CBG MEB

Public Assessment Report

Scientific discussion

Gliclazide Sandoz retard 60 mg, modified-release tablets

(gliclazide)

NL/H/3384/001/DC

Date: 19 January 2017

This module reflects the scientific discussion for the approval of Gliclazide Sandoz retard 60 mg, modified-release tablets. The procedure was finalised on 16 December 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Sandoz retard 60 mg, modified-release tablets from Sandoz B.V.

The product is 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.

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 innovator product Diamicron 60 mg, modified-release tablets (NL Licence RVG 102828) which has been registered in The Netherlands by Les Laboratoires Servier since 30 June 2010.

The concerned member states (CMS) involved in this procedure were Belgium, Bulgaria, Czech Republic, Estonia, France, Croatia, Hungary, Italy, Lithuania, Luxembourg, Latvia, Poland, Portugal, Slovenia and the Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Gliclazide Sandoz retard is a white to off-white, oval shaped modified-release tablet with a break line on both sides and debossed with '60' on one side of the break line on one surface. Each tablet contains 60 mg gliclazide and can be divided in equal doses of 30 mg.

The modified-release tablets are packed in clear PVC-Al blisters or clear PVC/Aclar-Al blisters.

The excipients are: calcium hydrogen phosphate dihydrate, povidone K30, hypromellose K100, hypromellose K4M and magnesium stearate.

II.2 Drug Substance

The active substance is gliclazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder and practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol (96%). The drug substance is not hygroscopic, there are no known polymorphs and it 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 Ph.Eur.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 6 production scale batches.

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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. It was adequately demonstrated that the tablet can be divided in two equal halves. The formulation development has been adequately described.

The product development objective was to develop a tablet that would be bioequivalent to the French innovator product Diamicron. Dissolution profiles demonstrate dissimilarity between test and reference products *in vitro* due to the matrix release mechanisms. This is accepted as per bioequivalence guideline CPMP /QWP/EWP/1401/98 Rev.1 it is stated that 'In the event that the results of comparative *in vitro* dissolution of the biobatches do not reflect bioequivalence as demonstrated *in vivo* the latter prevails'. Hence successful bioequivalence has been demonstrated.

Manufacturing process
The manufacturing process consists of a wet granulation followed by compression. Since the drug product is a modified-release tablet the process is non-standard. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 pilot scaled batches without and 3 with break line, and 3 production scaled batches, from the proposed production sites have been provided, demonstrating compliance with the specification. in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. including additional tests and limit. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, loss on drying, uniformity of dosage units, dissolutions, assay, degradation products and microbial enumeration. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 pilot scaled batches without and 3 with break line and 3 production scaled batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data of the product have been provided from three pilot scaled batches of tablets without break line stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) and three pilot scaled batches of tablets with break line stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are in accordance with applicable European guidelines. The batches were stored in the proposed packages. All observed trends remained within specifications. Furthermore, it was demonstrated that the product is photo stable and not sensitive to moisture. Based on these results, the proposed shelf-life of 24 months and storage condition 'Store below at 25°C' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gliclazide Sandoz retard 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 Sandoz retard 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 three bioequivalence studies in which the pharmacokinetic profile of the test product Gliclazide Sandoz retard 60 mg modified-release tablets (Sandoz B.V., The Netherlands) 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. This is in compliance with the requirements for modified-release formulations according to the European guideline (NfG CPMP/EWP/QWP 1401/98).

The test and reference products are considered acceptable. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I: Single-dose under fasted conditions

Design

A single-dose, balanced, open-label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-45 years. Each subject received a single dose (60 mg) of one of the 2 gliclazide formulations. The tablet was orally administered with 240 ml 20% glucose solution after an overnight fast of at least 8 hours. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The design of the bioequivalence study is adequate in relation to characterisation of the pharmacokinetics of gliclazide after oral administration. The absorption, distribution and elimination phases are all well characterised. The washout period of 10 days is considered adequate as gliclazide has an elimination half-life of 12-20 hours (about 17 hours in the actual study). The study medication was administered with a 20% glucose solution in water, which is considered justified in order to avoid hypoglycaemia.

Results

Of all 28 subjects, one subject voluntarily withdrew his consent, one was withdrawn due to missed blood draws, one was withdrawn due to a positive alcohol breath test and one did not return in between periods. Three subjects did not have three consecutive measurable concentrations and were excluded from the study. Therefore, 21 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gliclazide under fasted conditions.

