Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedures

Losartan potassium 25, 50 and 100 mg film-coated tablets

(losartan potassium)

Product Licence Numbers: PL 49445/0041-43

Amarox Limited

LAY SUMMARY

Losartan potassium 25, 50 and 100 mg film-coated tablets

(losartan potassium)

This is a summary of the Public Assessment Report (PAR) for Losartan potassium 25, 50 and 100 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 Losartan potassium tablets in this lay summary for ease of reading.

For practical information about using Losartan potassium tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Losartan potassium 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 Cozaar 25, 50 and 100 mg Film-coated tablets (Merck Sharp & Dohme Limited).

Losartan potassium tablets are used:
- To treat patients with high blood pressure (hypertension) in adults and in children and adolescents 6-18 years of age.
- To protect the kidney in hypertensive type 2 diabetic patients with laboratory evidence of impaired renal function and proteinuria ≥ 0.5 g per day (a condition in which urine contains an abnormal amount of protein).
- To treat patients with chronic heart failure when therapy with specific medicines called angiotensin-converting-enzyme inhibitors (ACE inhibitors, medicines used to lower high blood pressure) is not considered suitable by a doctor. If patients heart failure has been stabilised with an ACE inhibitors they should not be switched to losartan.
- In patients with high blood pressure and a thickening of the left ventricle, Losartan potassium has been shown to decrease the risk of stroke (“LIFE indication”).

How do Losartan potassium tablets work?
Losartan potassium tablets contain the active ingredient losartan potassium, which belongs to a group of medicines known as angiotensin-II receptor antagonists. Angiotensin-II is a substance produced in the body which binds to receptors in blood vessels, causing them to tighten. This results in an increase in blood pressure. Losartan prevents the binding of angiotensin-II to these receptors, causing the blood vessels to relax which in turn lowers the blood pressure. Losartan slows the decrease of kidney function in patients with high blood pressure and type 2 diabetes.

How are Losartan potassium tablets used?
The pharmaceutical form of these medicines is a tablet and the route of administration is by mouth (oral). The tablets should be swallowed whole with a glass of water. Patients should try to take their daily dose at about the same time each day. The tablet can be divided into equal doses (for 25 mg and 50 mg only).

A doctor will decide on the appropriate dose of Losartan potassium tablets, depending on the condition and whether patients are taking other medicines. It is important to continue taking Losartan potassium tablets for as long as a doctor prescribes it in order to maintain smooth control of the blood pressure.

Adult patients with high blood pressure
Treatment usually starts with 50 mg losartan (one tablet of Losartan potassium 50 mg) once a day. The maximal blood pressure lowering effect should be reached 3-6 weeks after beginning treatment. In some patients the dose may later be increased to 100 mg losartan (two tablets of Losartan potassium 50 mg or one tablet of Losartan potassium 100 mg) once daily. If patients have the impression that the effect of losartan is too strong or too weak, they should talk to a doctor.

Use in children and adolescents
Children below 6 years of age
Losartan potassium tablets are not recommended for use in children under 6 years old, as it has not been shown to work in this age group.

Children aged 6-18 years old
The recommended starting dose in patients who weigh between 20 and 50 kg is 0.7 mg of losartan per kg of body weight administered once a day (up to 25 mg of Losartan potassium). A doctor may increase the dose if blood pressure is not controlled.

Other form (s) of this medicines may be more suitable for children, patients should ask a doctor or pharmacist.

Adult patients with high blood pressure and Type 2 diabetes
Treatment usually starts with 50 mg losartan (one tablet losartan potassium 50 mg) once a day. The dose may later be increased to 100 mg losartan (two tablets of Losartan potassium 50 mg or one tablet of Losartan potassium 100 mg) once daily depending on the blood pressure response.

Losartan may be administered with other blood pressure lowering medicines (e.g. diuretics, calcium channel blockers, alpha-or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used medicines that decrease the level of glucose in the blood (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Adult patients with heart failure
Treatment usually starts with 12.5 mg losartan (one tablet Losartan 12.5 mg once a day). Generally the dose should be increased weekly step-by step (i.e., 12.5 mg daily during the first week, 25 mg daily during the second week, 50 mg daily during the third week, 100 mg daily during the fourth week, 150 mg daily during the fifth week) up to the maintenance dose as determined by a physician. A maximum dose of 150 mg losartan (for example, three tablets of Losartan potassium 50 mg or one tablet each of Losartan potassium 100 mg and Losartan potassium 50 mg) once daily may be used.

