CBG MEB

Public Assessment Report

Scientific discussion

Gliclazide Ranbaxy 60 mg, modified-release tablets

(gliclazide)

NL/H/3853/001/DC

Date: 11 October 2016

This module reflects the scientific discussion for the approval of Gliclazide Ranbaxy 60 mg, modified-release tablets. The procedure was finalised on 19 February 2015 with the United Kingdom as RMS (UK/H/5466/001/DC). The current RMS is the Netherlands (NL/H/3853/001/DC). For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gliclazide Ranbaxy 60 mg, modified-release tablets from Ranbaxy (UK) Ltd.

The product is indicated 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the Diamicron 60 mg modified-release tablets, registered by Les Laboratoires Servier. The originator product is Diamicron 80 mg tablets (NL license RVG 06702) authorised to Servier Nederland Farma B.V since 1974.

The RMS of the initial procedure was the United Kingdom, and the concerned member states (CMS) were France, Italy, the Netherlands, Poland, Romania and Spain. The role of RMS was transferred to the Netherlands on 22 June 2016. Consequently, the MA in the UK was withdrawn.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

This product is a modified-release tablet and contains 60 mg gliclazide, as active ingredient. It is a white to off white oval-shaped tablet, scored on both sides, engraved with ‘Z’ and ‘I’ on one side and plain on the other side. The tablet can be divided into equal doses.

The excipients present are pregelatinised maize starch, lactose monohydrate, sodium citrate (E331), hypromellose (E464) and magnesium stearate.

The finished product is packaged either in oriented polyamide/aluminium/polyvinylchloride aluminium (OPA/AL/PVC/Al) blister packs, polyvinylchloride/polyethylene/polyvinylidenechloride/aluminium (PVC/PE/PVdC/Al) blister packs or high density polyethylene (HDPE) bottles. The bottle is made of an absorbent cotton with child resistant closure and induction seal liner.

II.2 Drug Substance

The active substance is gliclazide, an established active substance, described in the European Pharmacopoeia. Gliclazide is a white to almost white powder, which is practically insoluble in water, freely soluble in dichloromethane, sparingly soluble in acetone and slightly soluble in ethanol. There are no known polymorphs and the drug substance has no chiral centres.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specifications ensure compliance with the Ph. Eur. monograph. A specification for drug substance particle size is additionally included in the specification adopted by the drug product manufacturer.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The objective of the development programme was to formulate safe, efficacious, modified-release tablets containing 60 mg gliclazide that are bioequivalent to the reference product Diamicron 60 mg modified release Tablets (Les Laboratoires Servier Industrie, France).

Comparative dissolution and impurity profiles have been presented for the proposed and reference products.

Manufacturing process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation on future full scale production batches will be performed post authorisation.

Control of excipients
All excipients used comply with their respective European Pharmacopoeia monographs.

Quality control of drug product
The finished product specification is 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 of drug product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing. A photostability study has been performed. The product is not susceptible to light.
Based on the results of the stability studies, shelf-lives of 21 months for blister packs and 100 days after opening the bottle pack with a storage condition “store below 30°C” are set. These are satisfactory.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gliclazide Ranbaxy 60 mg, modified-release tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Gliclazide Ranbaxy is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Diamicron, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Gliclazide is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted bioequivalence studies in which the pharmacokinetic profile of the test product Gliclazide Ranbaxy 60 mg (Ranbaxy (UK) Ltd) is compared with the pharmacokinetic profile of the reference product Diamicron 60 mg modified-release tablets (Les Laboratoires Servier, France).
One single dose study under fasted conditions, one single dose study under fed conditions and one multiple dose study under fed conditions were conducted.

The choice of the reference product is appropriate as it is approved in the Community for more than ten years.

Bioequivalence studies

Study TR-025-GLICL-12
Design
This was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose crossover bioequivalence study comparing the pharmacokinetics of the test product Gliclazide 60 mg modified release Tablets (Ranbaxy Laboratories Limited, India) with the reference product Diamicron modified release Tablets (Les Laboratoires Servier Industrie, France) in 41 healthy adult subjects, under fasting conditions.

The blood samples were collected pre-dose and at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 11.50, 12.00, 12.50, 13.00, 13.50, 14.00, 15.00, 16.00, 20.00, 24.00, 36.00, 48.00, 72.00 and 96.00 hours post-dose in each period, from each subject. The two dosing periods were separated by a wash-out period of 21 days.

Result

Ratios of LSM for (ln) transformed pharmacokinetic parameters for Gliclazide (90% Confidence Interval)

Parameter	Gliclazide Test (T) vs. Reference (R)
lnC_{max}	104.58% (96.42% – 113.42%)
ln AUC_{0-t}	99.55% (96.21% – 103.01%)
ln $AUC_{0-\infty}$	99.43% (96.16% - 102.81%)

Study TR-026-GLICL-12

Design

This was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose crossover bioequivalence study comparing the pharmacokinetics of the test product Gliclazide 60 mg modified release Tablets (Ranbaxy Laboratories Limited, India) with the reference product Diamicron modified release Tablets (Les Laboratoires Servier Industrie, France) in 23 healthy adult subjects, under fed conditions.