Treatment N=21	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h
Test	62.3 ± 25.6	65.1 ± 27.9	1.91 ± 0.53	12 (5 - 24)
Reference	60.2 ± 25.1	62.9 ± 27.2	1.98 ± 0.57	11 (6 – 12)
***Ratio (90% CI)**	1.05 (0.94 – 1.17)	0.99 (0.86 – 1.14)	--	--
CV (%)	20.1	27.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II: Single-dose under fed conditions

Design

A single-dose, balanced, open-label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 20-39 years. Each subject received a single dose (60 mg) of one of the 2 gliclazide formulations. The tablet was orally administered with 240 ml 20% glucose solution in water after an overnight fast of at least 8 hours followed by a standard high fat high caloric breakfast 30 minutes before dosing. The breakfast consisted of milk, one egg, and cheese, chicken, bread and butter (57 g fat, 48 g protein and 950 kcal). There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 2, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, 48, 72, 96 and 120 hours after administration of the products.

The design of the bioequivalence study is adequate in relation to characterisation of the pharmacokinetics of gliclazide after oral administration. The washout period is considered adequate as gliclazide has an elimination half-life of 12-20 hours (about 21 hours in the actual study). Administration with a 20% glucose solution in waters is justified in order to avoid hypoglycaemia.

Results

Of all 28 subjects, two subjects were withdrawn due to an adverse event, one subjects was withdrawn due to a positive urine scan for drug abuse, one subject was withdrawn due to four missed consecutive blood draws and one subject voluntarily withdrew his consent. Therefore, 23 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gliclazide under fed conditions.

Treatment N=23	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h
Test	69.4 ± 23.9	71.9 ± 26.6	2.85 ± 0.54	8 (4 – 16)
Reference	71.5 ± 27.5	74.2 ± 29.7	2.85 ± 0.65	8 (4 – 16)
***Ratio (90% CI)**	0.98 (0.93 – 1.03)	--	1.01 (0.93 – 1.09)	--
CV (%)	10.0	--	15.3	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
CV coefficient of variation

**ln-transformed values*

Bioequivalence study III: Multiple-dose under fed conditions

Design

A multiple-dose, two-way cross-over crossover bioequivalence study was carried out under fed conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (60 mg) of one of the 2 gliclazide formulations on a daily basis for 7 days. The tablets were orally administered with 240 ml 20% glucose solution in water after an overnight fast of at least 8 hours followed by a standard high fat high caloric breakfast 30 minutes before dosing. The breakfast was an Indian meal (24 g fat, 20 g protein and 576 kcal). Standard meals were provided on check-in day and at scheduled time at around -0.5, 5, 8 and 12 hours (day 1-7) and 24 hours post dose on day 8. The washout period was 14 days between periods.

The design of the bioequivalence study is adequate in relation to characterisation of the pharmacokinetics of gliclazide after oral administration. The washout period of 21 days is considered adequate as gliclazide has an elimination half-life of 12-20 hours (about 13 hours in the actual study). The composition of the breakfast is in accordance with the guideline requirements.

Results
Of all 36 subjects, one subject was withdrawn as he tested positive in an urine scan for drug abuse (marijuana). Therefore, 35 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD) of gliclazide after multiple doses under fed conditions

Treatment N=35	**AUC_τ** µg/ml/h	**C_{max}** µg/ml	**C_{min}** µg/ml	**PTF** %
Test	66.9 ± 20.7	4.16 ± 1.15	1.55 ± 0.65	97.6 ± 24.9
Reference	69.2 ± 21.2	4.43 ± 1.15	1.61 ± 0.88	1.03 ± 0.24
***Ratio (90% CI)**	0.97 (0.93 – 1.00)	0.93 (0.89 – 0.98)	0.97 (0.92 - 1.02)	--
CV (%)	8.75	12.7	--	--

AUC_τ area under the plasma concentration-time curve over the dosing interval
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF fluctuation index
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} after single dosing and for AUC_τ, C_{max} and C_{min} after multiple dosing are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Gliclazide Sandoz retard 60 mg is considered bioequivalent with Diamicron 60 mg.

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 Sandoz retard.- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypoglycaemia - Haemolytic anaemia
Important potential risks	None
Missing information	- Use during pregnancy and lactation - Use in paediatric 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 a

bioequivalence study 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Gliclazide Sandoz retard 30 mg, modified-release tablets (NL/H/1700-1701-1702/001). Differences in wording and word order in the proposed package leaflet as compared to already tested and approved package leaflet are mainly due to the new QRD template and due to the alignment with the package leaflet of Diamicron 60 mg tablets (reference product). These differences do not affect readability. The bridging report submitted has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gliclazide Sandoz retard 60 mg, modified-release tablets 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.

The Board followed the advice of the assessors.

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 Sandoz retard with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 December 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