

## **Public Assessment Report**

### **UK National Procedure**

**Perindopril 2 mg Tablets**

**Perindopril 4 mg Tablets**

**Perindopril 8 mg Tablets**

**PL 20075/0294-0296**

**Accord Healthcare Limited**

## LAY SUMMARY

This is a summary of the public assessment report (PAR) for Perindopril 2 mg, 4 mg and 8 mg Tablets. It explains how Perindopril Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Perindopril Tablets.

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

### **What are Perindopril Tablets and what are they used for?**

Perindopril 2 mg and 4 mg Tablets are generic medicines. This means that Perindopril 2 mg and 4 mg Tablets are similar to reference medicines already authorised in the European Union (EU) called Coversyl 2 mg and 4 mg.

Perindopril 8 mg Tablets is a hybrid medicine. It is similar to the reference medicines Coversyl 2 mg and 4 mg but is available in a higher strength.

Perindopril Tablets are used to treat high blood pressure (hypertension) and heart failure (a condition where the heart is unable to pump enough blood to meet the body's needs) and to reduce the risk of cardiac events, such as heart attack, in patients with stable coronary artery disease (a condition where the blood supply to the heart is reduced or blocked) and who have already had a heart attack and/or an operation to improve the blood supply to the heart by widening the vessels that supply it.

### **How do Perindopril Tablets work?**

Perindopril belongs to a group of medicines called ACE inhibitors. These work by widening the blood vessels. This makes it easier for your heart to pump blood through the body.

### **How are Perindopril Tablets used?**

A doctor will decide the amount of perindopril that should be taken. Perindopril may be used on its own, or with other medicines which lower blood pressure.

Perindopril Tablets should be taken in the morning before a meal. The tablets should be swallowed, preferably with a glass of water and at the same time each day.

The usual dose used to treat high blood pressure is 4 mg each day. After a month, this may be raised to 8 mg each day. In patients over 65 with high blood pressure the daily dose is usually 2 mg. After a month, this may be raised to 4 mg each day. A daily dose of 8 mg is the highest amount normally used to treat high blood pressure.

Patients taking water tablets (diuretics) may be advised by their doctor to stop taking them 2 to 3 days before they start taking perindopril tablets. This is to prevent a fall in blood pressure. If needed, patients can start taking water tablets again after they have started Perindopril Tablets. If it is not possible to stop taking water tablets then patients can take 2 mg of perindopril as well.

A doctor may start their patient with a dose of 2 mg perindopril if their blood pressure is very high, they do not have enough water in their body (they are dehydrated), they have a low level of salt in their blood, they have a heart problem which means that it has difficulty in pumping blood through the body (cardiac decompensation), or they have high blood pressure due to the blood vessels in the kidneys being blocked (constriction of the arteries).

The usual dose used to treat heart failure is 2 mg each day to start. After 2 weeks, this may be raised to 4 mg each day, which is the maximum recommended dose for heart failure.

The usual dose used to treat stable coronary artery disease is 4 mg once daily. After two weeks, this may be raised to 8 mg each day, which is the maximum recommended dose in this condition.

In older people with stable coronary artery disease the daily dose is usually 2 mg each day. After 1 week this may be raised to 4 mg each day and after a further week to 8 mg each day, which is the highest amount used. The dose should be increased only if the previous lower dose is well tolerated.

This medicine can only be obtained with a prescription and is not recommended for use in children and adolescents up to the age of 18 years.

#### **What benefit have Perindopril Tablets shown during studies?**

Because Perindopril Tablets are generic medicines, studies in patients have been limited to tests to determine that Perindopril Tablets are bioequivalent to the reference medicines, Coversyl tablets. Two medicines are bioequivalent when they produce the same levels of active substance in the body.

#### **What are the possible side effects from Perindopril Tablets?**

Because Perindopril Tablets are generic medicines, their benefits and possible side effects are taken as being the same as those of the reference medicines.

For the full list of restrictions, see the package leaflet.

#### **Why are Perindopril Tablets approved?**

It was concluded that, in accordance with EU requirements, Perindopril Tablets have been shown to be comparable to Coversyl tablets. Therefore, the MHRA decided that, as for Coversyl tablets, the benefits of Perindopril Tablets are greater than their risks.

