Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Perindopril 2mg Tablets
PL 11311/0446

Perindopril 4mg Tablets
PL 11311/0447

Perindopril 8mg Tablets
PL 11311/0448

Tillomed Laboratories Limited

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Perindopril 2mg, 4mg and 8mg Tablets (PL 11311/0446-8). It explains how Perindopril 2mg, 4mg and 8mg 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 these products.

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 Tablets are used to:

- treat high blood pressure
- treat heart failure (a condition where the body is unable to pump enough blood to meet the body's needs)
- Reduce the risk of cardiac events, such as heart attacks, 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 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 angiotensin-converting enzyme (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?
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The tablets are to be taken orally, once daily, in the morning before a meal.

How have Perindopril Tablets been studied?
Perindopril Tablets are "generic" versions of the Brand leader products Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier). In support of these applications, pharmacokinetic data from a study were submitted, comparing levels of the active substance of these products versus the Brand leader products in the blood, to show that the levels are comparable.

What are the possible side effects of Perindopril Tablets?
Because Perindopril Tablets are generic versions of the Brand leader products Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier), their benefits and possible side-effects are taken as being the same.

For further information, please see Section 4 the Package Leaflet.

Why are Perindopril Tablets approved?
It was concluded that Perindopril Tablets could be considered to be a generic medicinal products of the Brand leader products Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier), with the same benefit/risk profile.

What measures are being taken to ensure the safe and effective use of Perindopril Tablets?
A risk management plan (RMP) has been developed to ensure that Perindopril Tablets are used as safely as possible. Based on this plan, 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 and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Perindopril Tablets.
The UK first granted marketing authorisations for these products on 01 February 2008.

The full PAR for Perindopril Tablets follows this summary.

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

This summary was last updated in March 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Perindopril 2mg, 4mg, and 8mg Tablets to REG EUROPE, SARL on 1st February 2008. The products are prescription-only medicines for the:

- treatment of hypertension
- treatment of symptomatic heart failure
- reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC, claiming to be a generic medicinal product of the original products Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier), which have been authorised in at least one EU member state for at least 10 years.

The products contain the active ingredient perindopril tert-butylamine. Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough).

With the exception of two bioequivalence studies, no new non-clinical or clinical studies were conducted, which is acceptable given that the application is for a product that is identical to a reference product that has been granted in the UK for over 10 years. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

Since these products will be used in place of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

The pharmaceutical, non-clinical and clinical expert reports have been written by appropriately qualified persons and are suitable summaries of the data submitted.

The Marketing Authorisation Application (MAA) forms submitted are satisfactory.

The UK granted national marketing authorisations for these products to REG EUROPE, SARL on 1st February 2008 (PL 24590/0005-7). Following a Change of Authorisation Holder (CoA), these product licences were transferred to Tillomed Laboratories Limited on 22 May 2015 (PL 11311/0446-8).

II. QUALITY ASPECTS

II.1 INTRODUCTION

These are abridged applications for Perindopril 2mg, 4mg and 8mg Tablets, submitted under Article 10(1) of Directive 2001/83/EC. The proposed MA holder is Tillomed Laboratories Ltd, 3 Howard Road, Eaton Socon, St Neots, Cambridgeshire, PE19 8ET.

The application cross-refers to Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier), which has been registered in at least one EU member state for over 10 years.

Other ingredients consist of hydrophobic colloidal silica, microcrystalline cellulose, lactose monohydrate and magnesium stearate.

All strengths of product are packaged in polyvinylchloride/polyvinylidene chloride/ aluminium blisters or aluminium blisters in pack sizes of 14, 20, 28, 30, 56 and 60 tablets.

Not all pack sizes may be marketed.

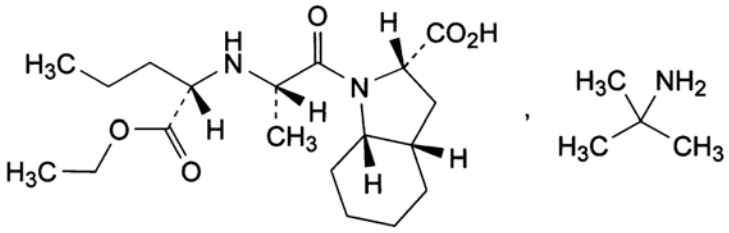
Specifications and certificates of analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

II.2 DRUG SUBSTANCE

INN: Perindopril erbumine
Ph Eur: Perindopril *tert*-butylamine

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

Structure:



Molecular formula: $C_{23}H_{43}N_3O_5.H_2O$ Molecular Mass: 459.6 g/mol

White or almost white, crystalline powder, slightly hygroscopic, which is freely soluble in water and in alcohol, and sparingly soluble in dichloromethane. Perindopril tert-butylamine has five chiral centres; all with S configurations.

