Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Perindopril Erbumine 2, 4 and 8 mg Film-coated Tablets

(perindopril Erbumine tert-butylamine salt)

Product Licence Numbers: PL 49565/0046-0048

Rudipharm Limited

LAY SUMMARY

Perindopril Erbumine 2, 4 and 8 mg Film-coated Tablets

(perindopril Erbumine tert-butylamine salt)

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

These products will be referred to as Perindopril Tablets in this lay summary for ease of reading.

For practical information about using Perindopril Tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Perindopril Tablets and what are they used for?
These applications are for hybrid medicines. This means that the medicines are similar to reference medicines already authorised in the United Kingdom (UK) called Coversyl Arginine 2.5 mg, 5 mg and 10 mg Film-coated Tablets, albeit with certain differences. In this case, the proposed products use a different salt of the active substance and have different strengths compared to the reference products.

Perindopril Erbumine Tablets are used:
- To treat high blood pressure (hypertension)
- To treat heart failure (a condition where the heart is unable to pump enough blood to meet the body's needs)
- To reduce the risk of cardiac event, 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 Tablets contain the active substance perindopril erbumine which belongs to a group of medicines known as angiotensin converting enzyme (ACE) inhibitors. These medicine works by making the blood vessels wider, which makes it easier for the heart to pump blood through them.

How are Perindopril Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

For further information on how Perindopril Tablets are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Perindopril Tablets have been shown in studies?
Because Perindopril Tablets are hybrid medicines, studies in healthy volunteers consist of tests to determine that they are therapeutically equivalent to the reference medicines.

What are the possible side effects of Perindopril Tablets?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of these medicines.

Because Perindopril Tablets are hybrid medicines and are therapeutically equivalent to the reference medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

Why were Perindopril Tablets approved?
It was concluded that Perindopril Tablets have been shown to be therapeutically equivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicines, the benefits are greater than the risks and recommended that they can be approved for use.

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 SmPCs and the PIL, 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
Marketing Authorisations for Perindopril Tablets were granted in the United Kingdom (UK) on 16 July 2021.

The full PAR for Perindopril Tablets follows this summary.

This summary was last updated in September 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Perindopril Erbumine 2, 4 and 8 mg Film-coated Tablets (PL 49565/0046-0048) could be approved.

The products are approved for the following indications:

Perindopril erbumine 2 mg, 4 mg film-coated tablets
Hypertension:

Treatment of hypertension.

Heart Failure:

Treatment of symptomatic heart failure.

Stable coronary artery disease:

Reduction of risk of cardiac events in patients with a history of myocardial infarction and/or revascularisation.

Perindopril erbumine 8mg film-coated tablets
Hypertension:
Treatment of hypertension.

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

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

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

These applications were approved under Regulation 52B of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be hybrid medicinal products of a suitable originator products, Coversyl Arginine 2.5 mg, 5 mg and 10 mg Film-coated Tablets (PL 05815/0035 - 0037), that have been licensed within the UK for a suitable time, in line with the legal requirements. The reference medicinal product, Coversyl Arginine 10 mg Film-coated Tablets (PL 05815/0037) is used to demonstration of bioequivalence.

No new non-clinical studies were conducted, which is acceptable given that the applications are for hybrid medicinal products of suitable reference products.

Data from one bioequivalence study was submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) on 16 July 2021.

II QUALITY ASPECTS

II.1 Introduction

These products consist of film-coated tablets. Each Film coated tablet contains 2, 4 or 8 mg perindopril erbumine tert-butylamine salt (as known as erbumine) as active substance.

In addition to perindopril erbumine tert-butylamine, these products also contain the excipients lactose monohydrate, microcrystalline cellulose, sodium hydrogen carbonate, crospovidone, eudragit EPO, colloidal anhydrous silica and magnesium stearate making up the tablet core. The film-coating is composed of hypromellose, titanium dioxide, macrogols, magnesium stearate and glycerin.