#### **What measures are being taken to ensure the safe and effective use of Perindopril Tablets?**

Suitable safety information has been included in the Summaries of Product Characteristics and the package leaflet for Perindopril Tablets, 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 and reviewed continuously.

#### **Other information about Perindopril Tablets**

The MHRA agreed to grant Marketing Authorisations for Perindopril Tablets on 24 July 2006.

For more information about treatment with Perindopril Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2015.

The full PAR for Perindopril Tablets follows this summary.

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## **I Introduction**

Based on the review of the data on quality, safety and efficacy, the MHRA considered that the applications for Perindopril 2 mg, 4 mg and 8 mg Tablets could be approved. These prescription only medicines (POM) are used for the treatment of hypertension, treatment of symptomatic heart failure and reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation. Perindopril can be used alone or in combination with other antihypertensive agents.

The applications for Perindopril 2 mg and 4 mg Tablets were made under Article 10(1) of Directive 2001/83/EC, as amended, as so-called generic applications. The application for Perindopril 8 mg Tablets was made under Article 10(3) of Directive 2001/83/EC, as amended, as a so-called hybrid application. The reference medicinal products for these applications are Coversyl 2 mg and 4 mg (PL 05815/0001-0002), which were first authorised to Les Laboratoires Servier on 15 December 1989. The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of these applications is acceptable.

Perindopril is an angiotensin-converting enzyme (ACE) inhibitor, used in the treatment of hypertension and heart failure. Perindopril is a prodrug which, following oral absorption, is hydrolysed to its active metabolite, perindoprilat. The beneficial haemodynamic effects resulting from ACE inhibition are a consequence of the reduction in angiotensin II causing dilatation of peripheral vessels and reduction in vascular resistance.

No new non-clinical data were submitted, which is acceptable given that the applications are for generic medicinal products of originator products that have been in clinical use for over 10 years.

Coversyl 8 mg was authorised to Les Laboratoires Servier as a line extension on 12 June 2002 and was used in the bioequivalence study submitted in support of these applications. The bioequivalence study compared Coversyl 8 mg and Perindopril 8 mg Tablets. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

Acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, copies of current manufacturer authorisations issued by inspection services of the competent authorities have been provided as certification that acceptable standards of GMP are in place at those sites.

The MHRA considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The lack of a Risk Management Plan (RMP) with these applications is acceptable as the applications were submitted on 2 February 2005.

The lack of an Environmental Risk Assessment (ERA) with these applications for generic products is acceptable.

The Marketing Authorisations were granted on 24 July 2006. Following a change of ownership on 29 August 2008 the Marketing Authorisations were transferred to Apotex Europe BV. Following a change of ownership on 13 July 2009 the Marketing Authorisations were transferred to Karib Kemi Pharm Limited. Following a change of ownership on 1 February 2010 the Marketing Authorisations were transferred to Accord Healthcare Limited.

## II Quality aspects

### II.1 Introduction

The 2 mg tablets are white, round and biconvex with ‘2’ engraved on one side and plain on the other side. The 4 mg tablets are white, capsule shaped and biconvex with ‘P’ Bisect ‘4’ engraved on one side and plain on the other side. The 8 mg tablets are white, capsule shaped and biconvex with ‘P’ Bisect ‘8’ engraved on one side and plain on the other side. The 4 mg and 8 mg tablets can be divided into equal halves.

The excipients in the medicinal products are anhydrous lactose and magnesium stearate.

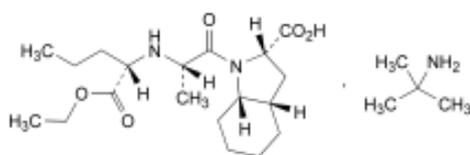
The tablets are presented in aluminum/PVC/PVAC blister packs. Pack sizes of 4, 7, 14, 15, 28, 30, 50, 56, 60, 90, 100, 112, 120 and 500 tablets have been authorised.