Synthesis of the drug substance from the designated starting material 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. No materials of animal or human origin are used in the production of the active substance.

Satisfactory characterisation of the drug substance has been provided in the Drug Master File from the Drug Substance Manufacturer (DSM) and by the Finished Product Manufacturer (FPM). All potential known impurities have been identified and characterised.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for working standards used.

Active perindopril erbumine monohydrate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Stability data have been provided in accordance with regulatory requirements and support the declared retest interval.

II.3 DRUG PRODUCT

Pharmaceutical development

The applicant has provided a suitable product development section. Dissolution data and impurity profiles support the pharmaceutical equivalence of the proposed products with their respective strength of reference product, Coversyl 2mg, 4mg and 8mg Tablets (Les Laboratoires Servier).

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of hydrophobic colloidal silica, which complies with a suitable in-house specification. Satisfactory specifications and Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, none of the excipients are sourced from materials of animal or human origin. Confirmation has been provided that lactose monohydrate is sourced from healthy animals under the same conditions as milk for human consumption.

Manufacturer(s)

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation has been carried out on batches of each strength of finished product. The results are satisfactory.

Finished product specification

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

Stability

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. Based on the results, a

shelf-life of 2 years with storage conditions of "Do not store above 25°C" and "Store in the original package in order to protect from moisture" have been set for all strengths of product in all pack types. These are satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that Marketing Authorisations are granted for these applications.

The requirements for generic medicinal products have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products. In addition, similar dissolution and impurity profiles have been demonstrated for the proposed products versus their respective reference products.

III NON-CLINICAL ASPECTS

III.1 Introduction

These are abridged applications for Perindopril 2mg, 4mg and 8mg Tablets, submitted under Article 10(1) of Directive 2001/83/EC. As the active substance perindopril *tert*-butylamine is a well-known active substance, no further studies are required and the applicant has not provided any.

III.2 Pharmacology

III.3 Pharmacokinetics

III.4 Toxicology

No new data have been submitted and none are required.

III.5 Environmental Risk Assessment

Since these products will be used in place of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

III.6 Discussion on non-clinical aspects

It is recommended that Marketing Authorisations are granted for these applications.

IV CLINICAL ASPECTS

IV.1 Introduction

These are abridged applications for Perindopril 2mg, 4mg and 8mg Tablets, submitted under Article 10(1) of Directive 2001/83/EC.

With the exception of two bioequivalence studies, no new data have been provided for these applications and none are required for applications of this type. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

IV.2 Pharmacokinetics

Bioequivalence was determined by two studies, the details of which are given below:

1. *An open-label, single-dose, randomised, two-way crossover study comparing Perindopril 4mg Tablets (Test) versus Coversyl 4mg Tablets (Reference).*

This study was conducted in healthy male volunteers according to current Good Clinical Practice (GCP). Blood samples were taken pre- and up to 120 hours post dose, with the two dosing periods separated by a 28-day washout period.

The results are as follows:

Summary of pharmacokinetic data for Perindopril (Geometric mean data)

Parameter	Test (SD)	Reference (SD)	Ratio (90% CI, Log transformed)
C_{max} (ng/ml)	55.28 (12.22)	55.00 (13.54)	100.48 (94.14 – 107.25)
AUC_{0-t} (ng.h/ml)	64.42 (13.84)	68.24 (14.21)	94.34 (90.68 – 98.14)
$AUC_{0-\infty}$ (ng.h/ml)	68.58 (14.28)	72.02 (14.36)	95.18 (91.54 – 98.96)
T_{max} (hours)	0.64 (0.25)	0.76 (0.27)	

Summary of pharmacokinetic data for Perindoprilat (Geometric mean data)

Parameter	Test (SD)	Reference (SD)	Ratio (90% CI, Log transformed)
C_{max} (ng/ml)	5.74 (2.55)	5.59 (2.38)	102.01 (94.74 – 110.16)
AUC_{0-t} (ng.h/ml)	255.33 (56.77)	239.63 (62.96)	106.51 (99.52 – 113.99)
$AUC_{0-\infty}$ (ng.h/ml)	414.34 (176.51)	375.40 (103.53)	106.87 (96.77 – 118.02)
T_{max} (hours)	9.15 (4.16)	8.65 (2.47)	

Bioequivalence was shown between the test and reference products.

