COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gliclazide retard Teva 60 mg, modified-release tablets

(gliclazide)

NL/H/5002/001/DC

Date: 10 September 2019

This module reflects the scientific discussion for the approval of Gliclazide retard Teva 60 mg, modified-release tablets. The procedure was finalised at 23 September 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 retard Teva 60 mg, modified-release tablets from Teva B.V.

Gliclazide reduces blood glucose levels by increasing the secretory potential of pancreatic β-cells in the islets of Langerhans.

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 Uno 60 mg modified release tablets which has been registered in the Netherlands by les laboratoires SERVIER through procedure FR/H/0171/002 since 27-10-2009 (original product).

The concerned member states (CMS) involved in this procedure were Austria, Denmark, Estonia, Spain, Croatia, Hungary, Italy, Lithuania, Latvia, and Portugal.

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

II. QUALITY ASPECTS

II.1 Introduction

Gliclazide retard Teva is a modified release tablet.

Each modified release tablet contains 60mg of gliclazide.

The 60 mg modified release tablets are white, biconvex, oval-shaped tablets, with a deep break-line on both sides and engraved with “GLI” and “60” on either side of the break-line on both sides, with dimensions 15.0 x 7.0 mm.

The 60 mg tablet can be divided into equal doses.

The modified release tablets are packed in PVC-PVDC/Al or PVC/Al foil blister in various pack sizes.

<u>Excipients</u>
Intragranular
Lactose monohydrate

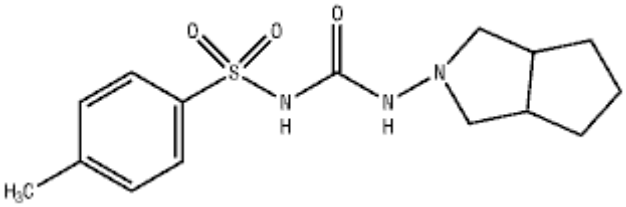
Hypromellose (HPMC K100 LV) E464
Hypromellose (HPMC K4M CR) E464

Extragranular
Hypromellose (HPMC K100 LV) E464
Hypromellose (HPMC K4M CR) E464
Magnesium stearate E572

II.2 Drug Substance

INN: Gliclazide

Chemical name:1-(Hexahydrocyclopenta©pyrrol-2(1H)-yl)-3[(4methylphenyl)sylphonyl]urea
Molecular formula: C15H21N3O3S
CAS number: 21187-98-4
Molecular mass: 323.4 g/mol
Structure:



The active substance is gliclazide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Gliclazide is a white or almost white powder. It is insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and slightly soluble in ethanol (96%). The active substance is controlled according to the requirements of the Ph.Eur. monograph with additional requirements for residual solvents.

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.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients justified and their functions explained.

Process validation has been fully validated and conducted using three batches. A flow chart of the manufacturing process including in-process controls has been provided.

Three batches have been included in process validation. Validations of the analytical methods have been presented. CoAs for three batches demonstrate that the finished product meets the specifications proposed.

The conditions used in the stability studies are according to EU/ICH requirements. The accepted packaging is PVC film/Al foil blister and PVC-PVDC film/Al foil blister.

A shelf-life period of 36 months and the storage condition “this medicinal product does not require any special storage condition” is accepted, based on presented stability data.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gliclazide retard Teva 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 retard Teva 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 Uno 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.

To support the application, the MAH has submitted a total of three bioequivalence studies. The formulation concerned is a multiple dose single-unit formulation. The number and type of studies are considered adequate in accordance with the Note for Guidance on Modified release oral and transdermal dosage forms: section II (CPMP/EWP/280/96 Corr *).

IV.2 Pharmacokinetics

Bioequivalence studies
The following bioequivalence studies have been performed with the 60 mg modified release tablets:
- Study 1: single-dose fasting conditions
- Study 2: single-dose fed conditions
- Study 3: steady state (one daily dose for five consecutive days)

The studies were GCP compliant.

Study 1: single-dose fasting conditions
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 seven days between the two administrations. One 60 mg modified release tablet was administered in each period.

24 healthy subjects (16 male and 8 female) aged 18 to 30 years (mean: 21 years) and BMI of 19.3 to 28.2 (mean: 22.9) were enrolled. The study population comprised of 17 (70.83%) subjects who were European, 6 (25.00%) subjects who were Asian and 1 (4.17%) subject who was Pacific Islander. All subjects completed the study

After an overnight fast of at least 10 hours starting at 08:00, the two treatments were administered with 240 ml of ambient-temperature 20% glucose solution in water. The subjects were fasting for 5 hours after drug administration. Standard lunch, dinner and a light snack was provided at approximately 5, 10 and 12 hours post-dose.