### II.2 Drug Substance

INN: Perindopril erbumine

Chemical name: 2-Methylpropan-2-amine (2S,3aS,7aS)-1-[(2S)-2-[[[(1S)-1-(ethoxycarbonyl)butyl]amino]propanoyl]octahydro-1H-indole-2-carboxylate

Structure:



Molecular formula:  $C_{23}H_{43}N_3O_5$

Molecular weight: 441.6

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

## **II.3 Medicinal Products**

### **Pharmaceutical development**

The aim of the pharmaceutical development of Perindopril 2 mg, 4 mg and 8 mg Tablets was to develop generic versions of the innovator products, Coversyl tablets.

The proposed and the reference products were tested for a number of parameters to support the claim that the products were comparable.

All excipients comply with their European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

The anhydrous lactose used to make the tablets is of animal origin. The supplier of lactose has provided a declaration referring to their compliance with the CHMP guideline EMEA/410/01 Rev. 2.

### **Manufacture of the product**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

### **Finished Product Specifications**

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

### **Stability of the products**

Stability studies were performed in accordance with current guidelines on batches of the finished products, packed in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years for the products when the storage precautions “Store below 25°C” and “Store in the original package” are applied.

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

The grant of marketing authorisations is recommended.

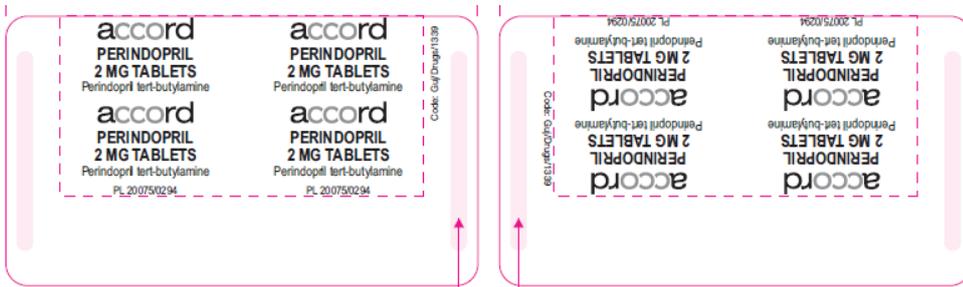
## **II.5 SmPC, PIL and labelling**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following product labelling was approved:

