Public Assessment Report

Scientific discussion

Gliclazid “Sigillata”

30 mg and 60 mg modified-release tablets

(Gliclazide)

DK/H/2377/001-002/DC

22 August 2016

This module reflects the scientific discussion for the approval of Gliclazid ”Sigillata”. The procedure was finalised on 24 March 2015. For information on changes after this date please refer to the module ‘Update’.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gliclazid "Sigillata" 30 mg and 60 mg modified-release tablets, from Sigillata Ltd.

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.

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 increasing the secretory potential of pancreatic β-cells in the islets of Langerhans. Increase in postprandial insulin and C-peptide secretion persists after two years of treatment.
In type 2 diabetics, gliclazide restores the first peak of insulin secretion in response to glucose and increases the second phase of insulin secretion. A significant increase in insulin response is seen in response to stimulation induced by a meal or glucose. In addition liclazide decreases microthrombosis by two mechanisms which may be involved in complications of diabetes:
- A partial inhibition of platelet aggregation and adhesion, with a decrease in the markers of platelet activation (beta thromboglobulin, thromboxane B2).
- An action on the vascular endothelium fibrinolytic activity with an increase in tPA activity.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Diamicron 30 mg and 60 mg modified-release tablets which has been registered by Les Laboratoires Servier since 2000 in France. In Denmark the reference product is Diamicron Uno 30 mg and 60 mg modified-release tablets, Les Laboratoires Servier, registered since 2001 and 2009, respectively. Since the reference product is not authorised in all Concerned Member States in both strengths, some Concerned Member States make reference to the reference product authorised in Denmark (European Reference Product).

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

II. QUALITY ASPECTS

II.1 Introduction

Each modified-release tablet contains 30 mg or 60 mg gliclazide.

The 30 mg modified-release tablets are white, oval, biconvex 5 x 11 mm tablets marked "G" on one side.
The 60 mg modified-release tablets are white, oval, biconvex 7 x 15 mm tablets scored on both sides, marked with "G" on one side of the score and "60" on the other side of the score. The tablets can be divided into equal doses.

The product is supplied in PVC/PVDC/Al blisters, PVC/PVDC/PVC/Al blisters and white HDPE containers closed with LDPE caps (for Duma) or PP caps (for Duma Twist-off).

The following pack sizes have been authorised:
Blisters: 10, 14, 30, 60, 90, 120 modified-release tablets.
Containers: 90, 100, 120 modified-release tablets.
However, not all pack sizes may be marketed.

The tablets contain: Lactose monohydrate; Hypromellose; Cellulose, microcrystalline; Silica, colloidal anhydrous and Magnesium stearate.

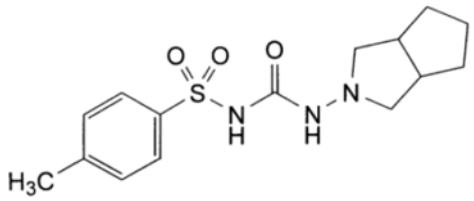
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance gliclazide is described in the European Pharmacopoeia. It is a white or almost white powder. It is practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, and slightly soluble in ethanol (96 per cent).

The chemical name is: 1-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-3-[(4-methylphenyl)sulphonyl]urea

The molecular structure is:



The molecular formula of gliclazide is $C_{15}H_{21}N_3O_3S$ and the molecular weight is 323.4.

Two active substance manufacturers are involved in the manufacture of the active substance; both manufacturers have obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The finished product manufacturer has presented an active substance specification in accordance with the Ph.Eur. monograph and additional requirements stated in the CEPs.

Certificates of analysis of the active substance from active substance source carried out by the finished product manufacturer as well as the respective ASMs have been provided and results comply with the specifications.

Re-test periods are according to the CEP or based on presented stability studies.

II.3 Medicinal Product

The formulation and manufacturing development of laboratory to pilot scale batches have been described.
Validation protocols and validation data have been presented. A flow chart of the manufacturing process including in-process controls has been provided.
All excipients are monographed in the European Pharmacopoeia.

