodipine besilate) 10 mg by Pfizer, UK and 2 tablets of Coversum® (perindopril erbumine) 4 mg by Servier, Germany.

For this application, the MAH has submitted two pharmacokinetic studies, which are discussed below. The pharmacological rationale for the use of perindopril and amlodipine in combination is adequately justified in the published literature. A bibliographical data analysis regarding efficacy and safety has presented in this application for both indications. No further studies have been performed and none are considered necessary.

IV.2 Pharmacokinetics

The pharmacokinetic properties of perindopril and amlodipine are well known. Two pharmacokinetic studies have been performed: study 1 for investigation of interaction potential and study 2 for establishing bioequivalence.

Pharmacokinetic, statistical and bioanalytical methods are acceptable for these studies. The MAH selected a different salt, perindopril tosylate instead of perindopril erbumine for the development of its formulations. In a bioequivalence study that was previously conducted, the MAH demonstrated bioequivalence of perindopril base and perindoprilat after the administration of perindopril erbumine and perindopril tosylate. There is no scientific reason that would imply different *in vivo* behaviour in humans of perindopril tosylate and perindopril erbumine in terms of bioavailability, efficacy or safety. Use of the different salt is therefore acceptable.

Interaction study 1

Design

This study was designed as a randomised, single-dose, open-label, 3-way crossover bioavailability study to compare the rate and extent of absorption of perindopril tosylate co-administrated with amlodipine besilate and when administrated separately, under fasting conditions.

The following treatments were administered in the 3 different periods, separated by a wash-out period of 28 days:

- the combination of 1 tablet of perindopril tosylate 10 mg (Teva Pharma Hungary) and 1 tablet of amlodipine besilate 10 mg (Istin® 10 mg, Pfizer).
- one single tablet of perindopril tosylate 10 mg (Perindopril tosylate 10 mg tablets by Teva Pharma, Hungary).
- one single tablet of amlodipine besilate 10 mg (Istin 10 mg tablets by Pfizer UK).

A total of 42 subjects were included in the study, both male and female Caucasians, Hispanics and African Americans aged 21 to 55. Blood samples were drawn for amlodipine before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48 and 72 hours post-dose. For perindopril analysis blood samples were drawn before dosing and at 0.17, 0.3, 0.5, 0.67, 0.8, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours post-dose. This design of the study is considered acceptable.

Results

There were 3 drop-outs: 2 subjects withdrew their consent and 1 was withdrawn due to vomiting. As 2 of these drop-outs finished 2 complete study periods, they could be included in the analyses. The total number of subjects included in pharmacokinetic and statistical analysis was therefore 40, for both compounds.

Table 1. Pharmacokinetic parameters for amlodipine (n=40, non-transformed values; arithmetic mean \pm SD, t_{\max} median, range)

| Treatment | AUC ₀₋₇₂ ng/ml/h | C _{max} ng/ml | t _{max} h |
|---|--------------------------------|---------------------------|-----------------------|
| Test <i>perindopril/ amlodipine</i> | 222 \pm 49 | 6.1 \pm 1.3 | 7.0 (5.0-10) |
| Reference <i>amlodipine</i> | 234 \pm 51 | 6.3 \pm 1.1 | 7.0 (5.0-12) |
| *Ratio (90% CI) | 0.95 (0.92-0.98) | 0.97 (0.93-1.00) | -- |
| AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to t=72 C_{max} maximum plasma concentration t_{max} time for maximum concentration | | | |

**ln-transformed values*

Table 2. Pharmacokinetic parameters for perindopril (n=40, non-transformed values; arithmetic mean \pm SD, t_{\max} median, range)

| Treatment | AUC _{0-t} ng/ml/h | AUC _{0-∞} ng/ml/h | C _{max} ng/ml | t _{max} h |
|---|-------------------------------|-------------------------------|---------------------------|-----------------------|
| Test <i>perindopril/ amlodipine</i> | 80 \pm 19 | 81 \pm 19 | 65 \pm 22 | 0.667 (0.5-2.0) |
| Reference <i>perindopril</i> | 79 \pm 17 | 80 \pm 17 | 67 \pm 18 | 0.667 (0.5-1.5) |
| *Ratio (90% CI) | 1.02 (0.98-1.05) | 1.02 (0.98-1.05) | 0.97 (0.88-1.07) | -- |
| AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum concentration | | | | |