PL 20075/0294

**Blister:**



Embossing space for Batch details  
EXP & Lot

**Carton:**



Keep area blank & back ground  
should be white for barcode

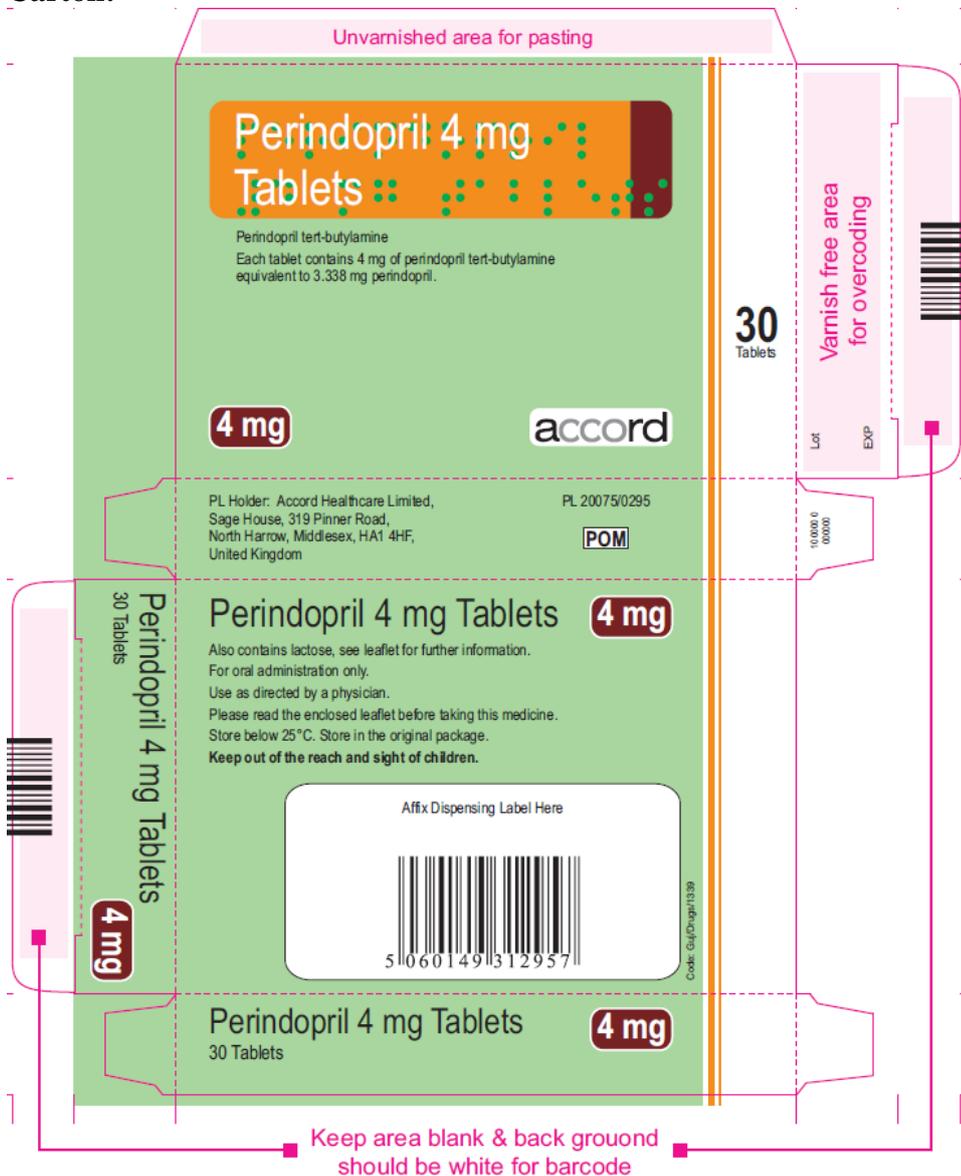
PL 20075/0295

**Blister:**



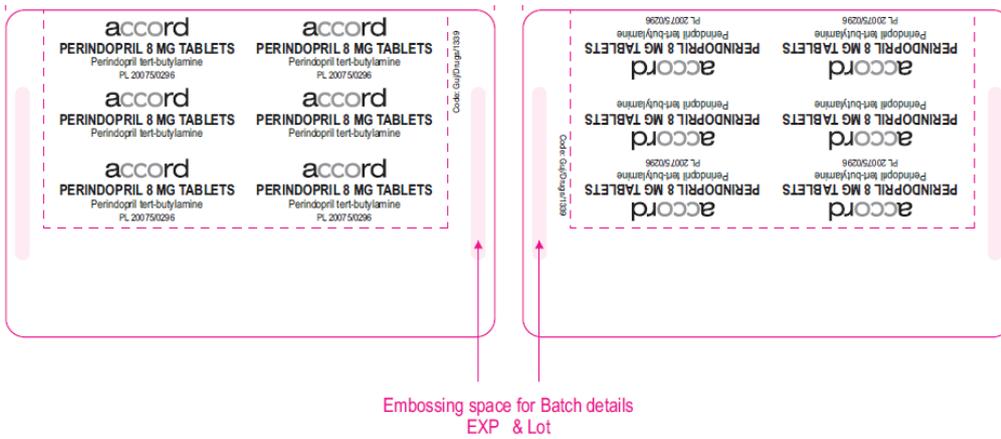
Embossing space for Batch details  
EXP & Lot