During the study 17 adverse events were experienced by 7 of the 24 participating subjects. 9 adverse events were reported following administration of the test product (1 not related, 2 possibly and 6 probably related) and 8 adverse events were reported following administration of the reference product (4 not related and 3 possibly and 1 probably related). All the adverse events were mild or moderate in intensity. The most commonly reported adverse event possibly related to the study medication was headache.

Blood samples were collected pre-dosing and at multiple times post-dosing up to 72 hours post administration.

The pharmacokinetic variables calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$, with the primary variables being $AUC_{0-\infty}$ and C_{max}.

Results:

Pharmacokinetic Parameters	**Test Treatment (B): Gliclazide modified release 60 mg Tablet Batch No.: HGQQ11003A (n=24) (mean ± S.D) (Range)**	**Reference Treatment (A): Diamicron® MR 60 mg Tablet Batch No.: 891699 (n=24) (mean ± S.D) (Range)**
$AUC_{0-\infty}$ (ng.hr/ml)	47883.46±20710.70 (20419.68-100790.20)	46570.45±20003.89 (21413.36-106421.90)
AUC_{0-t} (ng.hr/ml)	45406.68±17558.90 (19862.21-87530.30)	44489.84±17651.38 (20888.99-96766.88)
Cmax (ng/ml)	2444.99±649.65 (1436.37-3574.15)	2307.13±701.35 (1266.23-4437.75)
Tmax (hr)	6.53±2.11 (4.00-11.00)	7.31±2.82 (4.00-13.00)
$t_{1/2}$ (hr)	14.01±4.24 (7.10-23.57)	13.73±2.72 (9.26-19.30)

	$AUC_{0-\infty}$ (ng.hr/ml)	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
Gliclazide modified release 60 mg Tablet (Batch No.: HGQQ11003A) (Test)				
Geometric Mean	44166.75	42398.84	2360.68	6.24
S.D [c]	17911.06	16058.73	647.59	1.87
Range	20419.68-100790.20	19862.21-87530.30	1436.37-3574.15	4.00-11.00
Diamicron® MR 60 mg Tablet (Batch No.: 891699) (Reference)				
Geometric Mean	43427.35	41839.59	2215.40	6.83
S.D [c]	15741.65	14338.10	637.72	2.54
Range	21413.36-106421.90	20888.99-96766.88	1266.23-4437.75	4.00-13.00
P-Values	0.5902	0.6725	0.1394	-
Sequence	0.5873	0.5402	0.2946	-
Period	0.2592	0.3229	0.3633	-
Gliclazide modified release Tablet (Batch No.: HGQQ11003A) (Test) vs Diamicron® MR Tablet (Batch No.: 891699) (Reference)				
Mean Ratio % [a]	101.70	101.34	106.56	91.25
90% CI [b]	(0.964,1.072)*	(0.961,1.069)	(0.992,1.144)*	-

* 90% CI criteria used to establish bioequivalence of the Test and Reference formulations between 0.80 and 1.25 (80.00 to 125.00%) for $AUC_{0-\infty}$ and Cmax.

[a] Mean Ratio % = Mean $_{Test}$/Mean $_{Reference}$ x 100

[b] 90% Confidence Interval

[c] Jackknife Standard Deviation

Study 2: single-dose fed conditions

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 7 days between the two administrations. One 60mg modified release was administered in each period.

23 healthy subjects (10 male and 13 female) aged 20 to 27 years (mean: 21 years) and BMI of 19.4 to 30.6 (mean: 23.9) were enrolled in the study There were 15 (65.21%) subjects who were European, 2 (8.70%) subjects who were Asian, 2 (8.70%) subjects who were Maori/European, 1 (4.34%) subject who was Maori, 1 (4.34%) subject who was Assyrian (Middle Eastern), 1 (4.34%) subject who was Asian/European and 1 (4.34%) subject who was Pacific Islander. All subjects completed the study.

After an overnight fast of at least 9.5 hours and within 5-minutes of consuming a standardised high fat breakfast over a 30-minute period, the two treatments were administered with 240 ml of ambient-temperature water. Subjects did not receive any other food until at least 5 hours post-dose. The tablets were swallowed whole. Standard lunch, dinner and a light snack was provided at approximately 5, 10 and 12 hours post-dose.