2. *An open-label, single-dose, randomised, two-way, crossover study comparing Perindopril 8mg Tablets (Test) versus Coversyl 8mg Tablets (Reference)*

This study was conducted in healthy male volunteers according to current Good Clinical Practice (GCP). Blood samples were taken pre- and up to 120 hours post dose, with the two dosing periods separated by a 42-day washout period.

The results are as follows:

The 90% confidence intervals of Ln-transformed parameters for Perindopril

Parameters	Least Square Means		Ratio	90% Confidence Interval	
	Test	Reference		Lower	Upper
C_{max} (ng/mL)	125.89	119.52	105.33	95.50	116.17
$AUC_{(0-t)}$ (ng.hr/mL)	137.62	136.09	101.12	96.45	106.02
$AUC_{(0-\infty)}$ (ng.hr/mL)	141.41	139.34	101.49	96.99	106.20

The 90% confidence intervals of Ln-transformed parameters for Perindoprilat

Parameters	Least Square Means		Ratio	90% Confidence Interval	
	Test	Reference		Lower	Upper
C_{max} (ng/mL)	11.79	12.13	97.18	91.64	103.05
$AUC_{(0-120)}$ (ng.hr/mL)	211.24	216.41	97.61	93.16	102.28

Bioequivalence was shown between the test and reference products.

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy
No new efficacy data have been submitted with these applications and none are required.

IV.5 Clinical safety
With the exception of the data collected during the bioequivalence studies, no new safety data have been submitted and none are required for these applications. No new or unexpected safety issues were raised during either bioequivalence study.

IV.6 Risk Management Plan (RMP)
No RMP has been submitted with these applications.

IV.7 Discussion on the clinical aspects
The applicant has demonstrated bioequivalence between the 4mg and 8mg strength products and their respective reference products, in accordance with CPMP criteria. As these products meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 4mg and 8mg strengths can be extrapolated to the 2mg strength tablets.

The granting of marketing authorisations is recommended.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Perindopril 2mg, 4mg and 8mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL/CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

Two bioequivalence studies were carried out, both showing bioequivalence between these products and their respective reference products.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The summary of product characteristics (SmPC), patient information leaflet (PIL) and labelling are satisfactory, and consistent with that for the innovator products. The current approved UK labelling is provided in Annex 1 below.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with perindopril is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
IB	N/A	SmPC/PIL	03/12/2014	26/02/2016	Approval	Yes (Annex 1)

ANNEX 1

Our Reference:	PL 11311/0446-0020 PL 11311/0447-0017 PL 11311/0448-0015
Products:	Perindopril 2mg Tablets Perindopril 4mg Tablets Perindopril 8mg Tablets
Marketing Authorisation Holder:	Tillomed Laboratories Limited
Active Ingredient(s):	Perindopril *tert*-butylamine
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	Not applicable

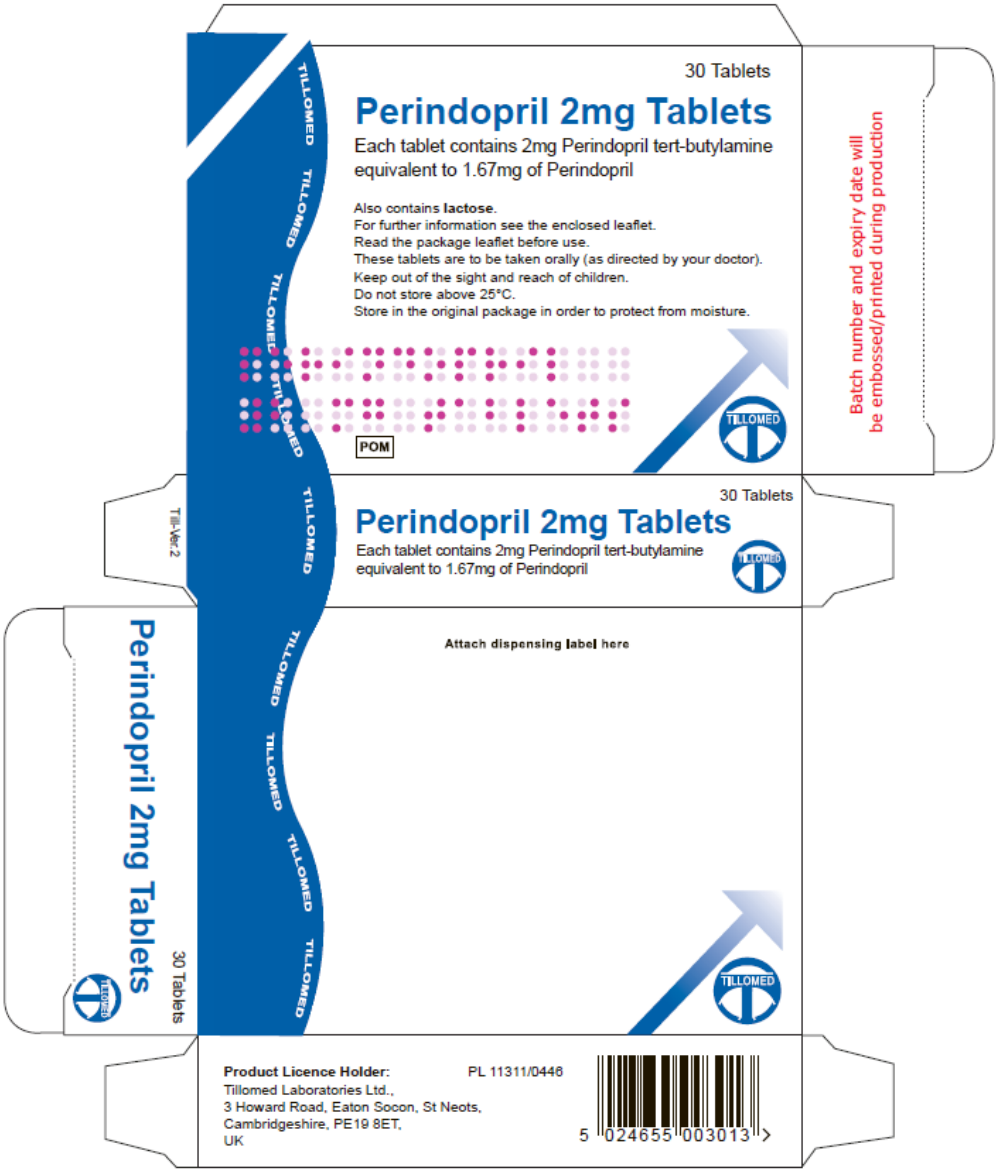
Reason:
To update the SmPCs and PIL to bring it in-line with PRAC recommendations, the innovator product and the current QRD guidelines. Consequently, the labelling has also been updated.

Supporting Evidence
Revised SmPC fragments, PIL and labelling.

Evaluation
The proposed changes to the SmPCs, PIL and labels are acceptable.

Conclusion
The proposed changes are acceptable. The amended labelling is provided below.

Decision- Approved on 26 February 2016.



Perindopril 2mg Tablets
PL Holder:
Tillomed Laboratories Ltd.
PL 11311/0446

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Tillomed Laboratories Ltd.
PL 11311/0446

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PL Holder:
Tillomed Laboratories Ltd.
PL 11311/0446


30 Tablets
Perindopril 4mg Tablets
Each tablet contains 4mg Perindopril tert-butylamine equivalent to 3.34mg of Perindopril
Also contains lactose.
For further information see the enclosed leaflet.
Read the package leaflet before use.
These tablets are to be taken orally (as directed by your doctor).
Keep out of the sight and reach of children.
Do not store above 25°C.
Store in the original package in order to protect from moisture.
POM
TILLOMED
Batch number and expiry date will be embossed/printed during production
Till-Ver.2
30 Tablets
Perindopril 4mg Tablets
Each tablet contains 4mg Perindopril tert-butylamine equivalent to 3.34mg of Perindopril
Perindopril 4mg Tablets
30 Tablets
Attach dispensing label here
Product Licence Holder:
PL 11311/0447
Tillomed Laboratories Ltd.,
3 Howard Road, Eaton Socon, St Neots,
Cambridgeshire, PE19 8ET,
UK
5 024655 003020
Perindopril 4mg Tablets
PL Holder:
Tillomed Laboratories Ltd.
PL 11311/0447
Perindopril 4mg Tablets
PL Holder:
Tillomed Laboratories Ltd.
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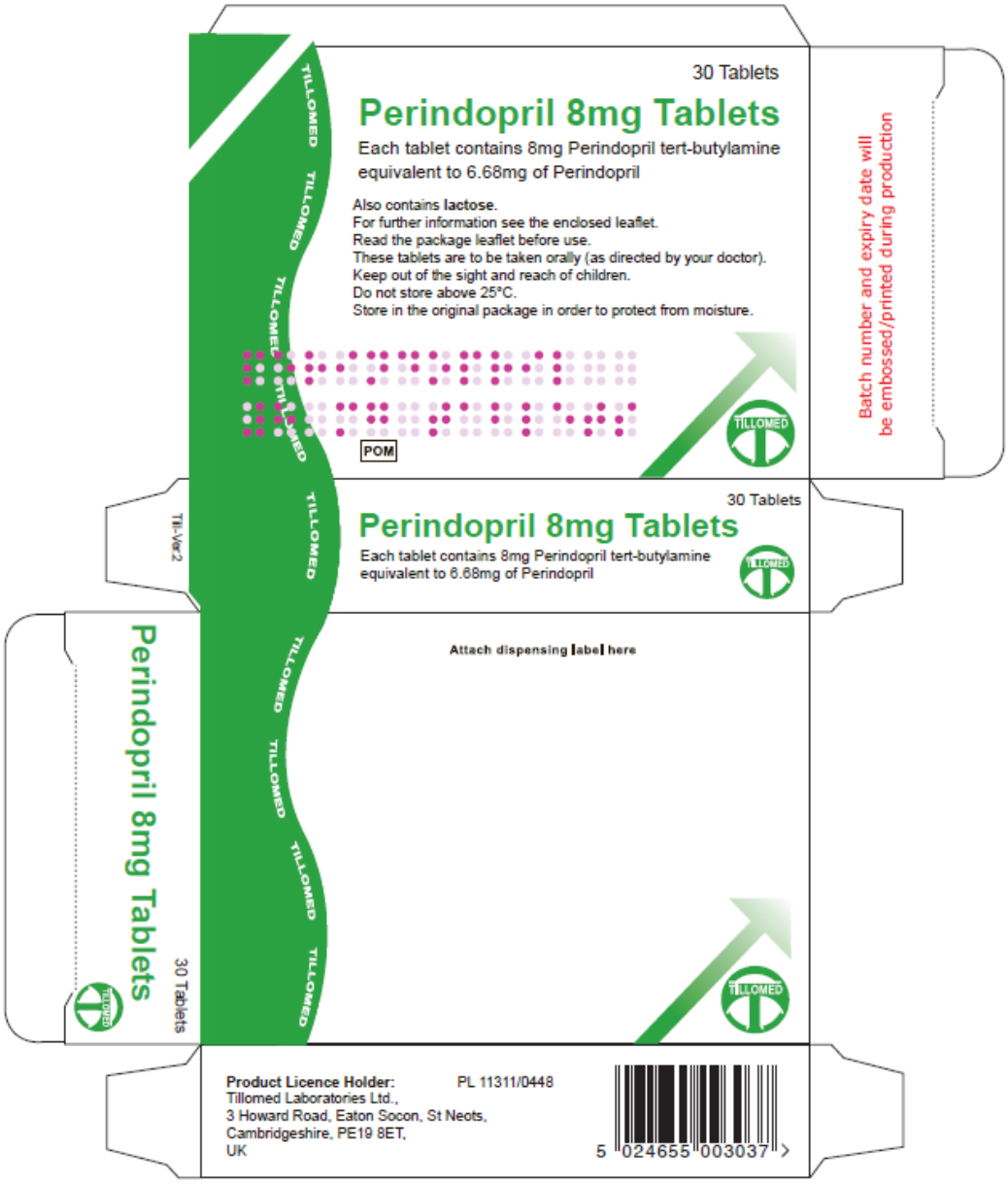
PL 11311/0447



Perindopril 8mg Tablets
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PL 11311/0448

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