**Carton:**

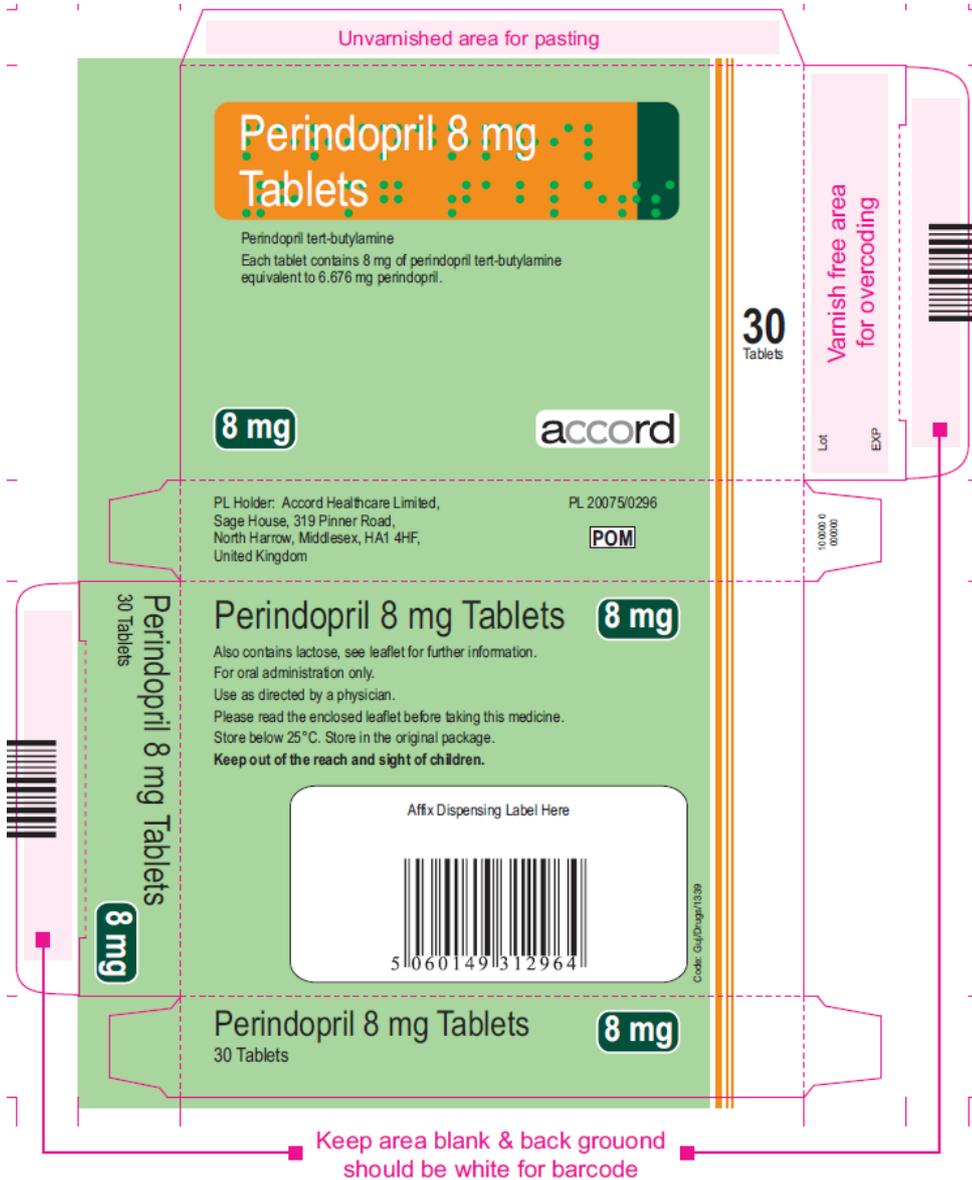


PL 20075/0296

**Blister:**



**Carton:**



### **III Non-clinical aspects**

#### **III.1 Introduction**

No new non-clinical data have been submitted and none are required for applications of this type. The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory.

#### **III.2 Pharmacology**

No new pharmacology data are required for these applications and none have been submitted.

#### **III.3 Pharmacokinetics**

No new pharmacokinetic data are required for these applications and none have been submitted.

#### **III.4 Toxicology**

No new toxicology data are required for these applications and none have been submitted.

#### **III.5 Ecotoxicity/environmental risk assessment (ERA)**

Since the formulations of Perindopril 2 mg, 4 mg and 8 mg Tablets are intended for generic substitution, they will not lead to an increased exposure to the environment. An ERA is therefore not deemed necessary.