**ln-transformed values*

Bioequivalence study 2

This study was designed as an open-label, single-dose, randomized, 2-period, 2-sequence, 2-treatment, crossover study under fasting conditions. The objective was to evaluate the comparative bioavailability of the combination tablet amlodipine/perindopril and 2 separate formulations of perindopril and amlodipine.

The following treatments were administered in the different periods, separated by a wash-out period of 28 days:

- one tablet a fixed-dose combination single dose of 10 mg amlodipine besilate and 10 mg perindopril tosilate (Perindopril tosilat/Amlodipine Teva 10 mg/10 mg tablets, Teva Nederland B.V.)
- concomitant administration of one tablet of 10 mg amlodipine besilate (Istin 10 mg tablets by Pfizer, UK) and two tablets of 4 mg perindopril erbumine (Coversum 4 mg tablets by Servier, Germany).

A total of 52 healthy subjects were included in the study, aged 22-55 years and of Asian, Black, White and Hispanic/Latino ethnicity.

Blood samples were drawn for amlodipine before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 48 and 72 hours post-dose. For perindopril blood samples were drawn before dosing and at 0.17, 0.3, 0.5, 0.67, 0.8, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48 and 72 hours post-dose.

This design is acceptable. In accordance with the protocol, for amlodipine the first 24 subjects completing the study are included.

Results

One subject withdrew for personal reasons during the study and a second subject was withdrawn due to an adverse event. Therefore, a total of 50 subjects were included in the analysis for perindopril. One subject was prescribed amoxicillin prior to the 72 hour blood draw and was therefore excluded from the amlodipine analysis.

Table 3. Pharmacokinetic parameters for amlodipine (n=24, non-transformed values; arithmetic mean \pm SD, t_{\max} median, range)

| Treatment | AUC ₀₋₇₂ ng/ml/h | C _{max} ng/ml | t _{max} h |
|---|--------------------------------|---------------------------|-----------------------|
| Test <i>perindopril/ amlodipine</i> | 251 \pm 69 | 6.8 \pm 1.6 | 6.0 (5.0-12) |
| Reference <i>amlodipine</i> | 251 \pm 68 | 6.7 \pm 1.5 | 5.5 (5.0-8.0) |
| *Ratio (90% CI) | 1.00 (0.97-1.03) | 1.02 (0.98-1.05) | -- |
| AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to t=72 C_{max} maximum plasma concentration t_{max} time for maximum concentration | | | |

**In-transformed values*

Table 4. Pharmacokinetic parameters for perindopril (n=50, non-transformed values; arithmetic mean \pm SD, t_{\max} median, range)

| Treatment | AUC _{0-t} ng/ml/h | AUC _{0-∞} ng/ml/h | C _{max} ng/ml | t _{max} h |
|---|-------------------------------|-------------------------------|---------------------------|-----------------------|
| Test <i>perindopril/ amlodipine</i> | 87 \pm 21 | 88 \pm 21 | 71 \pm 20 | 0.67 (0.33-2.0) |
| Reference <i>perindopril</i> | 80 \pm 19 | 80 \pm 19 | 67 \pm 19 | 0.67 (0.5-1.5) |
| *Ratio (90% CI) | 1.09 (1.07-1.11) | -- | 1.04 (0.98-1.11) | -- |
| AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration t_{max} time for maximum concentration | | | | |

**In-transformed values*

Conclusion on the pharmacokinetic studies

From the latter study it can be concluded that the 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 under fasted conditions it can be concluded that combination product Perindopril tosilat/Amlodipine Teva is bioequivalent with the administration of the separate reference products, Coversum and Istin.film-coated tablets, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

From the first study it is concluded that there is no pharmacokinetic interaction between the individual compounds of this fixed-dose combination product. The 90% confidence intervals for AUC and C_{max} are within the acceptance range of 0.80–1.25.

