CBG MEB

Public Assessment Report

Scientific discussion

Gliclazide Sandoz 30 mg, modified-release tablets

NL/H/3108/001/DC

Date: 16 February 2016

This module reflects the scientific discussion for the approval of Gliclazide Sandoz 30 mg, modified-release tablets. The procedure was finalised on 13 May 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

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 Sandoz 30 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 30 mg modified-release tablets (NL License RVG 25617) which has been registered by Les Laboratoires Servier in the Netherlands since 13 April 2001 by procedure FR/H/0171/001/MR.

The concerned member states (CMS) involved in this procedure were Belgium, Croatia, Czech Republic, Estonia, Greece, Hungary, Italy, Luxembourg, Portugal, Slovenia and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Gliclazide Sandoz 30 mg is a white to off-white, capsule shaped, biconvex uncoated tablets debossed '30' on one side and plain on the other side.

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

The excipients are: calcium hydrogen phosphate dihydrate, povidone (E1201), hypromellose (E464), magnesium stearate (E572).

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 methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol. 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 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 specification is in line with the Ph.Eur. and the CEP. An additional test for residual solvents is included. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data have been provided for three batches, demonstrating compliance with the current drug substance specification.

Stability of drug substance
The active substance is stable for 5 years if 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 development of the product has been described, the choice of excipients is justified and their functions explained. The product development objective was to develop a tablet that would be bioequivalent to the French innovator product Diamicron. A wet granulation method was chosen and optimised during pharmaceutical development. A bioequivalence study was carried out and supportive in-vitro dissolution studies in 5 different media were performed.
Manufacturing process development has been adequately described. The packaging material is commonly used for solid oral dosage forms. The suitability of the packaging material was tested in stability studies.

Manufacturing process
The manufacturing process consists of wet granulation, followed by compression and packaging, which are regarded as conventional manufacturing techniques. The manufacture of the specialised modified-release dosage form is however defined as a non-standard process, requiring process validation on production scale batches. Six batches have been adequately validated.

Control of excipients
All excipients comply with the European Pharmacopoeia. As pharmacopoeial methods are used, validation of the analytical procedures is not deemed necessary.

Quality control of drug product
The drug product specification includes tests for description, identification, water content, uniformity of dosage units, dissolution, assay, related substances and microbial contamination. Release and shelf-life limits for description, identification, uniformity of dosage units, dissolution and microbial quality are identical. The drug product specification is acceptable.
The analytical methods were adequately described. Satisfactory validation data for the analytical methods have been provided. Batch analytical data were provided for three batches, demonstrating compliance with the specification.

Stability of drug product
Stability data on the drug product was provided on three pilot-scale batches stored at 25°C/60% (24 months), 30°C/65% (12 months) and 40ºC/75% RH (6 months). The batches were stored in the proposed commercial packaging.
The conditions used in the stability studies are according to the ICH stability guideline. Furthermore a photostability study has been performed. The product is not susceptible to light.
Based on the stability data provided the proposed shelf life of 24 months if stored below 25°C can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies
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 30 mg 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 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 Sandoz 30 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Diamicron 30 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 in the bioequivalence study has been justified. 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 study I – single dose, fasted conditions

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 20-43 years. Each subject received a single dose (30 mg) of one of the 2 gliclazide formulations. The tablet was orally administered with 240 ml of 20% glucose solution in water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 10 days.

Blood samples were collected pre-dose and at 2.0, 3.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products.

The design of the bioequivalence study is adequate in relation to characterization of the pharmacokinetics of gliclazide after oral administration. The absorption, distribution and elimination phases are all well characterized. 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
One subject was withdrawn as he did not report to the facility on check-in day for period II, and one subject was discontinued from the study on medical ground as he had fever on check-in day of period II. Twenty-six subjects completed the study and were used for the pharmacokinetic and statistical analysis.

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

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	21567 ± 9572	22591 ± 10476	769 ± 231	7.8 (4.0-24)	17.6 ± 6.1
Reference	21733 ± 9466	22554 ± 10169	792 ± 203	8.3 (6.0-16)	17.8 ± 6.4
***Ratio (90% CI)**	0.99 (0.93-1.06)	1.00 (0.93-1.07)	0.96 (0.86-1.06)	--	--
CV (%)	14.6	14.5	22.1	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Safety
A total of two mild adverse events were reported during the entire study, both during period I. One subject had eosinophilia in post study safety assessment. Another subject had pyrexia on during check-in day of period II.

- <u>Bioequivalence study II – single dose, fed conditions</u>

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 28 healthy male subjects, aged 18-44 years. After an overnight fast of at least 10 hours and within 30 minutes after serving a high-fat, high calorie breakfast the subjects were administered a single 30 mg dose of the study medication with 240 ml of 20% glucose solution in water. The meal derives 287.6 kcal from carbohydrate, 538.65 kcal from fat and 150.08 kcal from protein. The total caloric content is 976.33 kcal. There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 2.0, 3.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 16.0, 24.0, 36.0, 48.0, 72.0, 96.0 and 120.0 hours after administration of the products.