#### **III.6 Discussion on the non-clinical aspects**

The grant of Marketing Authorisations is recommended.

### **IV Clinical aspects**

#### **IV.1 Introduction**

The applicant has submitted reports of a bioequivalence study in support of these applications. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

#### **IV.2 Pharmacokinetics**

##### **Bioequivalence study**

##### **Study design**

The study was a randomised, comparative and two-way crossover design bioequivalence study in 28 healthy, adult, human subjects under fasting conditions comparing Perindopril 8 mg Tablets with Coversyl 8 mg tablet.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to 120 hours following drug administration. The plasma samples from the subjects were analysed for perindopril using a validated method.

Samples from 26 subjects were considered in the PK analysis and the results are presented below:

**Summary pharmacokinetic data for perindopril: mean\* (%CV)**

Parameter	Apotex Perindopril 8 mg	Coversyl 8 mg	Relative mean** (%)	90% Confidence interval
C <sub>max</sub> (ng/ml)	75.5 (25)	73.0 (26)	103.8	97.4 – 110.6
AUC <sub>0-t</sub> (ng.hr/ml)	89.3 (24)	87.2 (22)	102.1	98.2 – 106.2
AUC <sub>0-∞</sub> (ng.hr/ml)	91.1 (24)	87.9 (22)	104.4	101.8 – 107.0
T <sub>max</sub> (hr)	0.66 (26)	0.66 (21)	113.2	

\* for raw data. For T<sub>max</sub> these are medians

\*\* based on least square means (geometric means for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub>; t<sub>max</sub> was calculated by a non-parametric method.

**Summary pharmacokinetic data for perindoprilat: mean\* (%CV)**

Parameter	Apotex Perindopril 8 mg	Coversyl 8 mg	Relative mean** (%)	90% Confidence interval
C <sub>max</sub> (ng/ml)	12.02 (48)	10.54 (46)	113.4	108.2 – 118.9
AUC <sub>0-t</sub> (ng.hr/ml)	190.1 (31)	184.1 (31)	103.7	100.7 – 106.9
AUC <sub>0-∞</sub> (ng.hr/ml)	230.0 (31)	225.7 (31)	102.4	99.4 – 105.4
T <sub>max</sub> (hr)	4.02 (32)	5.00 (36)	99.4	

\* for raw data. For T<sub>max</sub> these are medians

\*\* based on least square means (geometric means for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-∞</sub>; t<sub>max</sub> was calculated by a non-parametric method.

The 90% confidence intervals for AUC and C<sub>max</sub> were within the acceptance range of 80.00 to 125.00 % for both the parent compound and the metabolite. Bioequivalence between the test product and reference product has been adequately demonstrated.

**Biowaiver**

The applicant has submitted a single bioequivalence study using the 8 mg strength tablets only. The requirements of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) have been met with regards to a claim for a biowaiver for the 2 and 4 mg strength tablets.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data are required for these applications and none have been submitted.

**IV.4 Clinical efficacy**

No new clinical efficacy data are required for these applications and none have been submitted.

#### **IV.5 Clinical safety**

With the exception of the data generated during the bioequivalence studies, no new safety data are presented for these applications and none are required. No new or unexpected safety issues arose during the bioequivalence study.

#### **IV.6 Risk Management Plan**

The lack of a Risk Management Plan (RMP) with these applications is acceptable as the applications were submitted on 2 February 2005.

#### **IV.7 Discussion on the clinical aspects**

The grant of Marketing Authorisations is recommended for these applications.

