



Public Assessment Report

Decentralised Procedure

Lamzarin 30 and 60 mg Prolonged-release Tablets (Gliclazide)

Procedure No: UK/H/6769/001-2/DC

UK Licence No: PL 34424/0037-8

Key Pharmaceuticals Ltd

LAY SUMMARY

Lamzarin 30 and 60 mg Prolonged-release Tablets (Gliclazide)

This is a summary of the public assessment report (PAR) for Lamzarin 30 and 60 mg Prolonged-release Tablets (PL 34424/0037-8; UK/H/6769/001-2/DC). These products will be referred to as Lamzarin Tablets in the remainder of this summary, for ease of reading.

This summary explains how Lamzarin Tablets were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use these products.

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

What are Lamzarin Tablets and what are they used for?

Lamzarin Tablets are generic medicines. This means that Lamzarin Tablets are similar to ‘reference medicines’ already authorised in the UK called Diamicon 30 and 60 mg MR Tablets (Les Laboratoires Servier, UK; PL 05815/0019 and PL 05819/0073).

Lamzarin Tablets are used in a certain form of diabetes (type 2 diabetes mellitus) in adults, when diet, exercise and weight loss alone do not have an adequate effect on keeping blood sugar at the correct level.

How are Lamzarin Tablets used?

Lamzarin Tablets are taken by mouth. The whole tablet must be swallowed (without chewing) in one piece with a glass of water at breakfast time (preferably at the same time each day). The patient must always eat a meal after taking the tablet(s).

The dose is determined by a doctor, depending on the blood and possibly urine sugar levels. Change in external factors (e.g. weight reduction, change in life style, stress) or improvements in the blood sugar control may require changed Lamzarin Prolonged-release Tablet doses.

For 30mg Tablets:

The usual dose is one to four tablets (maximum 120mg) in a single intake at breakfast time. This depends on the response to treatment.

For 60mg Tablets:

The tablet can be divided into equal doses. The usual dose is half to two tablets (maximum 120mg) in a single intake at breakfast time. This depends on the response to treatment.

If a combination therapy of gliclazide with metformin, an alpha glucosidase inhibitor, a thiazolidinedione, a dipeptidyl peptidase-4 inhibitor, a GLP-1 receptor agonist or insulin is initiated a doctor will determine the proper dose of each medicine individually for a patient.

If a patient notices that the blood sugar levels are high although he/she is taking the medicine as prescribed, they should contact a doctor or pharmacist.

Lamzarin Tablets can only be obtained on prescription from a doctor.

For further information on how Lamzarin Tablets are used, please see the Summaries of Product Characteristics and the package leaflets available on the MHRA website.

How do Lamzarin Tablets work?

Lamzarin Tablets contain the active ingredient gliclazide which is an oral anti-diabetic medicine. This medicine belongs to the sulphonylurea group. It works by reducing blood sugar levels.

How have Lamzarin Tablets been studied?

Because Lamzarin Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the medicinal products, Diamicon 30 and 60 mg MR Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Lamzarin Tablets?

As Lamzarin Tablets are generic medicines that are bioequivalent to Diamicon 30 and 60 mg MR Tablets, their benefits and risks are taken as being the same as Diamicon 30 and 60 mg MR Tablets.

Why are Lamzarin Tablets approved?

It was concluded that, in accordance with EU requirements, Lamzarin Tablets have been shown to have comparable quality and to be bioequivalent to Diamicon 30 and 60 mg MR Tablets. Therefore, the view was that, as for Diamicon 30 and 60 mg MR Tablets the benefits outweigh the identified risks.

What measures are being taken to ensure the safe and effective use of Lamzarin Tablets?

A risk management plan has been developed to ensure that Lamzarin 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 leaflets for Lamzarin Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Lamzarin Tablets

Republic of Ireland and the UK agreed to grant Marketing Authorisations for Lamzarin Tablets on 14 September 2018. Marketing Authorisations were granted in the UK on 11 October 2018.

The full PAR for Lamzarin Tablets follows this summary.

This summary was last updated in November 2018.

TABLE OF CONTENTS

I	Introduction	Page 5
II	Quality aspects	Page 6
III	Non-clinical aspects	Page 7
IV	Clinical aspects	Page 8
V	User consultation	Page 12
VI	Overall conclusion, benefit/risk assessment and recommendation	Page 12
	Table of content of the PAR update for MRP and DCP	Page 19

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy the Member States considered that the applications for Lamzarin 30 and 60 mg Prolonged-release Tablets (PL 34424/0037-8; UK/H/6769/001-2/DC), are approvable. The products are prescription-only medicines (POM), indicated for non-insulin dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Republic of Ireland as Concerned Member State (CMS). The applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, as generic applications. The reference medicinal products for these applications are Diamicon 30 and 60 mg MR Tablets, which were authorised to Les Laboratoires Servier, UK (PL 05815/0019 and PL 05819/0073) on 07 December 2000 and 23 November 2009, respectively. The 60 mg tablet was never marketed in the UK, and the licence was cancelled in October 2017. Diamicon 30 and 60 mg MR tablets are in turn part of the global Marketing Authorisation for Diamicon 80 mg MR tablets, authorised since 1979 in the UK.