The study design was similar to the fasting study TR-025-GLICL-12. In this case, however, subjects fasted overnight for at least 10 hours prior to consuming a high fat high-fat breakfast 30-minute prior to drug dosing in each study period. A wash out period of 21 days was maintained between periods.

Result

Ratios of LSM for (ln) transformed pharmacokinetic parameters for Gliclazide (90% Confidence Interval)

Parameter	Gliclazide Test (T) vs. Reference (R)
lnC_{max}	99.04% (93.17% – 105.28%)
ln AUC_{0-t}	97.43% (93.13% – 101.93%)
ln $AUC_{0-\infty}$	97.78% (93.48% - 102.27%)

TR-027-GLICL-12

This was an open label, balanced, randomized, two-treatment, two-period, two-sequence, multiple-dose crossover bioequivalence study comparing the pharmacokinetics of the test product Gliclazide 60 mg modified release Tablets (Ranbaxy Laboratories Limited, India) with the reference product Diamicron 60 mg modified release Tablets (Les Laboratoires Servier Industrie, France) in 25 healthy adult subjects, under fed conditions.

Subjects received a standardized high-fat, high-calories breakfast on 7 consecutive days in each period of the study. Following an overnight fast, of at least 10 hours, subjects started the recommended breakfast (high-fat, high-calorie) 30 minutes prior to administration of the drug product on each day.

Blood samples were collected at predose [on days 01-07 (in double volume on day 01)] and on day 07 at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 11.00, 12.00, 13.00, 14.00, 15.00, 16.00, 20.00 and 24.00 hours post-dose in each period. The two treatment periods were separated by a washout period of 15 days.

Result

Ratios of LSM for (ln) transformed pharmacokinetic parameters for Gliclazide (90% Confidence Interval)

Parameter	Gliclazide Test (T) vs. Reference (R)
ln $[C_{max}]_{ss}$	97.86% (92.59% – 103.44%)
Ln C_{min}	99.39% (94.68% - 104.33%)
ln AUC_{0-tau}	98.52% (95.97% - 101.15%)

Conclusion on bioequivalence studies

Based on the submitted bioequivalence studies Gliclazide Ranbaxy 60 mg is considered bioequivalent with Diamicron 60 mg modified-release tablets according to the Note for Guidance on Modified Release Oral and Transdermal Dosage Forms Section II (Pharmacokinetic and Clinical evaluation (CPMP/EWP280/96)) and Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/ 1401/98 Rev. 1. The formulations are bioequivalent with respect to rate and extent of absorption under fasted and fed conditions, as well as at steady state.

The Member States have been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The 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 Gliclazide Ranbaxy.

Summary table of safety concerns

Summary of safety concerns	
Important identified risks	**1. Hypoglycaemia** **2. Use in patients with hepatic insufficiency** **3. Use in patients with severe renal insufficiency** **4. Secondary failure** **5. Haemolytic anaemia if used in patients with G 6PD-deficiency** **6. Use in patients with lactose/galactose intolerance of or glucose-galactose malabsortion** **7. Interactions leading to hypoglycemia:** • *Miconazole, fluconazole,* • *Phenylbutazone and other nonsteroidal anti-inflammatory agents.* • *Alcohol* • *antidiabetic agents (insulins, acarbose, metformin, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, GLP-1 receptor agonists)* • *beta-blockers,* • *angiotensin converting enzyme inhibitors (captopril, enalapril),* • *H2-receptor antagonists* • *MAO inhibitors,* • *Sulphonamides* **8. Interactions leading to hyperglycemia:** • *Danazol* • *Chlorpromazine* • *Glucococorticoids* • *Ritodrine, salbutamol, terbutaline* **9. Interaction leading to potentiation of anticoagulation:** • *anticoagulant therapy (warfarin)*
Important potential risks	**None**
Missing information	**10.Use during pregnancy and lactation** **11.Use in pediatric population**

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Diamicron. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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, as amended. The language used for the purpose of user testing the PL 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

Gliclazide Ranbaxy 60 mg has a proven chemical-pharmaceutical quality and is a generic form of Diamicron 60 mg modified-release tablets. Diamicron is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gliclazide Ranbaxy 60 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 February 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the batch size (including batch size ranges) of the finished product.	UK/H/5466/ 001/IB/001	IB	9-9-2015	22-15-2015	Approval	No
Change in the name of the finished product manufacturer.	UK/H/5466/ 001/IA/002	IA	18-11-2015	8-12-2015	Approval	No
Addition of a bioequivalence study in support of the subdivisibility of the 60 mg modified release tablets to provide a 30 mg dose and to add a new specification parameter to the specification with its corresponding test method.	UK/H/5466/ 001/II/003/ G	II/G	14-1-2016	16-6-2016	Approval	No
Transfer RMS from the United Kingdom to the Netherlands; UK/H/5466/DC -> NL/H/3853/DC	--	Transfer RMS	--	22-6-2016	Approval	No