Perindopril tosilate and amlodipine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of perindopril tosilate. Therefore, a food interaction study is not deemed necessary.

Safety

The most commonly reported treatment-emerging adverse event in study 1 was somnolence reported by 11.9% (n=5) of subjects who constituted the safety population. In the combination treatment group 1 time, in the perindopril treatment group 3 times and in the amlodipine treatment group 2 times. In study 2 the most frequently reported adverse event was hypertension, which was reported by 7 subjects (13.5% of subjects dosed) with a mild intensity, 5 times for the test formulation and 5 times for the reference formulation. The reported profile of adverse events is acceptable.

Biowaiver

The pharmacokinetic studies have been performed administrating the highest strength applied for: perindopril/amlodipine 10 mg/10 mg. The MAH applied for three more strengths: 5/5 mg, 10/5 mg and 5/10 mg. For these lower strengths a biowaiver has been granted in accordance with the guideline on the investigation of bioequivalence, as:

- the pharmaceutical products are manufactured by the same manufacturing process,
- the qualitative composition of the different strengths is the same,
- the composition of the strengths are quantitatively proportional,
- comparable *in vitro* dissolution has been demonstrated.

The MEB has been assured that the pharmacokinetic studies have 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 Pharmacodynamics

Calcium channel blockers, like amlodipine, inhibit the flow of calcium ions through L-type calcium channels into vascular smooth muscle, thereby dilating large resistance arteries. In addition, they promote fibrinolysis by increasing the activity of antithrombogenic tissue plasminogen activator (t-PA), decrease inflammatory markers after cardiac ischaemia, inhibit proliferation of vascular smooth muscle cells and extracellular matrix formation, and inhibit cytokine-induced apoptosis of endothelial cells. Beneficial effects have been shown on the heart (reduction in ischemia) and kidney. Other targets include the vessels (an anti-atherosclerotic effect), platelets, coagulation system, reduction of hypertrophy and metabolic effects.

The ACE inhibitors, such as perindopril, block the conversion of angiotensin I into angiotensin II, causing a reduction in circulating and tissue levels of angiotensin II. ACE inhibitors do not completely block the effects of angiotensin II because it can be formed by non-ACE pathways. Angiotensin II has CV adverse effects including vasoconstriction, increase in glomerular perfusion pressure, aldosterone and anti-diuretic hormone secretion with consequent volume expansion and remodelling and hypertrophy of heart and vessels. This inhibition of the renin-angiotensin system causes reduction of blood pressure, especially in hypertensive patients. In these patients, perindopril significantly reduces left ventricular mass index (LVMI). Administration of perindopril in congestive heart failure patients increased renal blood flow and reduced renal vascular resistance. Perindopril use for 3-9 months has been reported to produce marked and sustained reductions in micro-albuminuria in hypertensive diabetic patients at risk of developing diabetic nephropathy. ACE inhibitors are also demonstrated to have metabolic effects, effects on fibrinolysis, and effects on endothelial factors and atherosclerosis.

CCBs and ACE inhibitors have complementary mechanism of action in blood pressure reduction. CCBs are potent vasodilators that induce reflex activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). Combination with an ACE inhibitor leads to buffering of this neuroendocrine activation leading to greater blood pressure lowering and cardioprotective effects. Moreover, the safety profile of the combination compares favourably to that of the mono-components. It has been noted that oedema, which occurs frequently with CCBs is more reduced by ACE inhibitors than with diuretics.

The MAH has given an adequate overview of the pharmacodynamics of both components of the proposed fixed dose combination. The discussion in the clinical overview shows, that the components are likely synergistic in BP lowering and cardioprotective effects.

IV.4 Clinical efficacy and safety

Both mono-components are frequently used in clinical practice. The characteristics (efficacy and safety) of these mono-components are described in their respective approved SmPCs and this information is also reflected in the SmPC for Perindopril tosilat/Amlodipine Teva.