In the treatment of heart failure, losartan is usually combined with a diuretic (medicine that increases the amount of water that the patient pass out through the kidneys) and/or digitalis (medicine that helps to make the heart stronger and more efficient) and/or a beta-blocker.

Dosage in special patient groups
The doctor may advise a lower dose , especially when starting treatment in certain patients with liver impairment, or in patients over the age of 75 years. The use of losartan is not recommended in patients with severe hepatic impairment.

For further information on how Losartan potassium tablets are used, refer to the package leaflet and Summaries of Product Characteristics 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 Losartan potassium tablets have been shown in studies?
Because Losartan potassium tablets are generic medicines, studies in healthy volunteers have been limited to tests to determine that they are 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 Losartan potassium tablets?
Because Losartan potassium tablets are generic medicines and are bioequivalent to the reference medicines, their benefits and possible side effects are considered to be the same as the reference medicines.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summaries of Product Characteristics (SmPCs) available on the MHRA website.

Why were Losartan potassium tablets approved?
It was concluded that, in accordance with EU requirements, Losartan potassium tablets have been shown to be comparable to and to be bioequivalent to the reference medicines. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Losartan potassium tablets?
A Risk Management Plan (RMP) has been developed to ensure that Losartan potassium tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPCs and the package leaflet, 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 Losartan potassium tablets
Marketing Authorisations for Losartan potassium tablets were granted in the UK on 28 August 2020.

The full PAR for Losartan potassium tablets follows this summary.

This summary was last updated in October 2020.

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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 Losartan potassium 25, 50 and 100 mg film-coated tablets (PL 49445/0041-43) could be approved.

The products are approved for the following indications:

- Treatment of essential hypertension in adults and in children and adolescents 6-18 years of age.
- Treatment of renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Treatment of chronic heart failure in adult patients when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

Losartan is a synthetic oral angiotensin-II receptor (type AT1) antagonist Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT1 receptor. In vitro and in vivo losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II values fell within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT1-receptor than for the AT2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

These applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, as generic medicines of suitable originator medicinal products, Cozaar 25, 50 and 100 mg

Film-coated tablets (Merck Sharp & Dohme Limited), that have been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications are based on being generic medicinal products of reference products that have been in clinical use for over 10 years. 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 Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted for these products on 28 August 2020.

II QUALITY ASPECTS

II.1 Introduction

These products are tablets. Each tablet contains 25, 50 or 100 mg of losartan potassium as active substance.

In addition to losartan potassium, these products also contain the excipients cellulose microcrystalline (PH 102 & PH 200), lactose monohydrate, starch pregelatinized, low substituted hydroxyl propyl cellulose, crospovidone (Type A), magnesium stearate, hypromellose 6cP (E464), titanium dioxide (E171) and carnauba wax.

The tablets are packaged in alu- polyvinylchloride (PVC)/ polyvinylidene chloride (PVdC) blister strips which are further packaged into an outer carton 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.

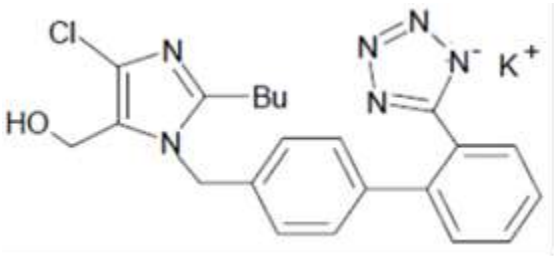
II.2 ACTIVE SUBSTANCE

rINN: Losartan potassium

Chemical Name: Potassium 5-[4'-[[2-butyl-4-chloro-5-(hydroxymethyl) - 1Himidazol-1-yl] methyl] biphenyl-2-yl] tetrazol-1-ide

Molecular formula: $C_{22}H_{22}ClKN_6O$

Chemical Structure:



Molecular Weight: 461 g/mol

Appearance: A white or almost white, crystalline powder.

Solubility: Slightly soluble in acetonitrile, freely soluble in water and in methanol.

Losartan potassium 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.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production

of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Confirmation has also 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 has been validated and has 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 2 years, with no special storage conditions is approved. However, the products should be stored in the original package in order to protect from moisture.

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 losartan potassium 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 an 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 losartan potassium are well-known. With the exception of data from one bioequivalence study, no new clinical data are provided or are required for this type of applications. 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 study was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Losartan potassium 100 mg tablets with Cozaar® 100 mg Tablets (Merck Sharp & Dohme Limited, UK) in healthy human adult subjects, under fasting conditions.