### **V User consultation**

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. 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**

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with perindopril is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

### **VII Steps taken for assessment**

1	The MHRA received the marketing authorisation applications on 2 February 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 30 August 2005
3	Following assessment of the applications the MHRA requested further information relating to the dossier on 12 October 2005, 8 March 2006 and 27 March 2006
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 8 March 2006, 24 March 2006 and 19 July 2006
5	The applications were determined on 24 July 2006

### VIII Steps taken after initial authorisation

<b>Date submitted</b>	<b>Application type</b>	<b>Scope</b>	<b>Outcome</b>
11/08/2008	Change of ownership	Change of ownership to Apotex Europe BV	29/08/2008
07/11/2008	Type IA variation	To change the source of the excipient magnesium stearate from an animal source to a vegetable source	17/12/2008
04/06/2009	Change of ownership	Change of ownership to Karib Kemi Pharm Limited	13/07/2009
13/08/2009	Type II variation	To update sections 4.3 (Contraindications), 4.4 (Special warnings) and 4.6 (Pregnancy and lactation) of the SmPC and the PIL as agreed by the PhVWP relating to the use of ACE inhibitors during pregnancy and lactation. Consequential changes to the PIL will be incorporated at the next reprint or by 19th August 2009, whichever is earlier, mock-ups will be submitted in the usual manner at submission of the next regulatory change.	18/08/2009
13/11/2009	Change of ownership	Change of ownership to Accord Healthcare Limited	01/02/2010
26/03/2007	PIU	Periodic Safety Update Report covering period 24/07/2006 - 23/01/2007	07/06/2010
03/07/2010	PIU	To update the change in the design of the mockups (carton, foil) for Perindopril tablets 2mg, 4mg, 8mg	21/07/2010
19/07/2010	PIU	To update the MA with respect to article 59(1) and 59(3) of Council Directive 2001/83/EC	16/06/2011
27/07/2010	Type IB variation	To register module 1.8.1 - Detailed Description of Pharmacovigilance System version 7.0 to the product licences.	29/09/2010
31/12/2010	Type IB variation	To update sections 3 (Pharmaceutical form), 4.2	08/02/2011

		<p>(Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), 4.9 (Overdose), 5.1 (Pharmacodynamic properties), 5.2 (Pharmacokinetic properties) and 6.6 (Special precautions for disposal) of the SmPC in line with the reference product Coversyl Tablets and the QRD template, with consequential changes made to the PIL. The PIL will be approved by the PIQ Unit as part of the application to update the MA with respect to article 59(1) and 59(3) of Council Directive 2001/83/EC.</p>	
11/10/2011	Type IA variation	<p>1. To register a change to the marking of tablets (Perindopril 2mg tablets) from White, round, biconvex tablets, engraved “APO” on one side and “PE2” on the other side to White, round, biconvex tablets, plain on both sides.</p> <p>2. To register a change to the marking of tablets (Perindopril 4mg tablets) from White, capsule shaped, biconvex tablets, engraved, “APO” on one side and “PE” bisect “4” on the other side to White capsule shaped, biconvex tablets, engraved “P” Bisect “4” on one side and plain on the other side.</p> <p>3. To register a change to the marking of tablets (Perindopril 8mg tablets) from</p>	08/02/2012

		White capsule shaped, biconvex tablets, engraved "APO" on one side and "PE" Bisect "8" on the other side to White capsule shaped, biconvex tablets, engraved "P" Bisect "8" on one side and plain on the other side.	
15/02/2012	Type IA variation	To register a change in the tablet engraving of Perindopril 2mg tablets from white, round, biconvex tablets, plain on both sides to white, round, biconvex tablets, engraved "2" on one side and plain on the other side.	21/08/2012
18/12/2012	Type IA variation	To register the replacement of the DDPS with the PSMF (Held by Accord Healthcare Limited).	04/01/2013
15/11/2013	Type IB variation	To update sections 4.2, 4.3, 4.4, 4.5, 4.8, 5.1, 5.2, 10 of the SPC, in line with the latest updated reference SmPC - Coversyl Arginine film-coated tablets (Dated: 8/2013). As a consequence, the PIL has been updated.	21/01/2014
03/12/2014	Type IB variation	To update SmPC sections: 2, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 in line with the PRAC recommendation for angiotensin-converting enzyme inhibitors (ACE-inhibitors). As a consequence, the PIL has been updated.	29/12/2014
27/03/2015	Type IB variation	To update sections 4.2 (posology and administration) and 5.1 (pharmacodynamics) of the SmPC in line with the reference product, Coversyl Arginine 2.5 mg/5mg/ 10mg film-coated tablets. As a consequence, the PIL has been updated.	Approved - 28/04/2015