The combined use of ACE inhibitors and CCBs, and specifically perindopril and amlodipine has been advocated in guidelines of the ESH/ESC since 2003. The pharmacologic mode of action of the two components used in combination provides a synergistic effect. Large-scale trials have been published

with such combinations (most notably ACCOMPLISH and ASCOT).

Co-prescription data (number of Rx prescribed by office based physicians) from the IMS database show that combination of amlodipine and perindopril has been extensively prescribed in five European Union countries (Germany, Italy, Spain, France and the United Kingdom) with over one million co-prescriptions per year in both 2009 and 2010 (IMS 2010).

IV.5 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 tosilat/Amlodipine Teva.

Summary table of safety concerns as approved in RMP

| | |
|----------------------------|---|
| Important Identified risks | <ul style="list-style-type: none">- Hypersensitivity reactions incl. angioedema and intestinal angioedema- Renal impairment (including renal failure)- Hepatitis (incl. fulminant hepatic failure and hepatic encephalopathy)- Hyperkalaemia- Hypotension (symptomatic)- Foetotoxicity- Decreases in blood counts (in particular neutropenia/agranulocytosis and thrombocytopenia)- Photosensitivity |
| Important potential risks | - -- |
| Missing information | <p>Safety regarding:</p> <ul style="list-style-type: none">- Exposure during breast feeding- Exposure in children and adolescents- Exposure in patients with hepatic impairment- Exposure in patients with severe renal impairment- Exposure in patients with other relevant morbidity (e.g. patients with cardiovascular disease and diabetes mellitus)- Sub-populations carrying known and relevant polymorphisms- Black patients |

The member states considered this RMP acceptable. No additional risk minimization activities are considered necessary at the moment.

IV.6 Discussion on the clinical aspects

The combined use of ACE inhibitors and calcium-channel blockers is well established. The literature data submitted by the MAH support the use of the perindopril/amlodipine combination. The pharmacokinetic studies investigating bioequivalence and interaction potential show satisfactory results: a single tablet of Perindopril tosilat/Amlodipine Teva can be used instead of co-administration of the separate products Coversum and Istin. Risk management is adequately addressed.

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 3 participants, followed by two rounds with 10 participants each. Twenty questions about the most critical parts of the package leaflet were asked, as well as three questions about the PL in general.

Taking into account the results for each question, more than 90% of the participants was able to find the section and answer the question correctly.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Perindopril tosilat/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg, tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Both perindopril and amlodipine are well known, established substances, which are used as a combination in clinical practice.

One pharmacokinetic study showed that there is no pharmacokinetic interaction between the individual compounds of this fixed-dose combination product. The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products Coversum and Istin. The efficacy and safety profile is considered the same as for the monocomponents.

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

The SmPC is consistent with those for the separate components. The SmPC, 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Perindopril tosilat/Amlodipine Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 February 2014.

List of abbreviations

| | |
|--------------------|--|
| ACE | Angiotensin-Converting Enzyme |
| ASMF | Active Substance Master File |
| AUC _{0-t} | Area under the plasma concentration-time curve from time zero to t hours |
| AUC _{0-∞} | Area under the plasma concentration-time curve from time zero to infinity |
| AUC ₇₂ | Area under the plasma concentration-time curve from time zero to t=72 |
| BP | Blood Pressure |
| CCB | Calcium Channel Blockers |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CI | Confidence Interval |
| C _{max} | Maximum plasma concentration |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CV | Cardiovascular |
| DBP | Diastolic Blood Pressure |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| ERA | Environmental Risk Assessment |
| ESC | European Society of Cardiology |
| ESH | European Society of Hypertension |
| EU | European Union |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference of Harmonisation |
| INN | International Nonproprietary Names |
| LVMI | Left Ventricular Mass Index |
| MAH | Marketing Authorisation Holder |
| MEB | Medicines Evaluation Board in the Netherlands |
| PAR | Public Assessment Report |
| Ph.Eur. | European Pharmacopoeia |
| PL | Package Leaflet |
| PP | Polypropylene |
| RAAS | Renin-Angiotensin-Aldosterone System |
| RMP | Risk Management Plan |
| Rx | Medical Prescriptions |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SmPC | Summary of Product Characteristics |
| t _½ | Half-life |
| t _{max} | Time for maximum concentration |
| TSE | Transmissible Spongiform Encephalopathy |