During the study 23 adverse events were experienced by nine of the 23 participating subjects. 18 adverse events were reported following administration of the test product (8 not related and 10 possibly related) and 5 adverse events were reported following administration of the reference product (4 not related and 1 possibly related). All the adverse events were mild or moderate in intensity. The most commonly reported adverse event possibly related to the study medication was headache.

Blood samples were collected pre-dosing and at multiple times post-dosing up to 72 hours post administration.

The pharmacokinetic variables calculated were AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, K_{el} and $t_{½\ el}$, with the primary variables being $AUC_{0-\infty}$ and C_{max}.

Results:

Pharmacokinetic Parameters	**Test Treatment (B): Gliclazide modified release 60 mg Tablet Batch No.: HGQQ11003A (n=23) (mean ± S.D) (Range)**	**Reference Treatment (A): Diamicron® MR 60 mg Tablet Batch No.: 891699 (n=23) (mean ± S.D) (Range)**
$AUC_{0-\infty}$ (ng.hr/ml)	44511.66±22557.56 (15050.58-107134.30)	44564.51±21611.70 (17247.04-93806.07)
AUC_{0-t} (ng.hr/ml)	42302.55±20088.36 (14683.77-98060.44)	42123.91±19186.69 (16816.22-87654.66)
Cmax (ng/ml)	2802.71±892.21 (1071.74-4798.87)	2631.64±966.41 (1299.53-5223.55)
Tmax (hr)	5.70±1.24 (2.00-9.00)	6.50±1.76 (4.00-11.02)
$t_{1/2}$ (hr)	13.91±4.20 (8.24-21.71)	14.17±4.23 (8.20-24.14)

	$AUC_{0-\infty}$ (ng.hr/ml)	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)
Gliclazide modified release 60 mg Tablet (Batch No.: HGQQ11003A) (Test)				
Geometric Mean	39763.47	38242.05	2661.53	5.54
S.D [c]	19179.15	17547.01	905.42	1.49
Range	15050.58-107134.30	14683.77-98060.44	1071.74-4798.87	2.00-9.00
Diamicron® MR 60 mg Tablet (Batch No.: 891699) (Reference)				
Geometric Mean	40113.41	38357.95	2477.12	6.29
S.D [c]	18620.75	16856.88	875.00	1.66
Range	17247.04-93806.07	16816.22-87654.66	1299.53-5223.55	4.00-11.02
P-Values	0.6434	0.8823	0.0551	-
Sequence	0.3826	0.3269	0.0717	-
Period	0.7691	0.6793	0.1288	-
Gliclazide modified release Tablet (Batch No.: HGQQ11003A) (Test) vs Diamicron® MR Tablet (Batch No.: 891699) (Reference)				
Mean Ratio % [a]	99.13	99.70	107.44	88.08
90% CI [b]	(0.961,1.023)*	(0.967,1.029)	(1.011,1.147)*	-

* 90% CI criteria used to establish bioequivalence of the Test and Reference formulations between 0.80 and 1.25 (80.00 to 125.00%) for $AUC_{0-\infty}$ and Cmax.

[a] Mean Ratio % = Mean $_{Test}$/Mean $_{Reference}$ x 100

[b] 90% Confidence Interval

[c] Jackknife Standard Deviation

Study 3: steady state fasting conditions

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 10 days between the last dosing in period 1 and the first dose in period 2. A 60 mg tablet was administered for 5 consecutive days in each period.

24 healthy adult subjects (12 male and 12 female), aged 19 to 26 years (mean: 21 years) and BMI of 20.2 to 34.7 (mean: 25.1) were enrolled. The study population comprised of 14 (58.33%) subjects who were European, 3 (12.50%) subjects who were Asian, 2 (8.33%) subjects who were Middle Eastern, 2 (8.33%) subjects who were Maori/European, 1 (4.17%) subject who was Asian/ European, 1 (4.17%) subject who was Pacific Islander/European and 1 (4.17%) subject who was Maori. 22 subjects completed both periods of the study.

The treatments were administered after pre-dose clinical assessments were complete and a blood sample (days 1 to 4 and at 0 hours on day 5 of each study period) was collected. Subjects reported to clinical site for blood sampling by venepuncture and dosing on days 1 to 4 of each study period. Subjects checked into the Clinical Site the evening prior to dosing day 5 of each study period and fasted overnight for at least 10 hours prior to dose administration. Subjects remained at the clinical site for 24 hours after dosing for the

collection of additional blood samples. The study products were administered with 240 ml of 20% glucose solution in water.
Standard lunch, dinner and a light snack was provided at approximately 5, 10 and 12 hours post-dose on days 5 and 19. On study days 5 and 19 water was not permitted for at least one hour prior to dosing and within one hour after dosing.

