IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lamzarin 60 mg prolonged-release tablets
Gliclazide
PA0343/006/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/6769/001-002/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 12th September 2019 under procedure number IE/H/1053/001-002/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0343/006/001-002
Marketing Authorisation Holder: Key Pharmaceuticals Ltd.

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

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 Diamicron 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. Diamicron 30 and 60 mg MR tablets are in turn part of the global Marketing Authorisation for Diamicron 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.

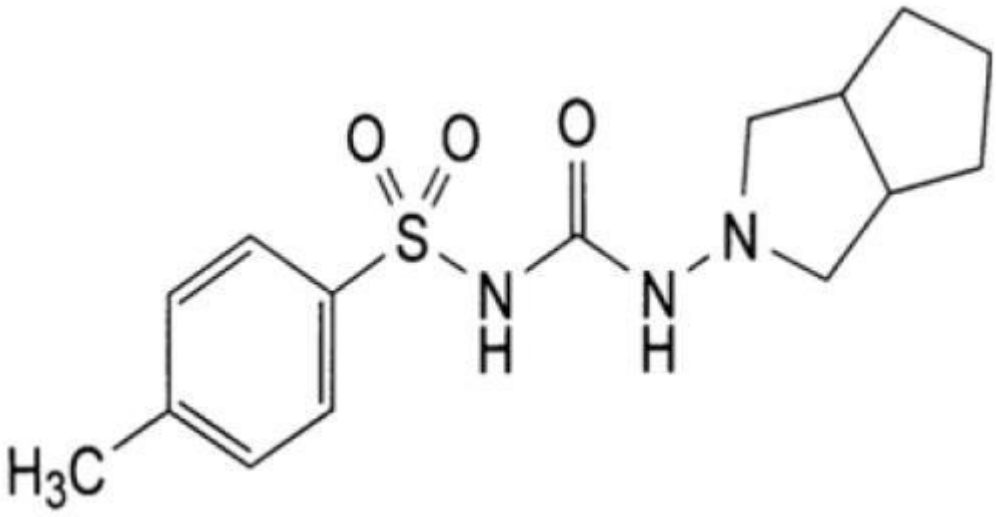
The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has 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, Diamicron 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 Diamicron 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 30mg MR tablets and Diamicron 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	
Cmax (ng/mL)	15.6	1545.486	1416.768	109.09	102.82	115.73	100.0
AUC0-t (ng.hr/mL)	9.2	31672.544	31407.310	100.84	97.38	104.43	100.0

Conclusion

The 90% confidence intervals for Cmax and AUC0-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 (Diamicron 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 Diamicron 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)

Test Gliclazide modified release 60 mg tablet (B) vs Reference Diamicron® MR 60 mg tablet (A)				
	Anova	**Mean ratio %**	**Geometric mean ratio**	**90% confidence interval**
$Log_{10}(AUC_{0-\infty})$	0.590	100.16	-	(0.964,1.072)*
$Log_{10}(AUC_{0-t})$	0.673	100.12	-	(0.961,1.069)
$Log_{10}(Cmax)$	0.139	100.82	-	(0.992,1.144)*
$AUC_{0-\infty}$	0.313	102.82	101.70	(0.981,1.075)
AUC_{0-t}	0.468	102.06	101.34	(0.973,1.069)
Cmax	0.229	105.98	106.56	(0.977,1.143)
Tmax	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 Cmax 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 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 Diamicron 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)

Test Gliclazide modified release 60 mg tablet (B) vs Reference Diamicron® MR 60 mg tablet (A)				
	Anova	**Mean ratio %**	**Geometric mean ratio**	**90% confidence interval**
$Log_{10}(AUC_{0-\infty})$	0.590	100.16	-	(0.964,1.072)*
$Log_{10}(AUC_{0-t})$	0.673	100.12	-	(0.961,1.069)
$Log_{10}(Cmax)$	0.139	100.82	-	(0.992,1.144)*
$AUC_{0-\infty}$	0.313	102.82	101.70	(0.981,1.075)
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Cmax	0.229	105.98	106.56	(0.977,1.143)
Tmax	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 Cmax 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)*
$Log_{10}(Cmax)$	0.216	100.62	-	(0.983,1.125)*
$Log_{10}(Cmin)$	0.134	99.05	-	(0.872,1.007)*
AUC_{0-t}	0.689	99.04	99.12	(0.950,1.031)
Cmax	0.523	102.95	105.15	(0.951,1.108)
Cmin	0.290	96.40	93.67	(0.907,1.021)
DF	0.056	111.58	-	(1.017,1.214)
Tmax	0.372	95.34	-	(0.865,1.041)

Conclusion

The 90% confidence intervals for Cmax 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 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	• 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	• Concomitant use of gliclazide with anticoagulant therapy (warfarin)
Missing information	• 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*.

V. OVERALL CONCLUSIONS

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.

VI. REVISION DATE

April 2021

VII. UPDATES

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval
RMS Transfer	From UK/H/6769/001-002/DC to IE/H/1053/001-002/DC	N/A	N/A	N/A	Approved 12/09/2019
MA Transfer	CRN00C5G7	SmPC section 7, 8, 10 Leaflet New MA holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/004/002	30/04/2021	30/04/2021	Approved