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 |
|-------|------------------|----------------------|--------------------------------|------------------------------|------------------------|----------------------------|
| | | | | | | |

Summary Public Assessment Report
non-generics

Perindopril tosilaat/Amlodipine Teva
5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg
and 10 mg/10 mg, tablets

(perindopril tosilate and amlodipine)

NL/H/2842/001-004/DC

Date: 25 August 2014

Summary Public Assessment Report

non-generics

Perindopril tosilaat/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg, tablets

Active substance: perindopril tosylate and amlodipine

This is a summary of the public assessment report (PAR) for Perindopril tosilaat/Amlodipine Teva. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Perindopril tosilaat/Amlodipine Teva.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Perindopril tosilaat/Amlodipine Teva and what is it used for?

Perindopril tosilaat/Amlodipine Teva tablets contain two active substances: perindopril tosylate and amlodipine. These substances are also available as separate tablets marketed under several trade names such as Norvasc® (amlodipine) and Coversyl® (perindopril).

These medicines are prescribed for treatment of high blood pressure (hypertension) and/or treatment of stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked).

Patients already taking perindopril and amlodipine as separate tablets may instead take one tablet of Perindopril tosilaat/Amlodipine Teva which contains both ingredients.

How does this medicine work?

The active substance perindopril is an ACE (angiotensin converting enzyme) inhibitor. The second active substance, amlodipine, is a calcium antagonist (which belongs to a class of medicines called dihydropyridines). Together they work to widen and relax the blood vessels so that blood passes through them more easily and makes it easier for the heart to maintain a good blood flow.

How is this medicine used?

The pharmaceutical form of Perindopril tosilaat/Amlodipine Teva is a tablet and the route of administration is oral. The medicine can only be obtained with a prescription.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of this medicine have been shown in studies?

Because Perindopril tosilaat/Amlodipine Teva is intended for substitution of separate tablets containing only perindopril or amlodipine, studies in patients have been limited to tests to determine that it is bioequivalent to the individual tablets and that there is no interaction between the two active substances when given in same tablet. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

The studies have shown that the same amount of perindopril and amlodipine is produced in the blood after administration of the combination tablet or the two separate tablets and that the two active substances in one tablet do not interact.

What are the possible side effects from this medicine?

The most common side effects with Perindopril tosilaat/Amlodipine Teva (which may affect up to 1 in 10 people) are headache, dizziness, sleepiness (especially at the beginning of treatment), vertigo, numbness or tingling sensation in your limbs, vision disturbances (including double vision), tinnitus (sensation of noises in the ears), palpitations (awareness of your heartbeat), flushing, light-headedness due to low blood pressure, cough, shortness of breath, nausea (feeling sick), vomiting (being sick), abdominal pain, taste disturbances, dyspepsia or difficulty of digestion, diarrhoea, constipation, allergic reactions (such as skin rashes, itching), muscle cramps, tiredness, weakness and ankle swelling (oedema).

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet.

Why is this medicine approved?

The Medicines Evaluation Board of the Netherlands decided that Perindopril tosilat/Amlodipine Teva's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?

A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Perindopril tosilat/Amlodipine Teva, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine

In the Netherlands, the marketing authorisation for Perindopril tosilat/Amlodipine Teva 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg and 10 mg/10 mg, tablets was granted on 14 April 2014.

The full PAR for this medicine can be found on the website <http://mri.medagencies.org/Human>. For more information about treatment with Perindopril tosilat/Amlodipine Teva, read the package leaflet (http://mri.medagencies.org/download/NL_H_2842_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in August 2014.