The medicinal product contains the active substance, gliclazide. Gliclazide is a hypoglycaemic, sulphonylurea, oral anti-diabetic active substance differing from other related compounds by an N-containing heterocyclic ring with an endocyclic bond.

Gliclazide reduces blood glucose levels by stimulating insulin secretion from the β -cells of the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.

With the exception of the bioequivalence studies, no new non-clinical or clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Both Member States agreed to grant Marketing Authorisations for the above products at the end of the procedure (Day 208 – 14 September 2018). After a subsequent national phase, the UK granted Marketing Authorisations (PL 34424/0037-8) for these products on 11 October 2018.

II QUALITY ASPECTS

II.1 Introduction

The products are prolonged release tablets. Each prolonged release tablet contains 30 mg or 60 mg gliclazide.

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, hypromellose and magnesium stearate. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. 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.

The finished product is packed in polyvinylchloride (PVC)/ polyvinylidenechloride (PVDC)/Alu blisters or PVC/Alu blister. The pack sizes are 14, 28 and 56 Prolonged-release Tablets.

Not all pack sizes may be marketed.

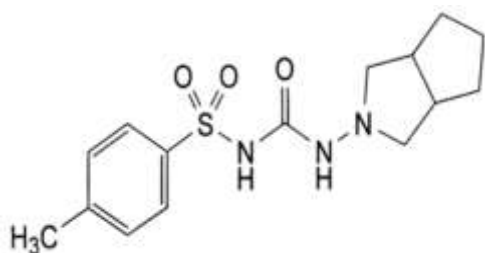
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2. Drug Substance

INN: Gliclazide

Chemical name(s): 1-(3-azabicyclo[3.3.0]oct-3-yl)-3-p-tolylsulphonylurea
1-(Hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4-methylphenyl) sulfonyl] urea (Ph. Eur.)

Structure:



Molecular formula: C₁₅H₂₁N₃O₃S

Molecular weight: 323.4 g/mol

Appearance: white or almost white powder.

Solubility: Gliclazide is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in alcohol.

Gliclazide is the subject of a European Pharmacopoeia monograph.

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

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable prolonged-released tablets containing 30 mg or 60 mg of gliclazide per tablet, that are generic versions of the reference products, Diamicon 30 and 60 mg MR Tablets (Les Laboratoires Servier, UK).

Comparative dissolution profiles have been presented for test and reference products.

Manufacture of the products

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated and have shown satisfactory results. Process validation data on commercial scale batches have been provided.

Finished Product Specifications

The finished product specifications proposed are acceptable. The test methods that have been described have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 3 years with no special storage conditions.

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

There are no objections to the approval of these applications from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of gliclazide are well-known. As this is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetic and toxicology.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since these products are intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

There are no objections to the approval of these applications from a non-clinical point of view.

IV CLINICAL ASPECTS

The clinical pharmacology of gliclazide is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of gliclazide.

Based on the data provided, Gliclazide 30 and 60 mg MR tablets can be considered bioequivalent to Diamicon 30 and 60 mg prolonged release Tablets (Les Laboratoires Servier, France).

IV.2 Pharmacokinetics

In support of these applications, the Marketing Authorisation Holder has submitted the following four bioequivalence studies:

Study 1

This is an open, randomised, single dose, two-treatment, two period, two-sequence, two-way crossover comparative bioavailability study of Gliclazide 30 mg MR tablets and Diamicon 30 mg prolonged release Tablets (Les Laboratoires Servier, France) in healthy, adult human subjects under fasting conditions.

Blood samples were collected at pre-dose and up to and including 96 hours after each administration. The washout period between the treatment phases was 8 days.

Results

Pharmacokinetic parameters for gliclazide (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

PK Parameter	ISCV (%)	Geometric Least Square Means		T/R Ratio (%)	90% Confidence Interval		Power (%)
		Test (T)	Reference (R)		LCL	UCL	
C _{max} (ng/mL)	15.6	1545.486	1416.768	109.09	102.82	115.73	100.0
AUC _{0-t} (ng.hr/mL)	9.2	31672.544	31407.310	100.84	97.38	104.43	100.0

Conclusion

The 90% confidence intervals for C_{max} and AUC_{0-t} were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Gliclazide 30 mg MR tablets) and the reference formulation (Diamicon 30 mg prolonged release Tablets) under fasting conditions.

Study 2

This is an open, randomised, single dose, two-treatment, two period, two-sequence, two-way crossover comparative bioavailability study of Gliclazide 60 mg MR tablets and Diamicon 60 mg prolonged release Tablets ((Les Laboratoires Servier, France) in healthy, adult human subjects under fasting conditions.

Blood samples were collected at pre-dose and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days.