The finished products are packaged in alu-polyvinylchloride (PVC)/polyethylene (PE)/ACLAR blister contains 30 tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

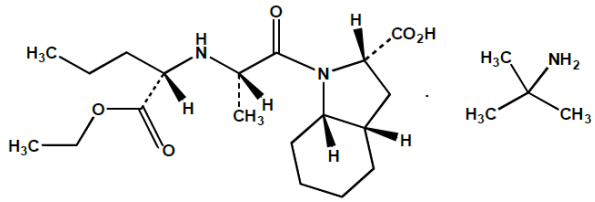
II.2 ACTIVE SUBSTANCE

rINN: Perindopril erbumine tert-butylamine

Chemical Name: 2-Methylpropan-2-amine 92S,3aS, 7aS)-1-[((2S)-2-[[(1S)-1(ethoxycarbonyl) butyl]amino] propanoyl] octahydro-1H-indole-2-carboxylate

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

Chemical Structure:



Molecular Weight: 441.6 g/mol

Appearance: White or almost white crystalline power; slightly hygroscopic.

Solubility: Freely soluble in water and in ethanol (96%), soluble or sparingly soluble in methylene chloride.

Perindopril tert-butylamine is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCTS

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

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

Satisfactory batch formulation data have 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 at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 24 months, with the storage condition "Store below 25ºC" is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of marketing authorisations is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of perindopril tert-butylamine are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for these applications.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for these applications.

III.4 Toxicology
No new toxicology data were provided and none were required for these applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these are hybrid applications of already authorised products, it is not expected that environmental exposure will increase following approval of the Marketing Authorisations for the proposed products.

III.6 Discussion on the non-clinical aspects
The grant of marketing authorisations is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, data from one bioequivalence equivalence study have been submitted with these applications. This study was conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics
In support of the applications, the applicant submitted the following.

This study was an open label, randomised, two-period, two treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of the test product Perindopril Erbumine 8 mg Tablets versus the reference product, Coversyl Arginine 10 mg Tablets in healthy adult human subjects under fasting conditions.

Subjects were administered a single dose of the test or reference product. Blood samples were taken pre-dose and up to 10 hours post dose, with a washout period of 14 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Pharmacokinetic parameter	Geometric mean				Ratio (%)
	N	Test	N	Reference	
Cmax (ng/ mL)	39	168.566	39	173.110	97.37
AUCt (ng.hr/ mL)	39	238.470	39	250.295	95.28
Pharmacokinetic parameter	**90% Confidence Intervals**		**Acceptance Criteria**		**Outcome of BE result**
Cmax (ng/ mL)	(89.02%;106.51%)		80.00% - 125.00%		Bioequivalent
AUCt (ng.hr/ mL)	(92.43%; 98.21%)		80.00% - 125.00%		

According to the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference products.

As the additional strengths (2 mg and 4 mg) of the products meet the biowaiver criteria specified in the current bioequivalence guideline the results and conclusions from the bioequivalence study on the product strength (8 mg) can be extrapolated to the other strengths (2 mg and 4 mg).

IV.3 Pharmacodynamics

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

IV.4 Clinical efficacy

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

IV.5 Clinical safety

With the exception of the safety data from the clinical study submitted with these applications, no new safety data were submitted. The safety data submitted showed that the products were well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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

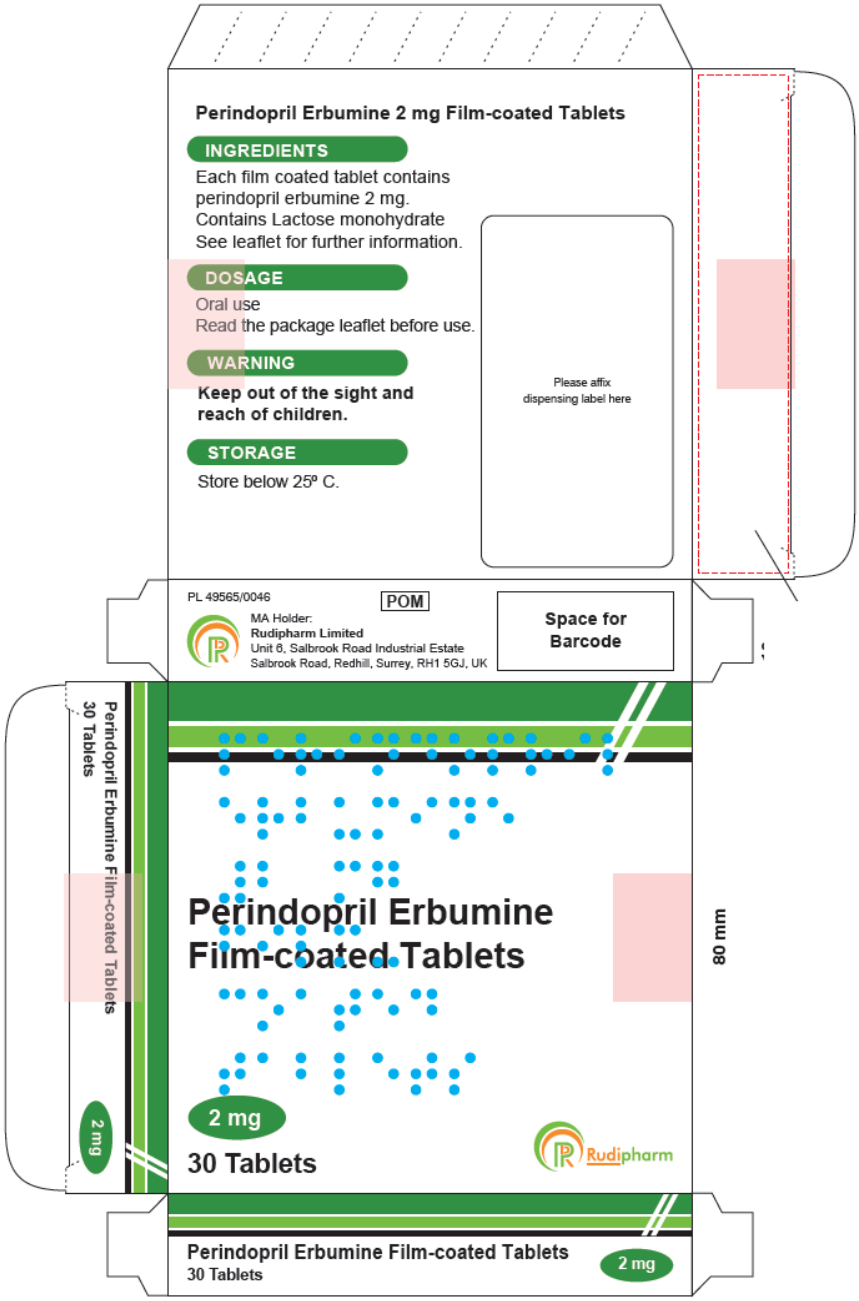
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with perindopril erbumine tert-butylamine is considered to have demonstrated the therapeutic value of the products.

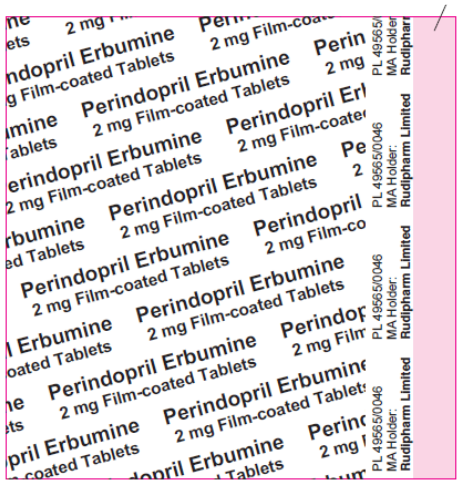
The benefit/risk is, therefore, considered to be positive.

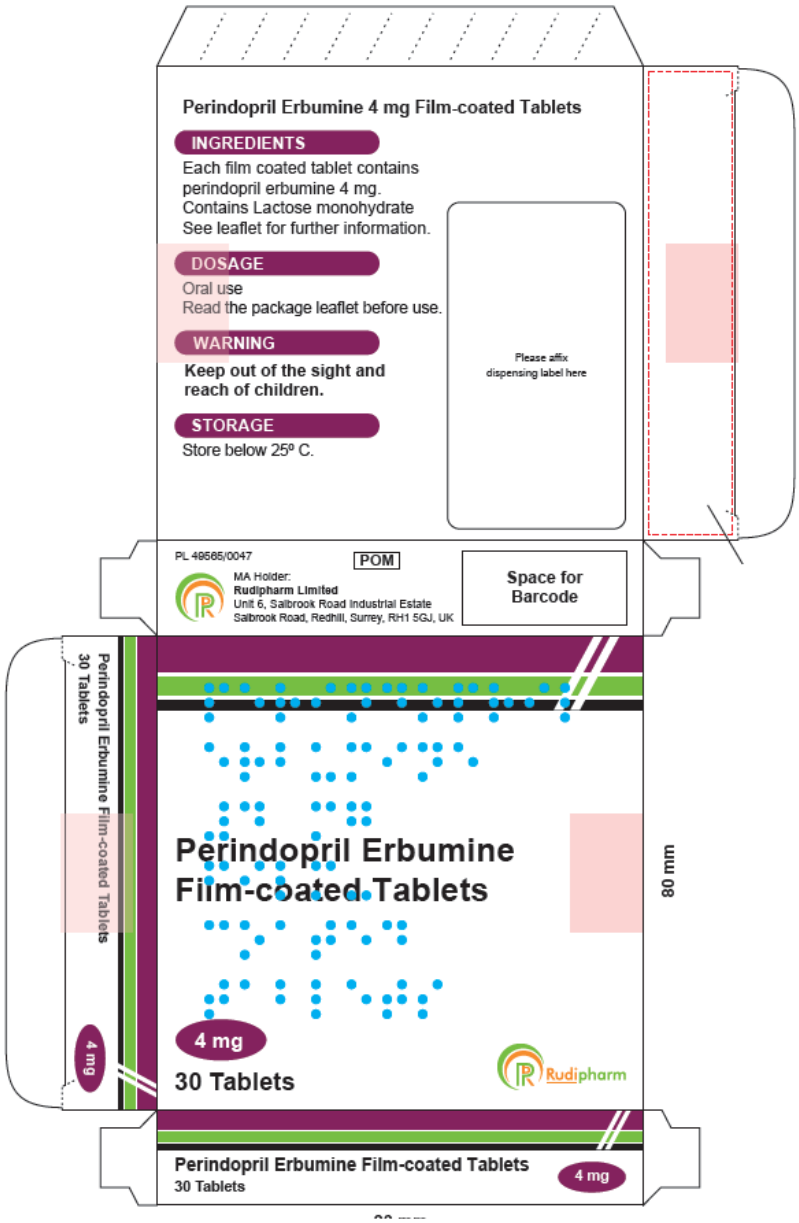
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory and in line with current guidelines.

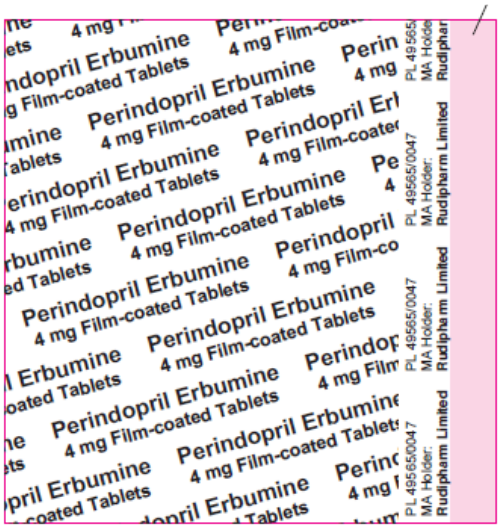
In accordance with legal requirements, the current approved versions of the SmPCs and PIL for these products are available on the MHRA website.

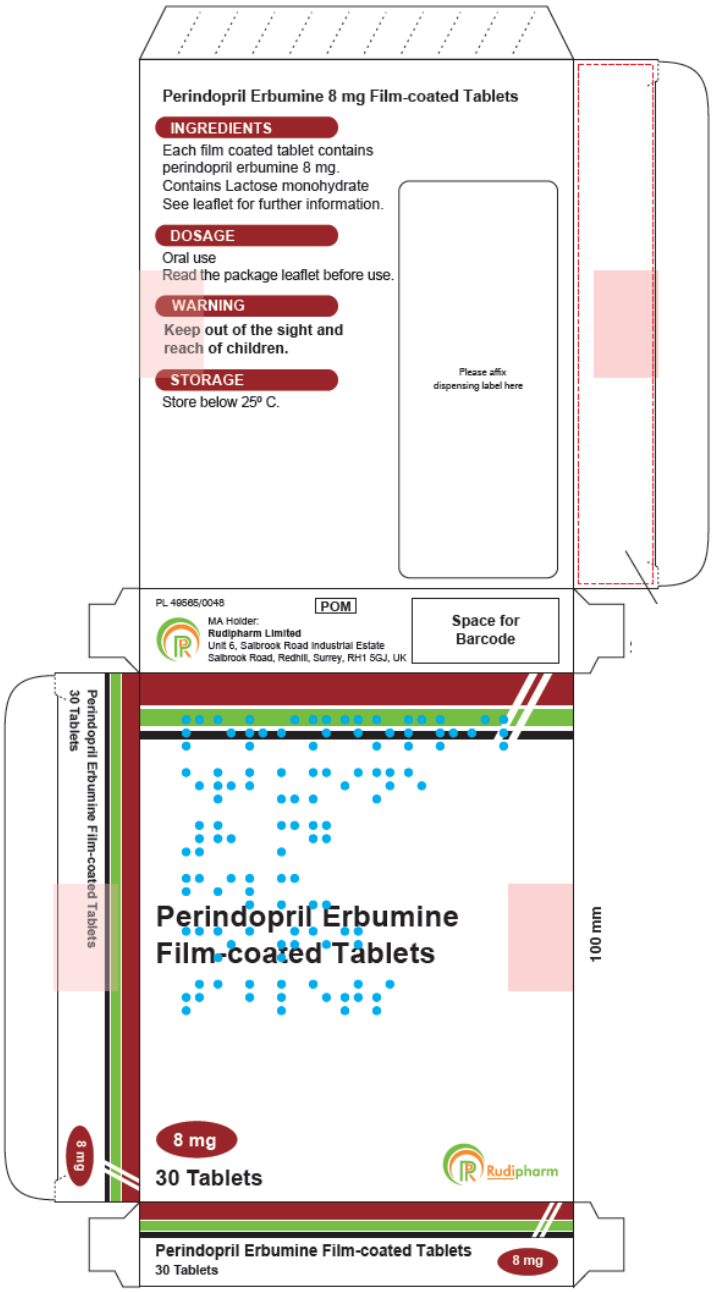
Representative copies of the labels at the time of licensing are provided below.