The release and shelf-life specifications are acepted. The methods are described and validated.

Stability data are provided. A shelf-life of 18 months and storage condition “Do not store above 25°C” was accepted for all applied container closure systems.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of gliclazide are well known. As gliclazide is a widely used well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers several publications up to year 2008. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of gliclazide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

IV. CLINICAL ASPECTS

IV.1 Introduction

Gliclazide is a well-known active substance with established efficacy and tolerability. As gliclazide is a widely used, well-known active substance, the MAH has not provided additional studies (apart from supportive bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers several publications up to year 2010. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Bioequivalence studies
A total of 4 bioequivalence studies have been carried out in support of the application. 3 studies were performed with the 60 mg strength and 1 was performed with the 30 mg strength. The following studies were presented:
- Single-dose fasting conditions (60 mg)
- Single-dose fed conditions (60 mg)
- Steady state (60 mg)
- Single-dose fasting conditions (30 mg)

Biowaiver
The application concerns two dosage strengths, 30 mg and 60 mg. Bioequivalence studies (single-dose fed/fasted and steady state) have been carried out with the 60 mg strength and a single dose study (fasted) has also been carried out with the 30 mg strength.
Waiver is therefore applied for the 30 mg strength - fed and steady state. Waiver of a single dose study (with 30 mg strength) under fed conditions and a steady state study is considered adequately justified.

Single-dose study under fasting conditions (60 mg)
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 16 days between the two administrations. 60 mg was administered in each period.

Gliclazid ”Sigillata” 60 mg modified-release tablets was compared to Diamicron Uno 60 mg modified-release tablets of Les Laboratoires Servier, France, from the German market.

36 healthy South Asian male subjects (20-41 years) participated in the study. 31 subjects completed the study and were included in the PK analysis and statistical analysis.

Primary pharmacokinetic variables were: AUC_{0-t} and C_{max}.

The 90% confidence interval for the ratio of test and reference products, based on the results obtained from the ANOVA on log-transformed AUC_{0-t} and C_{max} for gliclazide should be at least 80.00% and not more than 125.00% in order to conclude bioequivalence.

Results

Table 1. Summary of Pharmacokinetic data

Gliclazide Diamicron Uno® (Reference Product)

Pharmacokinetic parameter	Geomelric mean	Arithmetic mean	Standard deviation
AUC0-$_t$ (µg.h/mL)	60.61	64.45	22.920
Cmax (µg/mL)	2.04	2.10	0.547

Gliclazide (Test Product)

Pharmacokinetic parameter	Geomelric mean	Arithmetic mean	Standard deviation
AUC0-$_t$ (µg.h/mL)	62.46	65.43	20.361
Cmax (µg/mL)	2.28	2.35	0.606

Table 2. Ratio and 90% Confidence Intervals of test Product versus Reference Product

Pharmacokinetic parameter	Ratio(%)	90% Confidence Intervals		Intra Subject Variabilily (%)
		Lower90% CI(%)	Upper90% CI(%)	
AUC0-$_t$	102.79	95.39	110.77	17.37
Cmax	111.52	103.43	120.24	17.49

Based on the results obtained, Gliclazid ”Sigillata” 60 mg modified-release tablets and Diamicron Uno 60 mg modified-release tablets of Les Laboratoires Servier, France, are considered bioequivalent in healthy adult subjects, under fasting conditions. Both the test and reference product were found to be safe and well tolerated.
In the single dose study the 90% confidence interval for the difference between the Test and the Reference formulation least-squares means for the log-transformed parameters AUC_{0-t} and C_{max} were within the 80.00-125.00% acceptance range for demonstrating bioequivalence.

Single-dose study under fed conditions (60 mg)
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fed conditions with a wash out period of 16 days between the two administrations. 60 mg was administered in each period.

Gliclazid ”Sigillata” 60 mg modified-release tablets was compared to Diamicron Uno 60 mg modified-release tablets of Les Laboratoires Servier, France, from the German market.