Results

Pharmacokinetic parameters for gliclazide (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

<i>Test Gliclazide modified release 60 mg tablet (B) vs Reference Diamicon[®] MR 60 mg tablet (A)</i>				
	Anova	Mean ratio %	Geometric mean ratio	90% confidence interval
Log ₁₀ (AUC _{0-∞})	0.590	100.16	-	(0.964,1.072)*
Log ₁₀ (AUC _{0-t})	0.673	100.12	-	(0.961,1.069)
Log ₁₀ (C _{max})	0.139	100.82	-	(0.992,1.144)*
AUC _{0-∞}	0.313	102.82	101.70	(0.981,1.075)
AUC _{0-t}	0.468	102.06	101.34	(0.973,1.069)
C _{max}	0.229	105.98	106.56	(0.977,1.143)
T _{max}	0.232	89.22	91.25	(0.742,1.043)
t _{1/2}	0.566	102.07	-	(0.960,1.082)

Conclusion

The 90% confidence intervals for C_{max} and AUC were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Gliclazide 60 mg MR tablets) and the reference formulation (Diamicon 60 mg prolonged release Tablets) under fasting conditions.

Study 3

This is an open, randomised, single dose, two-treatment, two period, two-sequence, two-way crossover comparative bioavailability study of Gliclazide 60 mg MR tablets and Diamicon 60 mg prolonged release Tablets (Les Laboratoires Servier, France) in healthy, adult human subjects under fed conditions.

A standard high fat, high calorie breakfast was used in the fed study. The meal was started 30 minutes prior to drug administration, and had to be completed within 30 minutes, therefore dosing took place just after completing the meal, providing the most sensitive test of food effect.

Blood samples were collected at pre-dose and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days.

Results

Pharmacokinetic parameters for gliclazide (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

<i>Test Gliclazide modified release 60 mg tablet (B) vs Reference Diamicron[®] MR 60 mg tablet (A)</i>				
	Anova	Mean ratio %	Geometric mean ratio	90% confidence interval
Log ₁₀ (AUC _{0-∞})	0.590	100.16	-	(0.964,1.072)*
Log ₁₀ (AUC _{0-t})	0.673	100.12	-	(0.961,1.069)
Log ₁₀ (C _{max})	0.139	100.82	-	(0.992,1.144)*
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Conclusion

The 90% confidence intervals for C_{max} and AUC were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Gliclazide 60 mg MR tablets) and the reference formulation (Diamicron 60 mg prolonged release Tablets) under under fed conditions.

Study 4

This is an open, randomised, multiple dose, two-treatment, two-sequence, two period, two-way crossover comparative bioavailability study of Gliclazide 60mg MR tablets and Diamicron 60 mg modified release Tablets (Les Laboratoires Servier, France) in healthy, adult human subjects under fasting conditions steady state.

Blood samples were collected at pre-dose and up to and including 72 hours after each administration. The washout period between the treatment phases was 7 days.

Results

Pharmacokinetic parameters for gliclazide (In-transformed geometric mean, 90% Confidence Interval and test/Reference ratio)

	Anova	Mean ratio %	Geometric mean ratio	90% confidence interval
Log ₁₀ (AUC _{0,t})	0.739	99.92	-	(0.948,1.037)*
Log ₁₀ (C _{max})	0.216	100.62	-	(0.983,1.125)*
Log ₁₀ (C _{min})	0.134	99.05	-	(0.872,1.007)*
AUC _{0,t}	0.689	99.04	99.12	(0.950,1.031)
C _{max}	0.523	102.95	105.15	(0.951,1.108)
C _{min}	0.290	96.40	93.67	(0.907,1.021)
DF	0.056	111.58	-	(1.017,1.214)
T _{max}	0.372	95.34	-	(0.865,1.041)

Conclusion

The 90% confidence intervals for C_{max} and AUC were within the pre-defined acceptance criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/

Corr**). Bioequivalence has been shown for the test formulation (Gliclazide 60 mg MR tablets) and the reference formulation (Diamicon 60 mg prolonged release Tablets) under fasting conditions at steady state.

IV.3 Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for applications of this type.

IV.5 Clinical safety

No new safety data were submitted, and none are required.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lamzarin 30 and 60 mg Prolonged-release Tablets.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hypoglycaemia due to gliclazide use alone or associated with factors that increase the risk including renal impairment, hepatic impairment, and drug interactions. • Secondary failure of oral anti-hyperglycaemic therapy • Haemolytic anaemia in patients with G6PD deficiency • Hyperglycaemia associated with factors that increase the risk including surgery and drug interactions • Use in patients with lactose/galactose intolerance
Important potential risks	<ul style="list-style-type: none"> • Concomitant use of gliclazide with anticoagulant therapy (warfarin)
Missing information	<ul style="list-style-type: none"> • Use during pregnancy and lactation • Use in the paediatric population

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

No new clinical data were submitted, and none are required for applications of this type.

There are no objections to the approval of these applications from a clinical viewpoint.

The grant of Marketing Authorisations is recommended for these applications.

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use*.

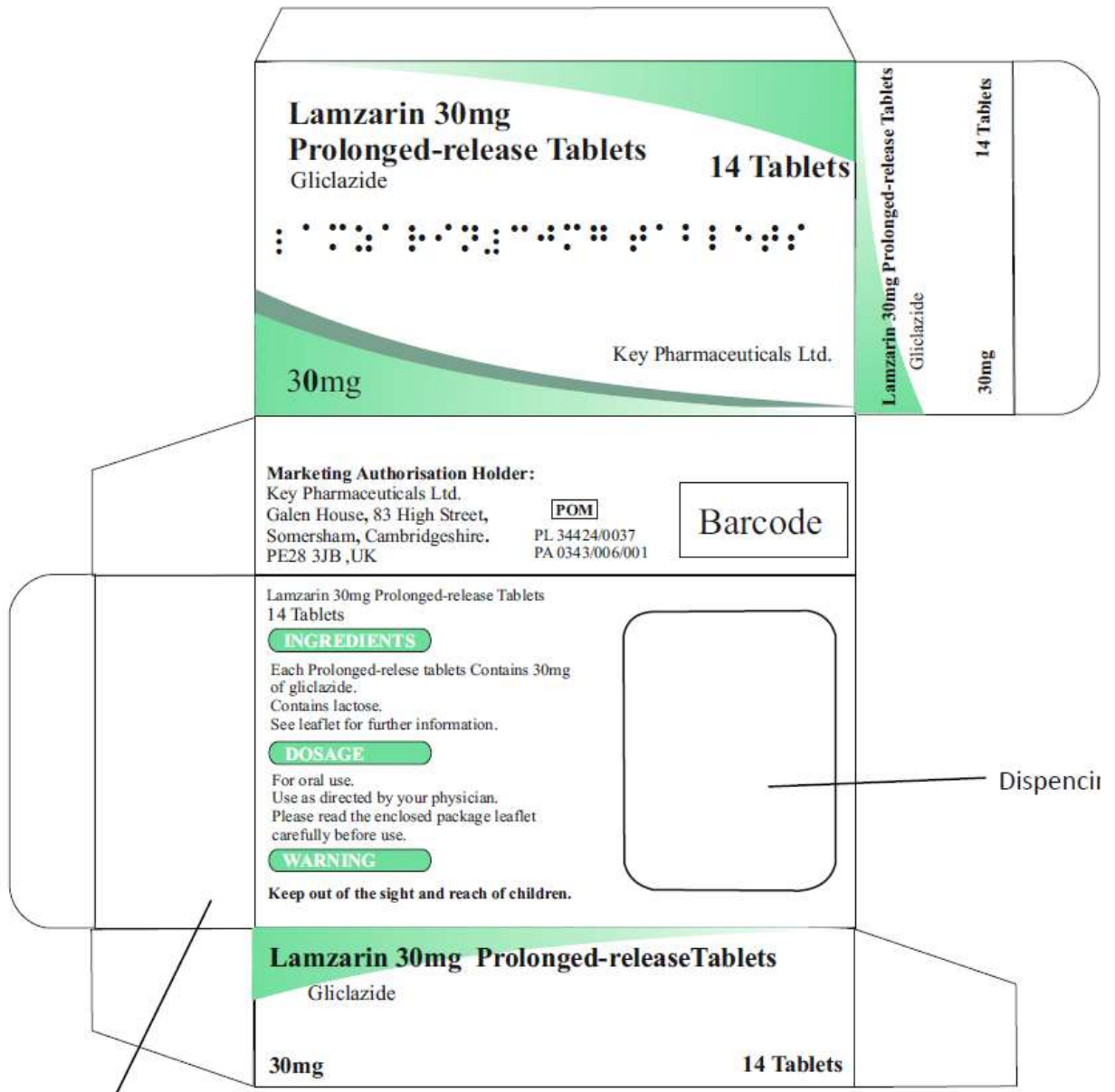
VI Overall conclusion, benefit/risk assessment and recommendation