Subjects were administered a single oral dose of either the test or the reference product under fasting conditions.

Blood samples were taken pre-dose and up to 24 hours post dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results are presented below:

Summary of Losartan pharmacokinetic results

Parameter	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	k_{el} (1/hr)	$t_{1/2}$ (hr)	AUC_%Extrap_obs (ng.h/mL)
Test Product							
Untransformed mean	1.175	961.6493	1460.9092	1490.5144	0.3793	2.1921	1.8675
Log-transformed * least square Mean	-	805.4975	1365.9189	1392.1616	-	-	-
Reference Product							
Untransformed mean	1.367	903.7459	1475.8442	1497.3805	0.3707	2.0436	1.5339
Log-transformed * least square Mean	-	801.1181	1384.4148	1406.0031	-	-	-
Log-transformed * data							
T/R Ratio	-	100.55	98.66	99.02	-	-	-
90% CI	-	87.78-115.17	94.40-103.12	94.69-103.54	-	-	-
Intra-subject variability (%)	-	41.23	12.94	13.09	-	-	-
Power (%)	-	85.71	100.00	100.00	-	-	-

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/*Corr***), the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

As the additional strengths of the product (25 and 50 mg) meet the biowaiver criteria specified in the current bioequivalence guideline, the results and conclusions from the bioequivalence study on the product strength can be extrapolated to the other strengths.

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 products were equally well tolerated. No new or unexpected safety issues were raised from the bioequivalence study.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, 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

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The 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.

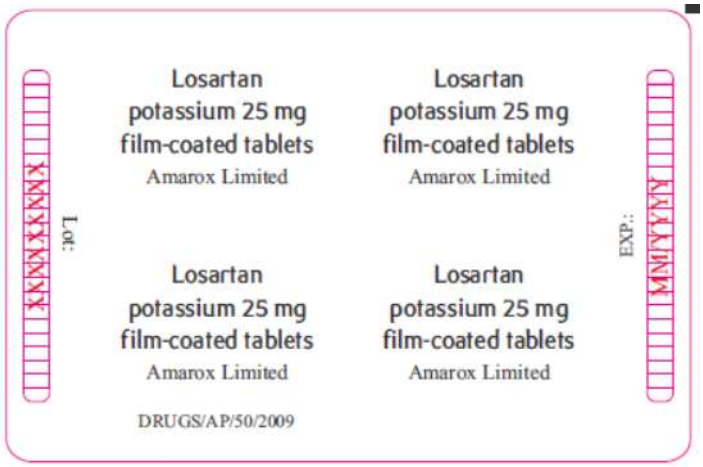
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

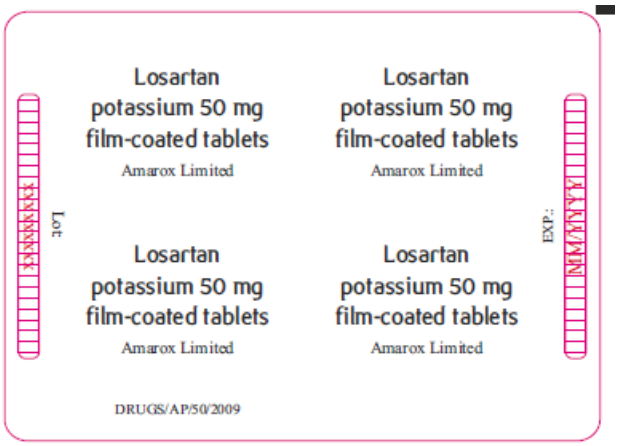
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory, in line with current guidelines and consistent with the reference products.

In accordance with Directive 2012/84/EU, 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 UK licensing are provided below.




20 mm
28 film-coated tablets
Losartan potassium
50 mg
film-coated tablets
50 mg
Each Losartan potassium 50 mg tablet contains 50 mg of losartan potassium.
Amarox
UNVARNISHARE A FORBATCHCOADING 66x20mm
2xxxxxx
Losartan potassium 50 mg film-coated tablets
28 film-coated tablets
Losartan potassium
50 mg
film-coated tablets
PL 49445/0042
POM
PL Holder:
Amarox Limited
Congress House, 14 Lyon Road
Harrow, Middlesex HA1 2EN
United Kingdom
28 film-coated tablets
Losartan potassium
50 mg
film-coated tablets
UN VARNISH AREA
Read the package leaflet before use.
Oral use.
DRUGS/AP/50/2009
Keep out of the sight and reach of children.
Also contains lactose monohydrate
See leaflet for further information.