Blood samples were collected pre-dosing from day 1 - day 5 and at multiple times up to 24 hours post-dosing on day 5 post administration.

The pharmacokinetic variables calculated were AUC_{0-t}, C_{max}, C_{min}, DF (fluctuation) and Tmax, with the primary variables being AUC_{0-t}, C_{max} and C_{min}.

Results:

Pharmacokinetic Parameters	**Test Treatment (B): Gliclazide modified release 60 mg Tablet Batch No.: HGQQ11003A (n=22) (mean ± S.D) (Range)**	**Reference Treatment (A): Diamicron® MR 60 mg Tablet Batch No.: 891699 (n=22) (mean ± S.D) (Range)**
AUC_{0-t} (ng.hr/ml)	44096.20±19611.62 (17221.77-88909.58)	44523.80±19736.66 (18224.29-84922.07)
Cmax (ng/ml)	3500.93±1275.20 (1605.89-6100.95)	3400.72±1464.68 (1153.54-7564.28)
Cmin (ng/ml)	1081.74±635.91 (289.40-2357.09)	1122.10±584.71 (396.44-2254.00)
DF (%)	142.58±41.14 (58.75-205.47)	127.78±36.92 (78.91-220.93)
Tmax (hr)	5.59±2.02 (4.00-14.00)	5.87±1.87 (3.00-11.00)

	AUC_{0-t} (ng.hr/ml)	Cmax (ng/ml)	Cmin (ng/ml)	Tmax (hr)
Gliclazide modified release 60 mg Tablet (Batch No.: HGQQ11003A) (Test)				
Geometric Mean	40319.78	3287.64	920.47	5.38
S.D [c]	17379.56	1205.11	541.13	1.36
Range	17221.77-88909.58	1605.89-6100.95	289.40-2357.09	4.00-14.00
Diamicron® MR 60 mg Tablet (Batch No.: 891699) (Reference)				
Geometric Mean	40676.05	3126.51	982.66	5.63
S.D [c]	17651.01	1324.45	528.90	1.60
Range	18224.29-84922.07	1153.54-7564.28	396.44-2254.00	3.00-11.00
P-Values	0.7392	0.2162	0.1337	-
Sequence	0.5127	0.5315	0.8613	-
Period	0.6350	0.7988	0.1945	-
Gliclazide modified release Tablet (Batch No.: HGQQ11003A) (Test) vs Diamicron® MR Tablet (Batch No.: 891699) (Reference)				
Mean Ratio % [a]	99.12	105.15	93.67	95.58
90% CI [b]	(0.948,1.037)*	(0.983,1.125)*	(0.872,1.007)*	-

* 90% CI criteria used to establish bioequivalence of the Test and Reference formulations between 0.80 and 1.25 (80.00 to 125.00%) for AUC_{0-t}, Cmax and Cmin.

[a] Mean Ratio % = Mean $_{Test}$/Mean $_{Reference}$ x 100

[b] 90% Confidence Interval

[c] Jackknife Standard Deviation

Conclusion on bioequivalence studies

Based on the submitted bioequivalence studies Gliclazide retard Teva 60 mg modified release tablets are considered bioequivalent with Diamicron Uno 60 mg modified release tablets.

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 Diamicron Uno.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hypoglycaemia • Use in patients with severe renal or hepatic insufficiency • Drug interaction with miconazole • Liver disorders (hepatitis, cholestatic

	jaundice) • Serious skin reactions, including bullous reactions (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) • Use in patients with type 1 diabetes • Increase in blood glucose levels following concomitant use of danazol, • chlorpromazine, glucocorticoids, ritodrine, salbutamol, terbutaline (i.v.)
Important potential risks	• Concomitant use of gliclazide with anticoagulant therapy • Haemolytic anaemia
Missing information	• Use in pregnancy and lactation • Use in children

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 Uno. 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 been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. 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.

The test consisted of a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gliclazide retard Teva 60 mg modified release tablets has a proven chemical-pharmaceutical quality and is a generic forms of Diamicron Uno 60 mg modified release tablets. Gliclazide is a well-known active substance with an established favourable efficacy and safety profile.

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

The marketing authorisation holder has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other gliclazide containing products.

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 essential similarity has been demonstrated for Gliclazide retard Teva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 23rd September 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse