Public Assessment Report

Decentralised Procedure

Zicron PR 30 mg prolonged-release tablets

(UK/H/5530/01/DC)

PL 17907/0398

Bristol Laboratories Ltd

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Zicron PR 30 mg prolonged-release tablets. It explains how Zicron PR 30 mg prolonged-release tablets 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 Zicron PR 30 mg prolonged-release tablets.

For practical information about using Zicron PR 30 mg prolonged-release tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product will be referred to as Zicron tablets in this summary.

What are Zicron tablets and what are they used for?
Zicron tablets is a 'generic medicine'. This means that Zicron tablets is similar to a 'reference medicine' already authorised in the European Union (EU) called DIAMICRON 30 mg MR Tablets.

Zicron tablets reduce blood sugar levels and are used to treat type 2 diabetes in adults, when diet, exercise and weight loss alone do not have an adequate effect on keeping blood sugar at the correct level.

How do Zicron tablets work?
Zicron tablets contain the active ingredient gliclazide. Gliclazide belongs to a group of medicines called the sulphonamides, which stimulate cells in the pancreas and increase the amount of insulin produced. Insulin is a hormone that is needed to control the levels of sugar in your blood.

How are Zicron tablets used?
The tablets should be swallowed whole with a glass of water. The usual dose is one to four tablets in a single intake at breakfast time. The dose to be taken is decided by a doctor and depends on the patient's blood, and possibly urine, sugar levels

The medicine can only be obtained with a prescription.

What benefits Zicron tablets have been shown in studies?
Because Zicron tablets is a generic medicine, studies in patients have been limited to tests to determine that the tablets are bioequivalent to the reference medicine, DIAMICRON 30 mg MR Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Zicron tablets?
Because Zicron tablets is a generic medicine and is bioequivalent to DIAMICRON 30 mg MR Tablets, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

Why are Zicron tablets approved?
It was concluded that, in accordance with EU requirements, Zicron tablets have been shown to have comparable quality and to be bioequivalent to DIAMICRON 30 mg MR Tablets. Therefore, the MHRA decided that, as for DIAMICRON 30 mg MR Tablets, the benefits of Zicron tablets are greater than its risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Zicron tablets?
A risk management plan has been developed to ensure that Zicron tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Zicron tablets, 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/reviewed continuously as well.

Other information about Zicron tablets
A Marketing Authorisation for Zicron tablets was granted on 4 September 2014.

The full PAR for Zicron tablets follows this summary.

For more information about treatment with Zicron tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in October 2014.

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Module 1

Information about Decentralised Procedure

Name of the product in the Reference Member State	Zicron PR 30 mg prolonged-release tablets
Type of application	Article 10 (1), generic
Name of the drug substance	Gliclazide
Pharmacotherapeutic classification (ATC code) of the medicinal product	Sulphonamides, urea derivative (A10BB09
Pharmaceutical form and strength of the medicinal product	Prolonged-release tablets; 30 mg
Reference number for the Decentralised Procedure	UK/H/5530/01/DC
Reference Member State	United Kingdom
Member States concerned	DE, ES, IE, MT, NL
Start date of the Decentralised Procedure	9 September 2013
End date of the Decentralised Procedure	7 August 2014 (day 210)
Marketing Authorisation number	PL 17907/0398
Name and address of the authorisation holder	Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Herts, HP4 1EG

Module 2

Summary of Product Characteristics

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

Module 3

Product Information Leaflet

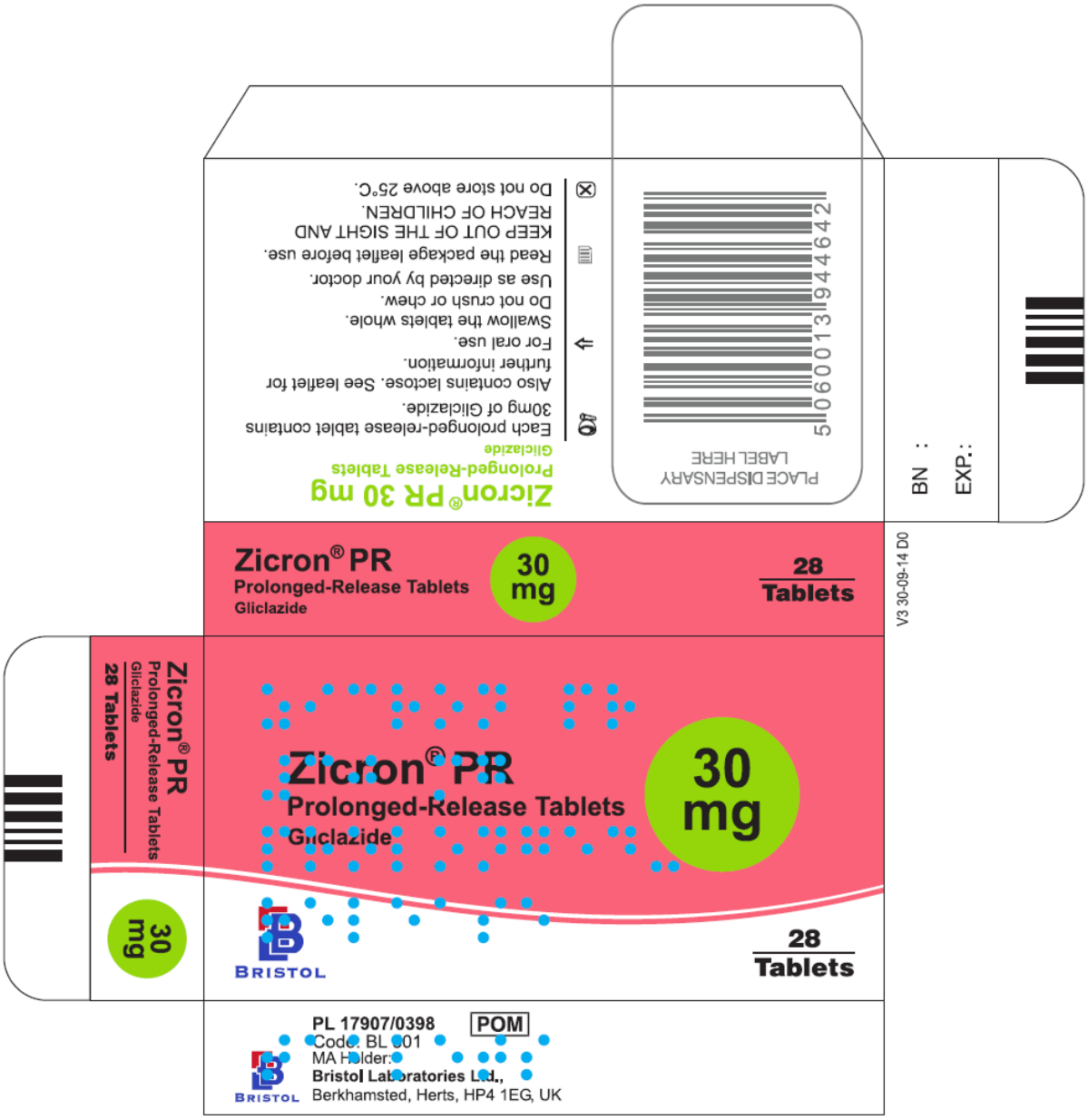
In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4

Labelling

Blister:

Cartons:


Zicron® PR 30 mg
Prolonged-Release Tablets
Gliclazide
Each prolonged-release tablet contains 30mg of Gliclazide.
Also contains lactose. See leaflet for further information.
For oral use.
Swallow the tablets whole.
Do not crush or chew.
Use as directed by your doctor.
Read the package leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.
Do not store above 25°C.
PLACE DISPENSARY LABEL HERE
5060013944642
BN :
EXP.:
Zicron® PR
Prolonged-Release Tablets
Gliclazide
30 mg
28 Tablets
V3 30-09-14 D0
Zicron® PR
Prolonged-Release Tablets
Gliclazide
28 Tablets
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BRISTOL
PL 17907/0398
POM
Code: BL 001
MA Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK


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5060013944659
BN :
EXP.:
Zicron® PR
Prolonged-Release Tablets
Gliclazide
30 mg
56 Tablets
V3 30-09-14 D0
Zicron® PR
Prolonged-Release Tablets
Gliclazide
56 Tablets
30 mg
Zicron® PR
Prolonged-Release Tablets
Gliclazide
30 mg
BRISTOL
56 Tablets
PL 17907/0398
POM
Code: BL501
MA Holder:
Bristol Laboratories Ltd.,
Berkhamsted, Herts, HP4 1EG, UK
BRISTOL

Module 5

Scientific Discussion during Initial Procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Zicron PR 30 mg prolonged-release tablets could be approved. This prescription only medicine (POM) is used for the treatment of non insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.

This Decentralised application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a so-called generic application. The reference medicinal product for this application is DIAMICRON 30 mg MR Tablets (PL 05815/0019) which was authorised in the UK to Les Laboratoires Servier on 7 December 2000. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

Gliclazide is a hypoglycaemic sulphonylurea oral antidiabetic 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. In addition to these metabolic properties, gliclazide has haemovascular properties.

No new non-clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the application was based on the product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

Three bioequivalence studies (single dose fed and fasted studies and a multiple dose study) comparing Zicron PR 30 mg prolonged-release tablets with DIAMICRON 30 mg MR Tablets were conducted in support of this application. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

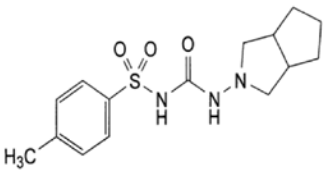
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations 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 of 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.

II QUALITY ASPECTS

ACTIVE SUBSTANCE: GLICLAZIDE

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

Structure:



Molecular formula: $C_{15}H_{21}N_3O_3S$
Molecular weight: 323.4
CAS number: 21187-98-4

General properties
Gliclazide is a white or almost white crystalline powder which is practically insoluble in water, freely soluble in dichloromethane, sparingly soluble in acetone and slightly soluble in ethanol (96%).

All aspects of the manufacture and quality control of the active substance are covered by a European Directorate for the Quality of Medicines & HealthCare Certificate of Suitability.

MEDICINAL PRODUCT: ZICRON PR 30MG PROLONGED-RELEASE TABLETS

Description and composition
Zicron PR 30 mg prolonged-release tablets are white to off white, capsule shaped, biconvex tablets debossed with ‘C12’ on one side and plain on the other side. The tablet dimensions are 10.00 mm x 4.00 mm.

Each prolonged-release tablet contains 30 mg of gliclazide and the excipients lactose monohydrate, maize starch, povidone, hypromellose, colloidal anhydrous silica and magnesium stearate.

All excipients comply with their European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption.

Pharmaceutical development
The aim of the pharmaceutical development was to obtain a generic formulation with a similar *in vitro* dissolution profile and *in vivo* pharmacokinetic performance to the reference product.

Comparative *in vitro* dissolution and impurity profiles have been provided for batches of the test and reference products. The dissolution and impurity profiles were satisfactory.

Manufacture
A satisfactory batch formula has been provided for the manufacture of the medicinal product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Control of medicinal products
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container closure system
The tablets come in clear, PVDC-coated PVC/aluminium blisters packaged in cardboard boxes. Pack sizes of of 7, 10, 14, 20, 28, 30, 56, 60, 84, 90, 100, 112, 120 and 180 tablets have been authorised, although 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 relevant regulations concerning use of materials in contact with food.

Stability
Stability studies were performed on batches of medicinal product in the packaging proposed for marketing and in accordance with current guidelines. The stability data support a shelf-life of 24 months when the storage precaution ‘Do not store above 25°C’ is applied.

Product literature
The SmPC, PIL and labelling are satisfactory from a pharmaceutical perspective.

Marketing Authorisation Application (MAA) forms
The MAA form is satisfactory from a pharmaceutical perspective.

Quality Overall Summary
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

As the pharmacological, pharmacokinetic and toxicological properties of gliclazide are well known, no further non-clinical studies are required and none have been provided.

Non-clinical Overview
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, pharmacokinetics and toxicology.

Environmental Risk Assessment
Since the product is intended for generic substitution, granting of a Marketing Authorisation will not lead to increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Product Literature
The product literature is acceptable from a non-clinical point of view.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

The clinical pharmacology of gliclazide is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamic or pharmacokinetic (PK) data are provided or are required for this application.

Bioequivalence study
To support the application, the applicant submitted the findings of three bioequivalence studies (single dose fasted/fed and multiple dose) described as follows:

(1) A randomised, open label, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of the proposed product and DIAMICRON 30 mg MR Tablets of Les Laboratoires Servier, France in healthy adult human subjects, under fasting condition.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to 72 hours following drug administration. The plasma samples from the subjects were analysed for gliclazide using a validated method.