Losartan potassium 50 mg film-coated tablets
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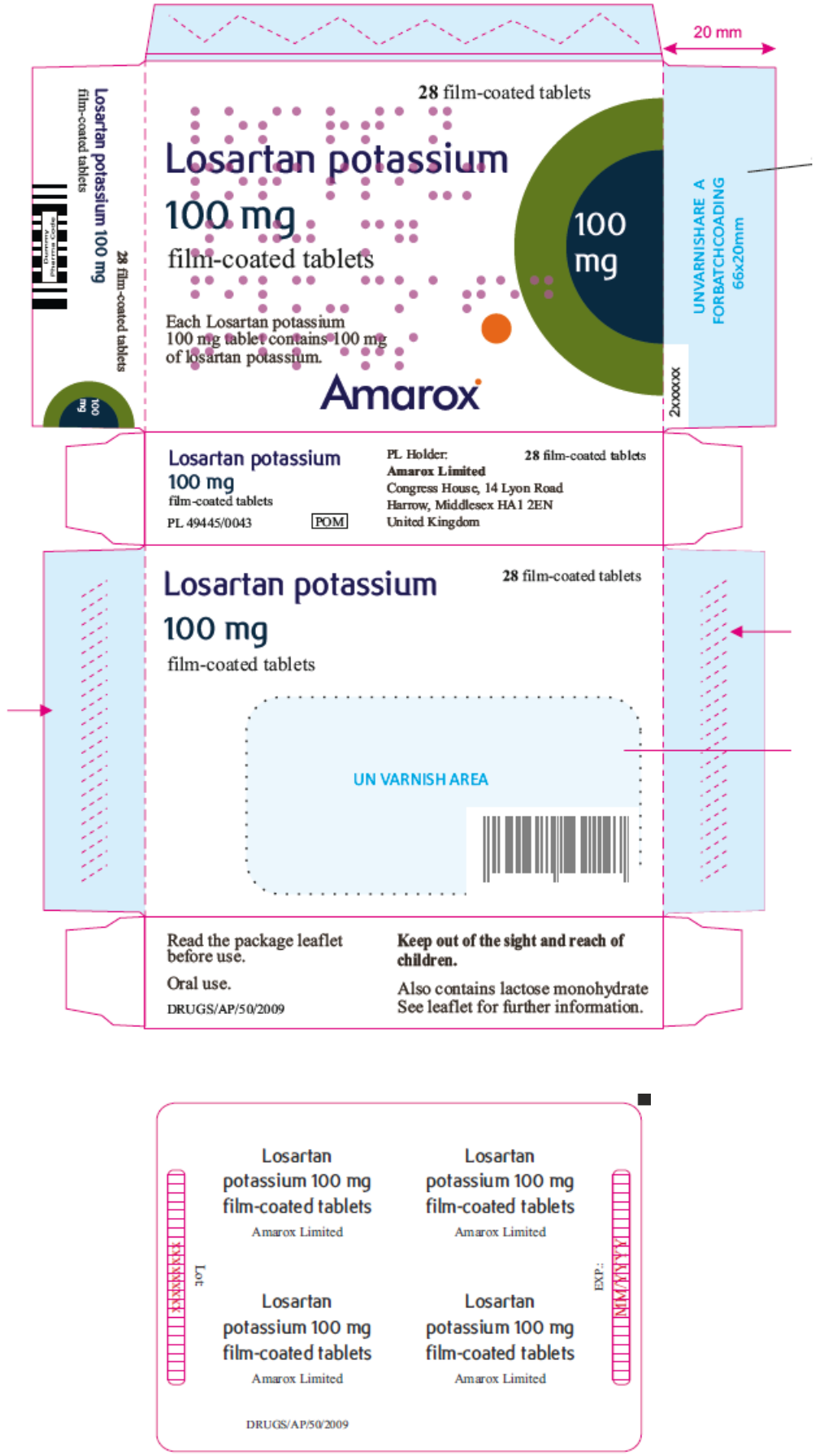
Losartan potassium 50 mg film-coated tablets
Amarox Limited
Lot
EXP:
DRUGS/AP/50/2009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Losartan potassium 100 mg film-coated tablets
Amarox Limited
Lot:
EXP.:
DRUGS/AP/50/2009

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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**