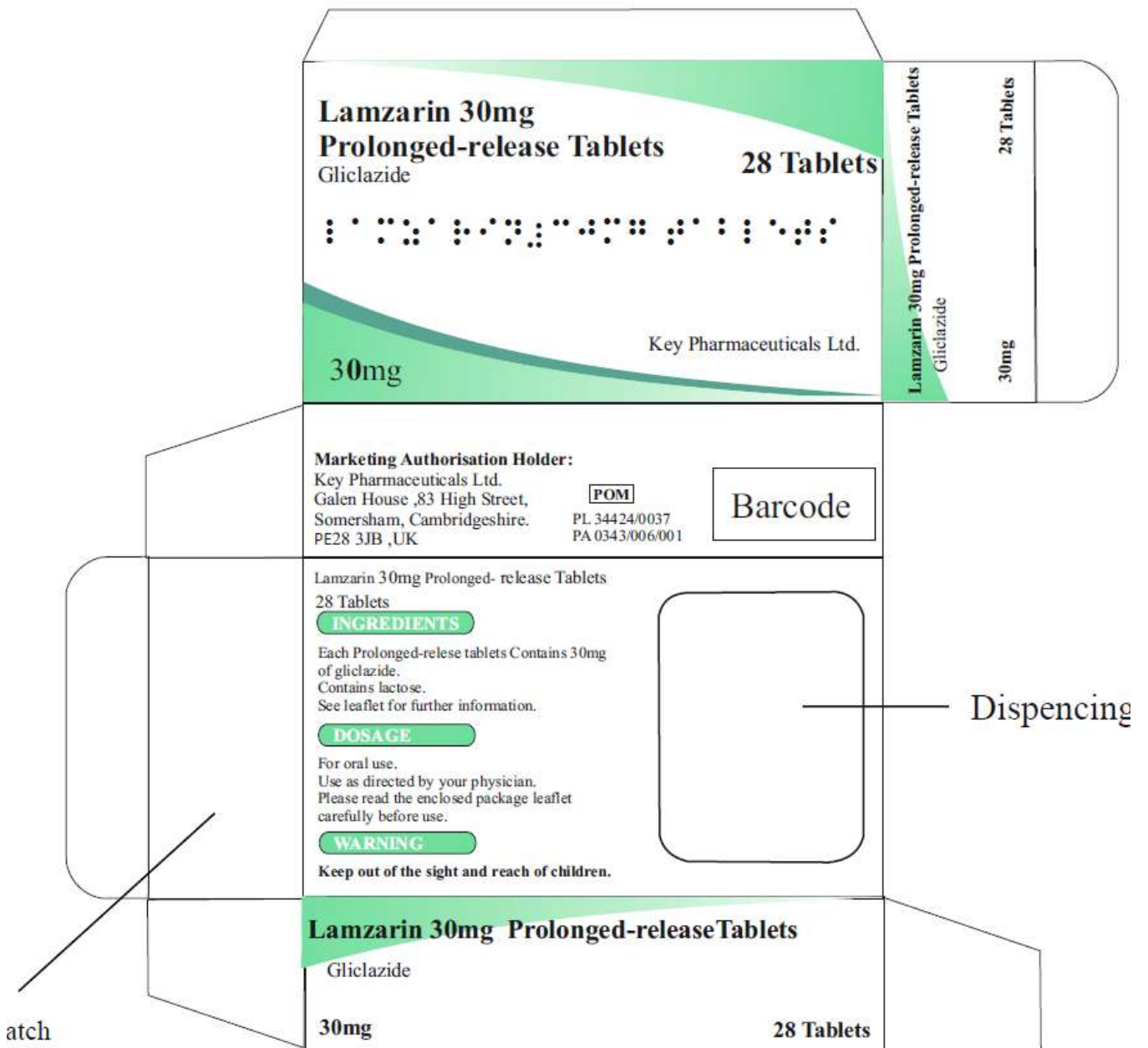
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with gliclazide is considered to have demonstrated the therapeutic value of the compound. The benefit risk assessment is, therefore, considered to be positive.

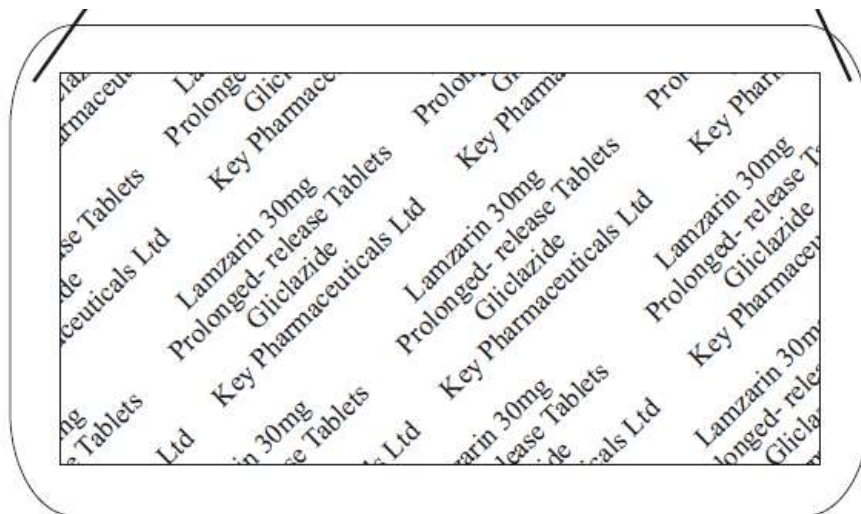
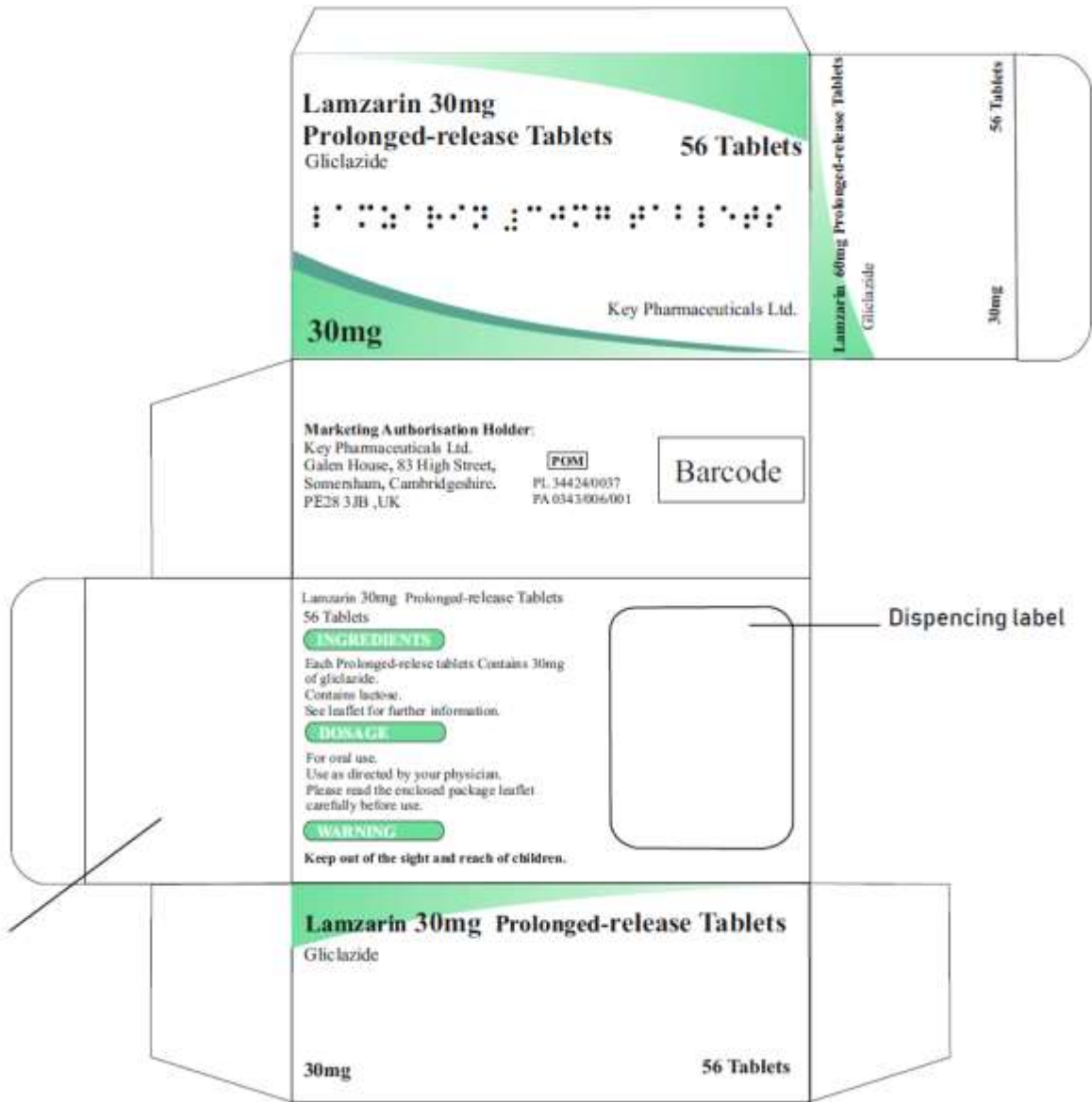
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

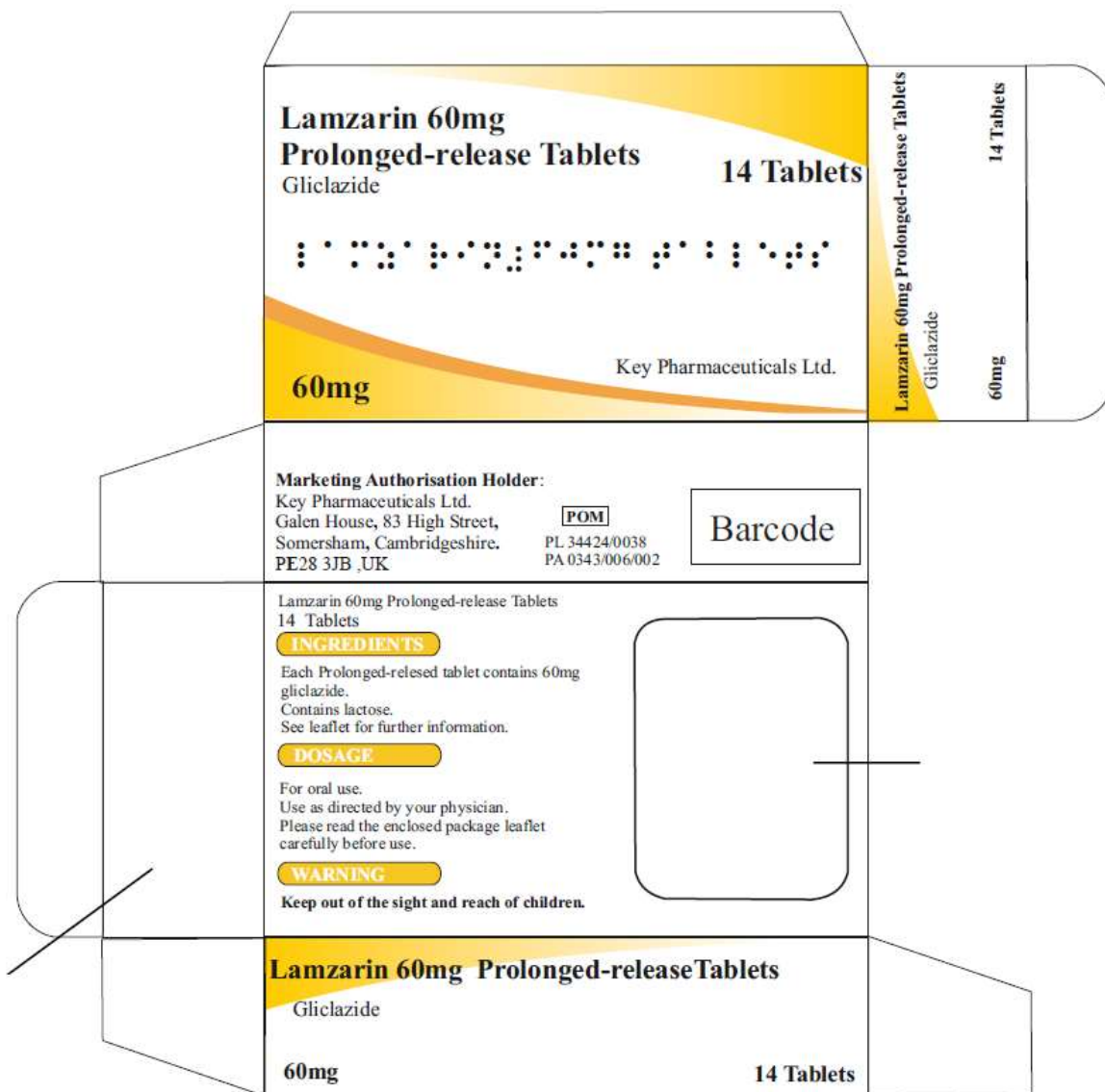
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

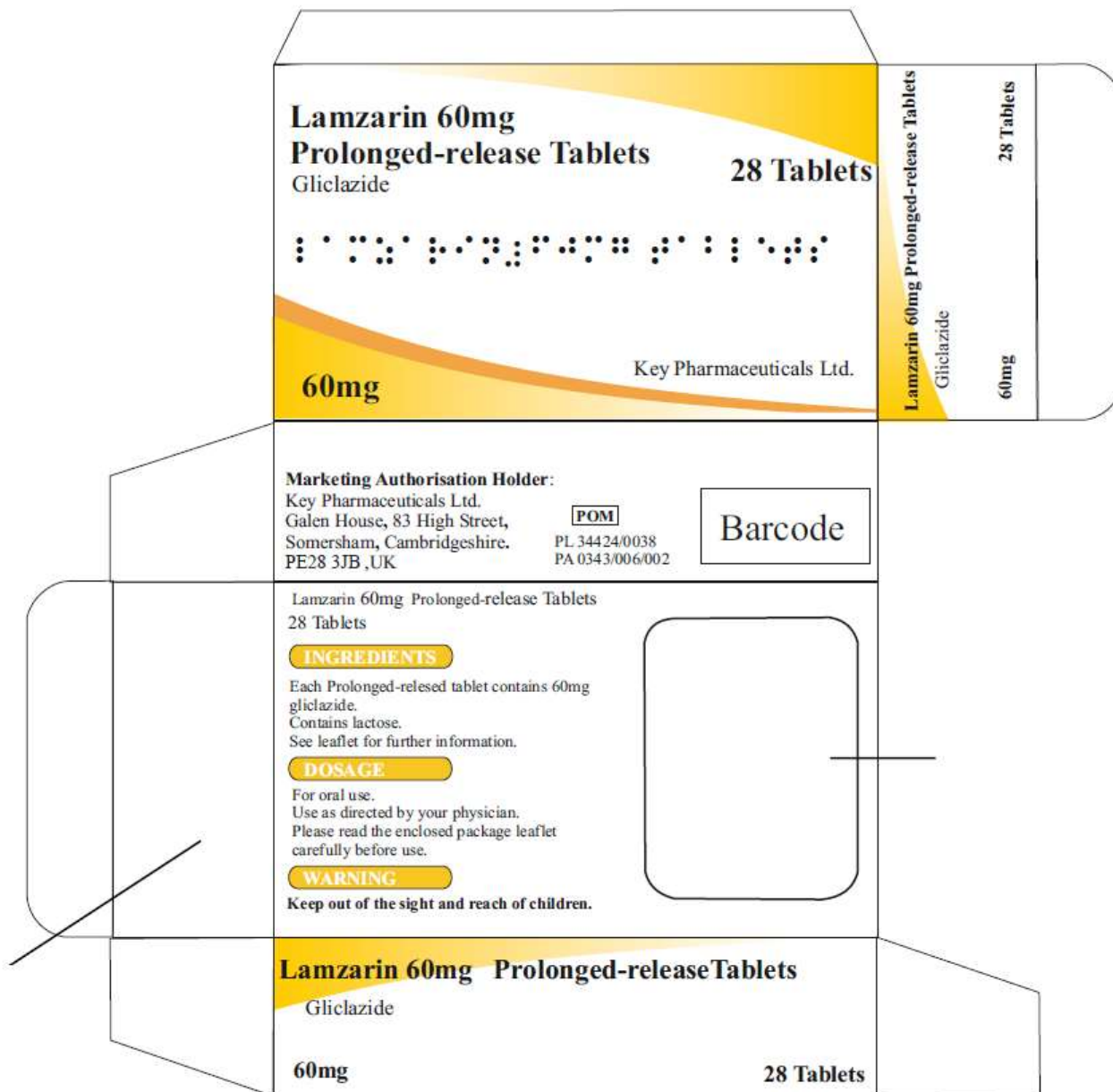
The approved labelling for Lamzarin 30 and 60 mg Prolonged-release Tablets is presented below:











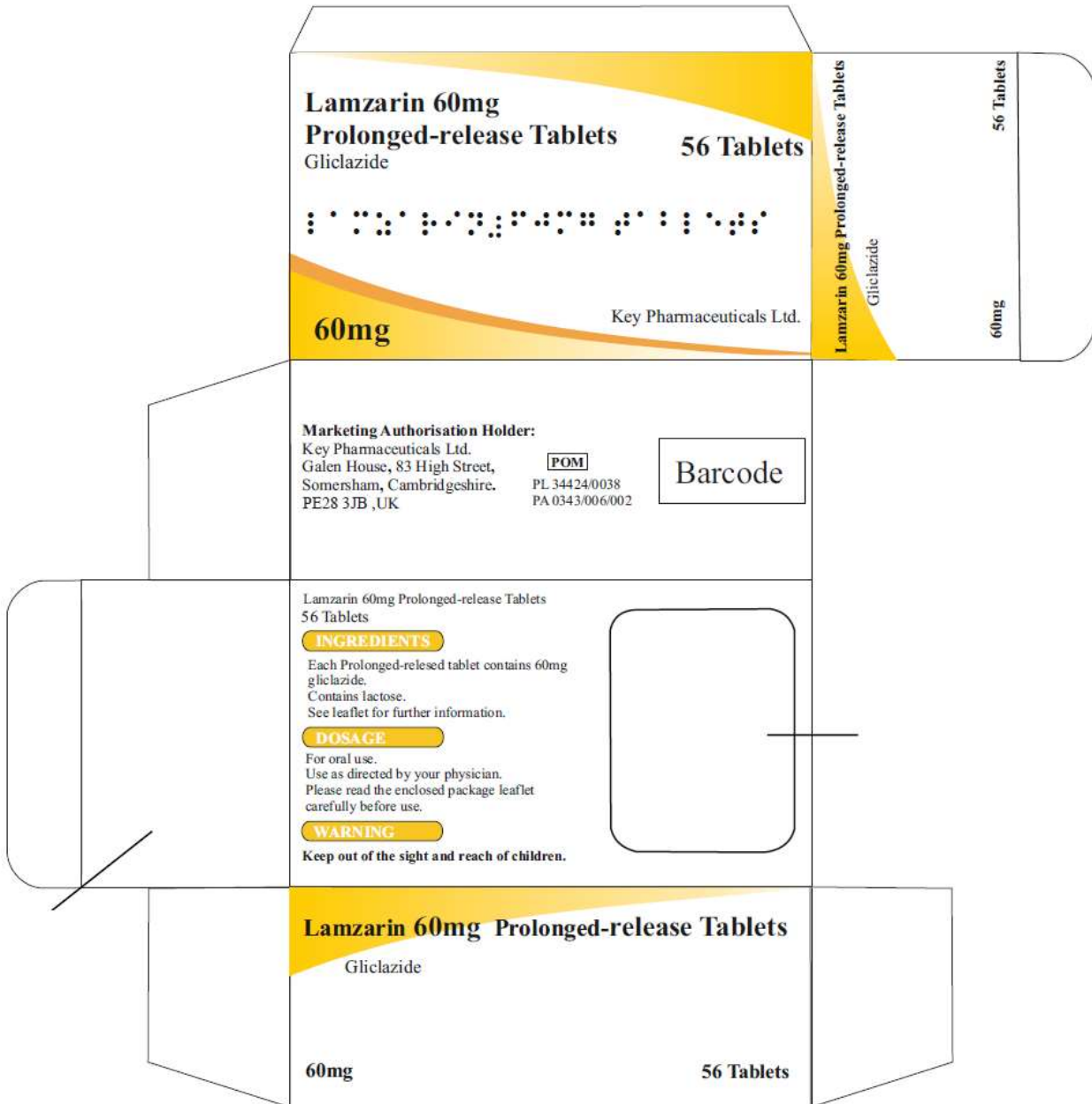


Table of content of the PAR update for MRP and DCP

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)