The design of the bioequivalence study is adequate in relation to characterization 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
Tow subjects were discontinued on medical ground (vomiting), one after dosing of period I, an the other after dosing of period II. Twenty-six subjects completed the study and were used for the pharmacokinetic and statistical analysis.

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

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	27286 ± 11623	29006 ± 13398	1082 ± 220	7.0 (5.0-12)	21.7 ± 10.0
Reference	24426 ± 9490	26628 ± 11015	1009 ± 192	7.0 (4.0-12)	21.8 ± 11.5
***Ratio (90% CI)**	1.10 (1.02-1.19)	1.07 (1.02-1.13)	1.07 (1.02-1.12)	--	--
CV (%)	15.5	10.3	10.2	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Safety
A total of 2 adverse events were reported by 2 subjects during the study. Both occurred after administration of the test product. One had vomiting after dosing of period I and the other had vomiting after dosing of period II. Both adverse events were of mild intensity and possibly related to the study medication.

- Bioequivalence study III – multiple dose, fed conditions

Design
A multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 32 healthy male subjects, aged 19-44 years.
After an overnight fast of at least 10 hours on day 01 to 05 subjects were served a standardised high-fat, high calorie breakfast about 30 minutes prior to administration of a single 30 mg dose of the study medication with 240 ml of 20% glucose solution in water. Standardized meal was served after 4 hours of dosing, snacks after 8 hours of dosing and dinner after 12 hours of dosing. The composition of the high-fat breakfast is presented in the study protocol. The meal derives 287.6 kcal from carbohydrate, 538.65 kcal from fat and 150.08 kcal from protein. The total caloric content is 976.33 kcal.
There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose (within 5 minutes prior to each dosing) on each day (Day 1 to Day 5) and on day 5 at 2.0, 3.0, 4.0, 5.0, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 11.0, 12.0, 16.0 and 24.0 hours post administration of a single-dose 30 mg modified release tablet for the analyses of gliclazide.

The design of the bioequivalence study is adequate in relation to characterization 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
A total of 32 subjects were dosed in the study while 28 subjects completed the study and were used for the pharmacokinetic and statistical analysis. One subject was discontinued on medical ground (vomiting) after day 02 dosing of period I. A second subject was discontinued on medical ground (vomiting) after day 03 dosing of period I. Another subject was discontinued on medical ground as he had an adverse event (stomatitis) on check in day of period II. A fourth subject was discontinued on his own accord, as he withdrew his consent for further participation in the study (did not report to facility on check-in day of period II).

Table 3. Pharmacokinetic parameters in steady state (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gliclazide after multiple doses under fed conditions.

Treatment N=28	**$AUC_{0-\tau,ss}$** ng/ml/h	**$C_{max,ss}$** ng/ml	**$C_{min,ss}$** ng/ml	**PTF** %
Test	25406 ± 12404	1850 ± 657	553 ± 380	72
Reference	24712 ±12493	1742 ± 606	569 ± 425	70
***Ratio (90% CI)**	1.03 (1.01-1.06)	1.06 (1.03-1.09)	1.00 (0.96-1.05)	-
CV (%)	4.7	6.0	9.4	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-\tau}$ area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
C_{min} minimum plasma concentration
PTF% fluctuation index
CV coefficient of variation

**ln-transformed values*

Safety
A total of six adverse events were reported during the entire study. Three adverse events were reported during period I and three adverse events were reported during post study safety assessment. All these events were considered mild. One of the subjects had vomiting after day 2 of dosing of period I and another person after day 3 dosing of period I; both occurred after administration of the reference product. These two events were declared as possibly related to the study medication. One subject had stomatitis on check-in day of period II. The event was declared as not related to the study medication.

Conclusion on bioequivalence studies
Based on the submitted bioequivalence studies Gliclazide Sandoz 30 mg is considered bioequivalent with Diamicron 30 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 MEB has 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 Sandoz.

Summary of safety concerns	
Important identified risks	Hypoglycemia
	Haemolytic anemia
Important potential risks	None
Missing information	Use during pregnancy and lactation
	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 has not been evaluated via a user consultation study. The MAH submitted a bridging statement referring to the already tested and approved package leaflet of another Sandoz product Gliclazide 30 mg modified release tablet (NL/H/1700-1701-1702/001/DC) and to the user-tested Sandoz house style. The member states agree that a separate user test is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gliclazide Sandoz 30 mg has a proven chemical-pharmaceutical quality and is a generic form of Diamicron 30 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 30 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 May 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