Perindopril Erbumine
2 mg Film-coated Tablets
PL 49565/0046
MA Holder:
Rudipharm Limited


Perindopril Erbumine 4 mg Film-coated Tablets
INGREDIENTS
Each film coated tablet contains perindopril erbumine 4 mg.
Contains Lactose monohydrate
See leaflet for further information.
DOSAGE
Oral use
Read the package leaflet before use.
WARNING
Keep out of the sight and reach of children.
STORAGE
Store below 25º C.
Please affix dispensing label here
PL 49565/0047
POM
MA Holder:
Rudipharm Limited
Unit 6, Salbrook Road Industrial Estate
Salbrook Road, Redhill, Surrey, RH1 5GJ, UK
Space for Barcode
Perindopril Erbumine Film-coated Tablets
30 Tablets
4 mg
Perindopril Erbumine Film-coated Tablets
80 mm
4 mg
30 Tablets
Rudipharm
Perindopril Erbumine Film-coated Tablets
30 Tablets
4 mg


Perindopril Erbumine
4 mg Film-coated Tablets
PL 49565/0047
MA Holder:
Rudipharm Limited


Perindopril Erbumine 8 mg Film-coated Tablets
INGREDIENTS
Each film coated tablet contains perindopril erbumine 8 mg.
Contains Lactose monohydrate
See leaflet for further information.
DOSAGE
Oral use
Read the package leaflet before use.
WARNING
Keep out of the sight and reach of children.
STORAGE
Store below 25º C.
Please affix dispensing label here
PL 49565/0048
POM
MA Holder:
Rudipharm Limited
Unit 6, Salbrook Road Industrial Estate
Salbrook Road, Redhill, Surrey, RH1 5GJ, UK
Space for Barcode
Perindopril Erbumine Film-coated Tablets
30 Tablets
8 mg
Perindopril Erbumine
Film-coated Tablets
100 mm
8 mg
30 Tablets
Rudipharm
Perindopril Erbumine Film-coated Tablets
30 Tablets
8 mg

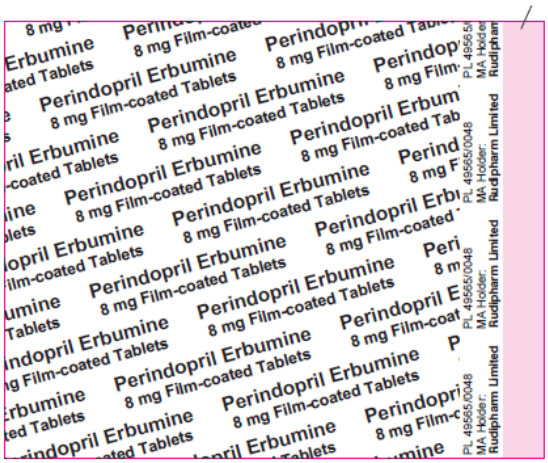

Perindopril Erbumine
8 mg Film-coated Tablets
PL 49565/0048
MA Holder:
Rudipharm Limited

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**