36 healthy South Asian male subjects (18-38 years) participated in the study.
The pharmacokinetic and statistical analysis was done on 33 subjects.

Primary pharmacokinetic variables were: AUC_{0-t} and C_{max}.

The 90% confidence interval of the test/reference ratio (difference in least square means) from the ANOVA of the log-transformed AUC_{0-t} and C_{max} for gliclazide should be at least 80.00% and not more than 125.00% in order to conclude bioequivalence.

Results

Table 3. Summary of Pharmacokinetic data

Gliclazide Diamicron Uno® (Reference Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (µg.h/mL)	64.48	68.43	24.108
C_{max} (µg/mL)	2.78	2.85	0.611

Gliclazide (Test Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (µg.h/mL)	65.60	69.96	25.379
C_{max} (µg/mL)	3.09	3.16	0.682

Table 4. Ratio and 90% Confidence Intervals of test Product versus Reference Product

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals		Intra Subject Variability (%)
		Lower 90% CI (%)	Upper 90% CI (%)	
AUC_{0-t}	103.23	99.74	106.85	8.11
C_{max}	110.79	105.23	116.64	12.37

Based on the results obtained, Gliclazid ”Sigillata” 60 mg modified-release tablets and Diamicron Uno 60 mg modified-release tablets of Les Laboratoires Servier, France, are considered bioequivalent in healthy adult subjects, under fed conditions. Both the test and reference product were found to be safe and well tolerated.
In the single dose study the 90% confidence interval for the difference between the Test and the Reference formulation least-squares means for the log-transformed parameters AUC_{0-t} and C_{max} were within the 80.00-125.00% acceptance range for demonstrating bioequivalence.

<u>Multiple-dose study under fasting conditions (60 mg)</u>
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, multiple-dose bioavailability study conducted under fasting conditions with a wash out period of 8 days between the two administrations. 60 mg was administered in 7 days in each period.

Gliclazid ”Sigillata” 60 mg modified-release tablets was compared to Diamicron Uno 60 mg modified-release tablets of Les Laboratoires Servier, France, from the German market.

36 healthy South Asian male subjects (22-44 years) participated in the study. 31 subjects completed the study and 31 were analysed in PK and statistical analysis.

Primary pharmacokinetic variables were: $C_{max(ss)}$, $C_{min(ss)}$ and $AUC_{0-\tau(ss)}$.

The 90% confidence interval of the test/reference ratio (difference in least square means) from the ANOVA of the log-transformed $C_{max(ss)}$, $C_{min(ss)}$, and $AUC_{0-\tau(ss)}$ for gliclazide should be at least 80.00% and not more than 125.00% in order to conclude bioequivalence.

Results

Table 5. Summary of Pharmacokinetic data

Diamicron Uno® (Reference Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
$C_{max(ss)}$ (µg/mL)	3.17	3.36	1.138
$C_{min(ss)}$ (µg/mL)	1.03	1.22	0.701
$AUC_{0-\tau(ss)}$ (µg.h/mL)	52.86	57.19	23.056

Gliclazide (Test Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
$C_{max(ss)}$ (µg/mL)	3.56	3.77	1.272
$C_{min(ss)}$ (µg/mL)	1.06	1.28	0.741
$AUC_{0-\tau(ss)}$ (µg.h/mL)	56.81	62.21	26.054

Table 6. Ratio and 90% Confidence Intervals of test Product versus Reference Product

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals		Intra Subject Variability (%)
		Lower 90% CI (%)	Upper 90% CI (%)	
$C_{max(ss)}$	112.01	106.63	117.66	11.43
$C_{min(ss)}$	102.19	89.90	116.16	30.34
$AUC_{0-\tau(ss)}$	107.37	101.17	113.96	13.85

Based on the results obtained, Gliclazid "Sigillata" 60 mg modified-release tablets and Diamicron Uno 60 mg modified-release tablets of Les Laboratories Servier, France, are considered bioequivalent in healthy adult subjects, under fasting conditions. Both the test and reference product were found to be safe and well tolerated.