In all, 44 subjects completed the clinical phase of the study successfully. Plasma samples from the subjects were considered in the PK analysis and the results are presented below.

Results

Parameters (Units)	Ln-transformed Geometric Least Squares Means and it's ratio (N = 44)			Intra subject %CV	90% Confidence Interval	Power
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (µg/mL)	1.068	0.973	109.82%	20.26%	102.20% - 118.01%	99.95%
AUC_{0-t} (hr*µg/mL)	24.986	24.732	101.03%	17.20%	95.02% - 107.41%	100.00%
AUC_{0-inf} (hr*µg/mL)	29.145	29.700	98.13%	16.49%	92.53% - 104.07%	100.00%

(2) A randomised, open label, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of the proposed product and DIAMICRON 30 mg MR Tablets of Les Laboratoires Servier, France in healthy adult human subjects, under fed condition.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to 72 hours following drug administration. The plasma samples from the subjects were analysed for gliclazide using a validated method.

In all, 45 subjects completed the clinical phase of the study successfully. Plasma samples from the subjects were considered in the PK analysis and the results are presented below.

Results

Parameters (Units)	Ln-transformed Geometric Least Squares Means and it's ratio (N = 45)			Intra subject %CV	90% Confidence Interval	Power
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (µg/mL)	1.245	1.172	106.27%	12.23%	101.78% - 110.96%	100.00%
AUC_{0-t} (hr*µg/mL)	28.341	27.720	102.24%	14.39%	97.18% - 107.56%	100.00%
AUC_{0-inf} (hr*µg/mL)	32.991	32.238	102.34%	15.68%	96.84% - 108.15%	100.00%

(3) A randomised, open label, two-treatment, two-period, two-sequence, multiple-dose, crossover, oral bioequivalence study of the proposed product and DIAMICRON 30 mg MR Tablets of Les Laboratoires Servier, France in healthy adult human subjects, under fasting steady-state condition.

Blood samples were collected from each subject in each period at pre-dose and at intervals up to 72 hours following drug administration. The plasma samples from the subjects were analysed for gliclazide using a validated method.

In all, 46 subjects completed the clinical phase of the study successfully. Plasma samples from the subjects were considered in the PK analysis and the results are presented below.

Results

PK Parameters (Units)	Geometric Least Square Mean and It's Ratio			90% CI	Intra-subject CV(%)	Power (%)
	Test Product (T)	Reference Product (R)	(T/R) (%)			
$C_{max,ss}$ (µg/mL)	1.522	1.449	105.10	99.10% - 111.47%	16.91	100.00
$AUC_{0-\tau,ss}$ (hr*µg/mL)	22.190	21.584	102.81	98.01% - 107.85%	13.73	100.00
$C_{min,ss}$ (µg/mL)	0.454	0.451	100.67	94.17% - 107.62%	19.23	99.99

The 90% confidence intervals for AUC and C_{max} were within the acceptance range of 80.00 to 125.00 % in all three studies. Bioequivalence between the test product and reference

product has been adequately demonstrated.

Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for this application.

Clinical Efficacy
No new efficacy data are presented for this application and none are required.

Clinical Safety
With the exception of the data generated during the bioequivalence studies, no new safety data are presented for this application and none are required. No new or unexpected safety issues arose during the bioequivalence studies.

Pharmacovigilance System
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk management plan (RMP)
An RMP has been submitted in accordance with the EU RMP template and is acceptable.

Clinical Overview
A Clinical Overview written by an appropriately qualified physician has been provided and is a satisfactory summary of the clinical aspects of the dossier.

Product Literature
All product literature (SmPC, PIL and labelling) is clinically acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidelines. The labelling is in line with the current guidelines.

Conclusion
The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PILs for Metformin Tablets 850mg (PL 11311/0096) and Gliclazide 40mg tablets (PL 17907/0067). The bridging report submitted by the applicant has been found acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Zicron PR 30 mg prolonged-release tablets are well defined and controlled. The specifications and batch analytical results indicate consistency

from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

CLINICAL
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. Bioequivalence has been demonstrated between Zicron PR 30 mg prolonged-release tablets and DIAMICRON 30 mg MR Tablets.

With the exception of the data from the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. As the safety profile of gliclazide is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are in line with those for the reference product and current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with gliclazide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome