Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Lisinopril 2.5, 5, 10 and 20 mg Tablets

(lisinopril)

Product Licence Numbers: PL 28444/0196-0199

Actavase Pharmaceuticals Limited

LAY SUMMARY

Lisinopril 2.5, 5, 10 and 20 mg Tablets

(lisinopril)

This is a summary of the Public Assessment Report (PAR) for Lisinopril 2.5, 5, 10 and 20 mg Tablets. It explains how these products were assessed and their authorisations 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 Lisinopril Tablets in this lay summary for ease of reading.

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

What are Lisinopril Tablets and what are they used for?
These applications are for generic medicines. This means that these medicines are the same as, and considered interchangeable with reference medicines already authorised in the European Union (EU) called Zestril 2.5 mg, 5 mg , 10 mg and 20 mg Tablets (AstraZeneca Limited, UK).

Lisinopril tablets are used in the treatment of high blood pressure (hypertension), heart failure, kidney problems caused by Type II diabetes in people with high blood pressure and patients who have recently had a heart attack (myocardial infarction).

How do Lisinopril Tablets work?
Lisinopril Tablets contain the active ingredient lisinopril, which belongs to a group of medicines called Angiotensin-Converting Enzymes (ACE) inhibitors. These work by expanding the blood vessels and making it easier for the heart to pump blood to all parts of the body.

How are Lisinopril Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth). The tablet should be swallowed whole with a drink of water. Patients should take the tablets at the same time each day, before or after food.

Patients also should take this medicine for as long as a doctor tells them to, it is a long-term treatment. It is important to keep taking Lisinopril tablets every day.

Patients should take special care when they have their first dose of Lisinopril tablets or if the dose is increased. It may cause a greater fall in blood pressure than later doses.
This may make patients feel dizzy or light-headed. If this happens, it may help to lie down. If patients are concerned, they should talk to a doctor as soon as possible.

Adults
A dose depends on patient's medical condition and whether they are taking any other medicines. A doctor will tell patients how many tablets to take each day. They should check with a doctor or pharmacist if they are unsure.

For high blood pressure
- The usual starting dose is 10 mg once a day.
- The usual long-term dose is 20 mg once a day.

For heart failure
- The usual starting dose is 2.5 mg once a day.
- The long-term dose is 5 to 35 mg once a day.

For kidney problems caused by diabetes
- The usual dose is either 10 mg or 20 mg once a day.

If patients are elderly, have kidney problem or are taking diuretic medicines a doctor may give them a lower dose than the usual dose.

Children and adolescents (6 to 16 years old) with high blood pressure
- Lisinopril is not recommended for children under 6 years or in any children with severe kidney problems.
- The doctor will work out the correct dose for your child. The dose depends on the child's body weight.
- For children who weigh between 20 kg and 50 kg, the usual starting dose is 2.5 mg once a day.
- For children who weigh more than 50 kg, the usual starting dose is 5 mg once a day

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

These medicines 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 Lisinopril Tablets have been shown in studies?
Because Lisinopril Tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that their bioequivalent to the reference medicines. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Lisinopril 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 this medicine.

Because Lisinopril Tablets are for generic medicines and are bioequivalent to the reference medicines, its benefits and possible side effects are considered to be the same as the reference medicines.

Why were Lisinopril Tablets approved?
It was concluded that, Lisinopril Tablets have been shown to be comparable to and bioequivalent 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 Lisinopril Tablets?
A satisfactory pharmacovigilance system has been provided to monitor the safety of these products.

Other information about Lisinopril Tablets
Marketing Authorisations for Lisinopril Tablets were originally granted to Milpharm Limited (PL 16363/0182-0184 and PL 16363/0187) on 28 June 2012. Marketing Authorisations subsequently underwent change of ownership procedures to the Marketing Authorisation Holder Wilcare Pharma Limited (PL 42930/0024-0027) and then to Activase Pharmaceuticals Limited (PL 28444/0196-0199) on 25 February 2017.

The full PAR for Lisinopril Tablets follows this summary.

This summary was last updated in July 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 Lisinopril 2.5, 5, 10 and 20 mg Tablets (PL 28444/0196-0199) could be approved.

The products are approved for the following indications:

Hypertension
Treatment of hypertension.

Heart failure
Treatment of symptomatic heart failure.

Acute myocardial infarction
Short-term (6 weeks) treatment of haemodynamically stable patients within 24 hours of an acute myocardial infarction.

Renal complications of diabetes mellitus
Treatment of renal disease in hypertensive patients with Type 2 diabetes mellitus and incipient nephropathy

Lisinopril is a peptidyl dipeptidase inhibitor. It inhibits the angiotensin-converting enzyme (ACE) that catalyses the conversion of angiotensin I to the vasoconstrictor peptide, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex. Inhibition of ACE results in decreased concentrations of angiotensin II, which results in decreased vasopressor activity and reduced aldosterone secretion. The latter decrease may result in an increase in serum potassium concentration.

These applications were approved under Regulation 51B of The Human Medicines Regulation 2012, as amended (previously Article 10(1) of Directive 2001/83/EC, as amended), as generic medicines of suitable originator medicinal products, Acerbon 2.5 mg, 5mg, 10mg, 20 mg Tablets, (AstraZeneca, Germany), that have been licensed within the UK for a suitable time, in line with the legal requirements. The corresponding reference products in the UK, Zestril 2.5 mg, 5 mg, 10 mg and 20 mg Tablets (AstraZeneca Limited, UK), which were first authorised in the UK on May 1988).

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

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of suitable reference products. The bioequivalence 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 summary of the pharmacovigilance system has been provided with these applications and is satisfactory.

National marketing authorisations were granted in the United Kingdom (UK) granted to Milpharm Limited (PL 16363/0182-0184 and PL 16363/0187) on 28 June 2012. Marketing Authorisations subsequently underwent change of ownership procedures to the Marketing Authorisation Holder Wilcare Pharma Limited (PL 42930/0024-0027) and then to Activase Pharmaceuticals Limited (PL 28444/0196-0199) on 25 February 2017.

II QUALITY ASPECTS

II.1 Introduction

These products are tablets. Each tablet contains lisinopril dihydrate equivalent to 2.5, 5, 10 and 20 mg lisinopril as an active substance.

In addition to lisinopril, these products also contain the following excipients mannitol, calcium hydrogen phosphate dihydrate, maize starch, pregelatinised starch, magnesium stearate and colloidal anhydrous silica.

The finished products are packaged in a blister constituted from a polyvinylchloride PVC/polyvinyldichloride (PVdC) and aluminium foil with a pack containing 28 tablets.

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

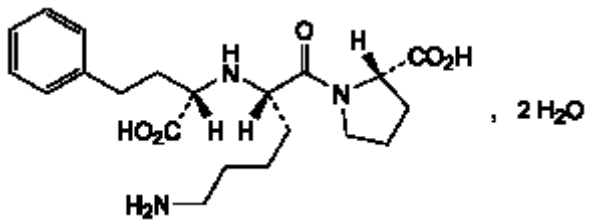
II.2 ACTIVE SUBSTANCE

rINN: Lisinopril

Chemical Name: (2S)-1-[(2S)-6-amino-2-[[(1S)-1-carboxy-3-phenylpropyl] amino]hexanoyl]pyrrolidine-2- carboxylic acid dihydrate

Molecular Formula: $C_{21}H_{31}N_3O_5 2H_2O$

Chemical Structure:



Molecular Weight: 441.5 g/mol

Appearance: A white or almost white crystalline powder.

Solubility: Soluble in water, sparingly soluble in methanol and practically insoluble in acetone and in anhydrous ethanol.

Lisinopril 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.

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 to support a suitable retest periods for the active substance when stored in the proposed packaging.

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.

No excipients of animal or human origin are used in the finished products. 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 formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process have been validated and have shown satisfactory results.

Finished Product Specifications
The finished product specifications 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 36 months with storage conditions ‘Do not store above 25°C’ and ‘Store in the original package’ are approved.

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 lisinopril 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 the applications are for generic versions of already authorised products, an increase in environmental exposure is not anticipated 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

The clinical pharmacology, efficacy and safety of lisinopril is well known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of application. An overview based on a literature review and a review of this study is, thus, satisfactory.

IV. 2 Pharmacokinetics

In support of the applications, the applicant submitted the following bioequivalence study.

This is a single-dose, randomized, double-blind, two-period, two-way, crossover study to compare the pharmacokinetics of the test product Lisinopril 20 mg Tablets versus the reference product, Acerbon 20 mg Tablets (AstraZeneca, Germany) in healthy adult male subjects under fasted conditions.

Blood samples were taken for the measurement of pharmacokinetic parameters pre-dose and up to 216 hours post dose. The washout period between the two treatment arms was 28 days. The pharmacokinetic results are presented below:

Pharmacokinetic parameters (geometric least squares mean, ratios and confidence intervals [CI]) of lisinopril:

	Test	**Reference**	**Test/Ref Ratio (%)**	**90% CI**
C_{max} (ng/ml)	61.60	62.28	0.96	82-114
AUC_{0-t} (ng.h/ml)	103.14	103.14	1.00	89-113
AUC_{0-inf} (ng.h/ml))	113.07	115.51	0.98	89-115

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
90% geometric CI calculated from ln-transformed data

The 90% confidence intervals for AUC and C_{max} for test versus reference product for lisinopril are within the acceptance criteria specified in the Note for *Guidance on the Investigation of Bioequivalence (*CPMP/EWP/QWP/1401/98 Rev 1/, Corr*)*, Thus, the data support the claim that the test product Lisinopril 20 mg Tablets is bioequivalent to the reference product Acerbon 20 mg Tablets (AstraZeneca, Germany).

As the additional strength of the products (2.5, 5 and 10 mg) meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the

bioequivalence study on the 20 mg product strength can be extrapolated to the other strengths (2.5, 5 and 10 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 were submitted with these applications and none were required.

IV.5 Clinical safety

With the exception of the safety data submitted with the bioequivalence study, no new safety data were submitted with these applications.

The safety data from the bioequivalence study showed that the test and reference product were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Pharmacovigilance System and Risk Management Plan (RMP)

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

Suitable justification has been provided for not submitting a risk management plan for these products.

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 applications 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 lisinopril is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

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

In accordance with legal requirements, the current approved UK 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.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 2.5mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains Lisinopril dihydrate equivalent to 2.5 mg lisinopril.

3. LIST OF EXCIPIENTS

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4. PHARMACEUTICAL FORM AND CONTENTS

28 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Ltd.,
11 Boumpoulinas,
Nicosia 1060, Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 28444/0196

13. BATCH NUMBER

B.No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Please read the enclosed leaflet carefully.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

Lisinopril 2.5mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 2.5mg tablets
Lisinopril Dihydrate equivalent to 2.5mg lisinopril

2. NAME OF THE MARKETING AUTHORIZATIO HOLDER

Activase Pharmaceuticals Ltd., PL 28444/0196

3. EXPIRY DATE

EXP

4. BATCH NUMBER

B.No.

5. **OTHER**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 5mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains Lisinopril dihydrate equivalent to 5 mg lisinopril.

3. LIST OF EXCIPIENTS

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4. PHARMACEUTICAL FORM AND CONTENTS

28 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Ltd.,
11 Boumpoulinas,
Nicosia 1060, Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 28444/0197

13. BATCH NUMBER

B.No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Please read the enclosed leaflet carefully.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

Lisinopril 5mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 5mg tablets
Lisinopril Dihydrate equivalent to 5mg lisinopril

2. NAME OF THE MARKETING AUTHORIZATIO HOLDER

Activase Pharmaceuticals Ltd., PL 28444/0197

3. EXPIRY DATE

EXP

4. BATCH NUMBER

B.No.

5. **OTHER**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 10 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains Lisinopril dihydrate equivalent to 10 mg lisinopril.

3. LIST OF EXCIPIENTS

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4. PHARMACEUTICAL FORM AND CONTENTS

28 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Ltd.,
11 Boumpoulinas,
Nicosia 1060, Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 28444/0198

13. BATCH NUMBER

B.No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Please read the enclosed leaflet carefully.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

Lisinopril 10 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 10mg tablets
Lisinopril Dihydrate equivalent to 10 mg lisinopril

2. NAME OF THE MARKETING AUTHORIZATIO HOLDER

Activase Pharmaceuticals Ltd., PL 28444/0198

3. EXPIRY DATE

EXP

4. BATCH NUMBER

B.No.

5. **OTHER**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 20 mg tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains Lisinopril dihydrate equivalent to 20 mg lisinopril.

3. LIST OF EXCIPIENTS

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4. PHARMACEUTICAL FORM AND CONTENTS

28 Tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Not applicable

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25° C. Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not Applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Ltd.,
11 Boumpoulinas,
Nicosia 1060, Cyprus

12. MARKETING AUTHORISATION NUMBER(S)

PL 28444/0199

13. BATCH NUMBER

B.No.

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Please read the enclosed leaflet carefully.
Take as directed by your doctor.

16. INFORMATION IN BRAILLE

Lisinopril 20 mg tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Lisinopril 20 mg tablets
Lisinopril Dihydrate equivalent to 20 mg lisinopril

2. NAME OF THE MARKETING AUTHORIZATIO HOLDER

Activase Pharmaceuticals Ltd., PL 28444/0199

3. EXPIRY DATE

EXP

4. BATCH NUMBER

B.No.

5. **OTHER**

TABLE OF CONTENTS 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**
Type IB	To update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPCs in line with the referenced products (Zestril, 5,10 and 20 mg tablets; AstraZeneca UK Limited, UK). To also amend sections 2 and 3 of the SmPCs in line with the latest Quality Review of Documents (QRD) template and SmPC guidelines. The PIL has also been amended to reflect the changes.	SmPCs and PIL	16/06/2021	Approved	Y

Annex 1

Reference: PL 28444/0196-0199 - 0011
Product: Lisinopril 2.5, 5, 10 and 20 mg Tablets
Type of Procedure: National
Submission category: Type IB Variation

Reason
To update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPCs in line with the referenced products (Zestril, 5,10 and 20 mg tablets; AstraZeneca UK Limited, UK). To also amend sections 2 and 3 of the SmPCs in line with the latest Quality Review of Documents (QRD) template and SmPC guidelines. The PIL has also been amended to reflect the changes.

Supporting evidence
The Company has submitted updated sections of the SmPCs and PIL.

Evaluation
The updated documents are satisfactory.

Conclusion
The proposed changes are acceptable.

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

Decision: Grant

Date: 16 June 2021