In the steady state study the 90% confidence intervals derived from the analysis of the log transformed pharmacokinetic parameters AUC_{0-t}, C_{max} and C_{min} of gliclazide were within the 80.00-125.00% acceptance range.

<u>Single-dose study under fasting conditions (30 mg)</u>
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 12 days between the two administrations. 30 mg was administered in each period.

28 healthy South Asian male subjects (18-41 years) participated in the study. 27 subjects completed the study. 27 were included in the PK analysis and statistical analysis.

Primary pharmacokinetic variables were: AUC_{0-t} and C_{max}.

The 90% confidence interval of the test/reference ratio (difference in least square means) from the ANOVA of the log-transformed AUC_{0-t} and C_{max} for gliclazide should be at least 80.00% and not more than 125.00% in order to conclude bioequivalence.

Results

Table 7. Summary of Pharmacokinetic data

Diamicron® (Reference Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (µg.h/mL)	28.27	30.20	11.430
C_{max} (µg/mL)	0.94	0.98	0.269

Gliclazide (Test Product)

Pharmacokinetic parameter	Geometric mean	Arithmetic mean	Standard deviation
AUC_{0-t} (µg.h/mL)	29.63	31.22	10.358
C_{max} (µg/mL)	1.03	1.09	0.342

Table 8. Ratio and 90% Confidence Intervals of test Product versus Reference Product

Pharmacokinetic parameter	Ratio (%)	90% Confidence Intervals		Intra Subject Variability (%)
		Lower 90% CI (%)	Upper 90% CI (%)	
AUC_{0-t}	104.69	93.72	116.93	24.12
C_{max}	108.78	97.19	121.76	24.59

Based on the results obtained, Gliclazid ”Sigillata” 30 mg modified-release tablets and Diamicron 30 mg modified-release tablets of Les Laboratories Servier, France are considered bioequivalent in healthy adult subjects, under fasting conditions. Both the test and reference product were found to be safe and well tolerated.
In the single dose study the 90% confidence interval for the difference between the Test and the Reference formulation least-squares means for the log-transformed parameters AUC_{0-t} and C_{max} were within the 80.00-125.00% acceptance range for demonstrating bioequivalence.

Pharmacokinetic conclusion
Based on the submitted documentation bioequivalence between test and reference products can be concluded.

The results of studies with the 60 mg formulation can be extrapolated to other strength 30 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The RMS has been assured that the bioequivalence studies has 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.2 Pharmacovigilance system & Risk Management Plan

Pharmacovigilance system
The Applicant has submitted a signed Summary of the MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Gliclazid "Sigillata".

The following summary list of safety concerns has been agreed with no additional pharmacovigilance or risk minimisation measures:

Table 1: Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Use in patients with severe renal or hepatic insufficiency • Hypoglycaemia (as an individual reaction or as a consequence of drug interaction) • Allergic skin reactions, including bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) • Use in patients with type I diabetes • Increase in blood glucose levels following concomitant use of danazol, chlorpromazine, glucocorticoids, ritodrine, salbutamol, terbutaline (i.v.)
	• Liver disorders
Important potential risks	• Haemolytic anaemia in patients with glucose-6-phosphate (G6PD)-deficiency • Weight gain • Concomitant use of gliclazide with anticoagulant therapy
Missing information	• Use in children and adolescents • Use in pregnancy and lactation

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 Gliclazid "Actavis", DK/H/1685/001/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gliclazid ”Sigillata” 30 mg and 60 mg modified-release tablets has a proven chemical-pharmaceutical quality and is comparable to Diamicron. 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.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that a marketing authorisation for Gliclazid ”Sigillata” could be granted. The decentralised procedure was finalised on 24 March 2015. Gliclazid ”Sigillata” was authorised in Denmark on 4 August 2015.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), PSURs are to be submitted every 5 years. The next DLP is 28 February 2021.

The date for the first renewal will be: 24 March 2020.

The following post-approval commitment has been made during the procedure:

- The MAH commits to provide a valid QP declaration not later than 2 months (60 days) after Day 210.