Bundesinstitut
für Arzneimittel
und Medizinprodukte

PUBLIC ASSESSMENT REPORT

Decentralised Procedure

Gliclada 90 mg Tabletten mit veränderter Wirkstofffreisetzung

Procedure Number: DE/H/0892/003/DC

Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung

Procedure Number: DE/H/0894/003/DC

Active Substance:
Gliclazide

Dosage Form:
Modified release tablet

Marketing Authorisation Holder in the RMS, Germany:
KRKA d.d. NOVO mesto

Publication:
12.09.2019

This module reflects the scientific discussion for the approval of Gliclada / Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung. The procedure was finalised on 16.12.2015.

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Gliclada 90 mg Tabletten mit veränderter Wirkstofffreisetzung; Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung
Name of the drug substance (INN name):	Gliclazide
Pharmaco-therapeutic group (ATC Code):	A10BB09
Pharmaceutical form(s) and strength(s):	Modified release tablet
Reference Number(s) for the Decentralised Procedure	DE/H/0892/03/DC ; DE/H/0894/03/DC
Reference Member State:	DE
Member States concerned:	AT; BG; CZ; EE; HR; LT; LV; PL; PT; RO; SI; SK (DE/H/0892/03/DC) BE; ES; IT (DE/H/0894/03/DC)
Marketing Authorisation Holder (name and address)	KRKA d.d. NOVO mesto Smarjeska cesta 6 8501 NOVO MESTO Slovenia
Names and addresses of all manufacturer(s) responsible for batch release in the EEA	Krka, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia TAD Pharma GmbH Heinz-Lohmann-Straße 5 27472 Cuxhaven Germany

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Gliclada 90 mg/Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung, in the treatment of: "Non-insulin dependent diabetes mellitus (Type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood sugar."

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

Active Substance
The active drug substance is gliclazide, a hypoglycaemic sulphonylurea oral antidiabetic substance, ATC code is A10BB09.

Drug Product
The present formulation is a prolonged release tablet.

Development Programme
The development of the new dosage strength 90 mg modified release tablet by Krka, d.d.Novo mesto, is based on 60 mg strength by Krka, d.d.Novo mesto. The objective of the development programme was to formulate a robust, stable, acceptable formulation of gliclazide 90 mg tablets, comparable in performance to Diaprel® 60 mg modified-release tablets, which has been the reference product in the submitted bioequivalence studies for this application.

Claimed indication
"Non-insulin dependent Diabetes mellitus (Type II) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose.
Claimed Posology
The daily dose of gliclazide may vary from 30 to 120 mg taken orally in a single intake at breakfast time.

Initial dose
The recommended initial dose is 30 mg daily. If blood glucose is effectively controlled, this dose may be used for maintenance treatment. If blood glucose is not adequately controlled, the dose may be increased to 60, 90 or 120 mg daily, in successive steps. The interval between each dose increment should be at least 1 month except in patients whose blood glucose has not reduced after two weeks of treatment. In such cases, the dose may be increased at the end of the second week of treatment.
The maximum recommended daily dose is 120 mg.
One 90 mg modified-release tablet corresponds to one and a half 60 mg modified-release tablets.
For details see SPC.

The indication and posology suggested for the 90 mg dose strength are in line with those of the already licensed 30 mg and 60 mg strenghts and those of the reference product.

II.3 General comments on the submitted dossier

This decentralised application is submitted as hybrid applications under article 10 (3) of the Directive 2001/83/EC in combination with a line extension in line with Annex 1 of Regulation No. 1234/2008/EC, point 1.3.1, "Addition of a new strength/ potency".
The application is an extension - an addition of a new strength 90 mg modified release tablets - to an existing marketing authorisation (Gliclada 60 mg/Glibemat 60 mg modified release tablets) in the Community with the same marketing authorisation holder (Krka, d.d.Novo mesto).
The applicant refers to the reference medicinal product which has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA, which is Diamicron 80 mg modified release tablet. The marketing authorisation holder of this reference is Servier Nederland B.B., the date of authorisation is 25.09.1974.
The reference medicinal product for this application in Germany is Diamicron uno 60 mg modified release tablets, by Les Laboratoires Servier, which was granted marketing authorisation on 28.06.2010.
The reference product from Slovenia Diaprel MR 60 mg modified release tablets, manufacturer Les Laboratories Servier Industrie, France, was used in the bioequivalence studies.

The additional dose 90 mg was selected based on a clinical rationale in order to fulfil various needs of patients, when higher than 60 mg daily doses are needed. The use of only one tablet of 90 mg gliclazide modified release tablet also simplifies the regimen.
No clinical studies on Gliclazide 90 mg modified-release tablet have been conducted.
Instead, three bioequivalence studies have been submitted to support the claim that Gliclazide 90 mg modified-release tablets, by Krka d.d. Novo mesto, proposed for marketing is essentially similar to the reference Diaprel® 60 mg modified-release tablets (Servier).

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP: The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations.

GLP: not applicable since no preclinical studies were performed with this well-known substance.

GCP: the Applicant states that pharmacokinetic studies to demonstrate bioequivalence with the originator product were carried out according to GCP. During review, no concerns regarding GCP compliance arose.

The applicant provided information that the clinical, bioanalytical and PK/statistical analysis sites were inspected by agencies..

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

The chemical-pharmaceutical documentation and the Quality Overall Summary with reference to 90 mg gliclazide containing modified release tablets have been updated satisfactorily. The remaining issues are solved. From the quality point of view a marketing authorisation can be granted.

Drug substance
The active ingredient is Gliclazide whose pharmaceutical quality is monographed in the European Pharmacopoeia, monograph: 1524, current edition. For each manufacturer a CEP was issued.

The control tests and specifications for drug substance are adequately drawn up. Stability studies have been performed with two pilot scale batches and one lab scale batch of undefined batch size. No significant changes in tested quality attributes were observed. The proposed shelf life of 24 months for gliclazide drug substance manufactured at one manufacturing site is justified. For gliclazide drug substance manufactured at the alternate manufacturing site a re-test period of 5 years is granted by a CEP when stored in double polyethylene bags kept in a fibre drum.

Drug Product
The development of the new medicinal product has been acceptably described.
The product composition has been described sufficiently. With respect to the specific dosage form (modified release tablet), the manufacturing process presented for the medicinal product is considered as a non-standard process. Validation data on three pilot scale batches of the Gliclazide tablets, manufactured in accordance with the final commercial manufacturing process, have been provided for the minimal batch size. In the course of a post-approval-commitment the applicant commits that the process validation for the maximal batch size will be carried out on three consecutive industrial scale batches according to the validation protocol provided in the MAA documentation before placing the product to the market.

All excipients used in the manufacture of Gliclazide tablets are compendial (Ph. Eur.), have been specified and will be tested in accordance to the respective monographs. Sufficient TSE/BSE declarations have been provided for Lactose monohydrate. Magnesium stearate Ph. Eur. is of vegetable origin.
Release and shelf-life specification are acceptable. The analytical methods for release and stability testing have been adequately described and validation data in accordance with the requirements of the relevant ICH guidelines have been provided.
Batch analyses data for three pilot scale batches have been presented. The batch analyses data together with the results obtained from stability testing confirm consistency and uniformity of the product based on the parameters tested and the limits set.
Reference standards have been adequately characterised.
The packaging concepts applied for, Al/Al blisters are standard for solid oral formulations. The specifications and information provided for the proposed container closure systems are considered as sufficient for their intended use. Suitability of the primary packaging components for commercial use and bulk packaging has been proved.
Stability data have been provided.
No storage precautions are needed. Therefore, upon request the storage conditions were changed as follows: “This medicinal product does not require any special storage conditions.”

III.2 Non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of gliclazide are well known. As gliclazide is a well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is dated 11.12.2014. The report refers to 88 publications up to the year 2004. The non-clinical overview is appropriate and is presented adequately.

Environmental Risk Assessment (ERA)
Since Gliclada 90 mg, Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung are 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.3 Clinical aspects

The pharmacokinetic and pharmacodynamic properties, the efficacy and safety profile of gliclazide are well known.
The clinical overview is dated 18.12.2014. The basic clinical pharmacology including mechanism of action, pharmacokinetics and dosage have been outlined and efficacy and safety have been discussed. The report refers to 19 publications up to the year 2010.
Finally the bioequivalence studies to support the application have been reviewed and discussed.
The clinical overview is appropriate and is presented adequately.

The indication and dose regimen given in the proposed SPC are identical with the originators SPC (Diamicron UNO 60 mg modified release tablets).

To support essential similarity with the reference product the applicant has submitted three bioequivalence studies. The applicant states that all studies were performed in compliance with ICH E6 Good Clinical Practice (GCP), Consolidated Guidance, including the archiving of essential documents. The Reports were prepared according to the ICH Topic E3: Structure and Content of Clinical Study reports, Step 4, Consensus Guideline, 30.11.95.

Bioequivalence studies

To demonstrate essential similarity with the reference product Diamicron uno 60 mg modified release tablets, by Les Laboratoires Servier the applicant has submitted three bioequivalence studies, two single dose studies (Study 14-414 under fasting condition and Study 14-415 under fed condition) and one multiple dose study (Study 14-416 under fed condition). The reference product Diaprel MR 60 mg modified release tablet from Slovenia was used in the three bioequivalence studies.

The objectives of the studies were to evaluate the bioequivalence of Gliclazide 90 mg prolonged release formulation following a single oral dose of 1 tablet of TEST formulation versus an equal dose of REFERENCE formulation (1and ½ tablet of Diaprel MR 60 mg modified release (divisible) tablets, SERVIER, France) under fasting or fed conditions or following multiple doses of TEST or REFERENCE under fed conditions. The reference, Diaprel MR 60 mg modified release tablets, manufacturer Les Laboratories Servier Industrie, France, were especially formulated to allow division into equal doses and therefore, the splitting of a tablet in two halves did not alter the modified-release characteristics of the formulation. Thus the administration of the two study formulation in equal dose was guaranteed.

Study design, PK parameter and statistical analyses were in line with the relevant *Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms* (EMA/CPMP/EWP/280/96/Corr1).

Study KRKA 14-414 (single dose, fasting conditions)
Bioequivalence of the test product (Gliclazide 90 mg prolonged release tablets) with the reference product (Diaprel 60 mg modified release tablets by Laboratoires Servier, France, given as 1 and ½ tablets) has been investigated in this study under fasting conditions. The 90% confidence intervals of the ratio AUC_{0-t}, AUC_{0-inf}, and C_{max} were within the accepted range of 0.80 - 1.25 for gliclazide, thus bioequivalence can be concluded. There were no statistical significant differences between test and reference product in respect to t_{max}, MRT and $T_{½}$.

Test name	Parameter	Test value (test/reference)	Lower 90% CL	Upper 90% CL
Classic 90% CI	AUC_{0-t}	100.719	92.800	109.314
Classic 90% CI	C_{max}	92.190	84.852	100.163

Study KRKA 14-415 (single dose, fed conditions)
Bioequivalence of the test product (Gliclazide 90 mg prolonged release tablets) with the reference product (Diaprel 60 mg modified release tablets by Laboratoires Servier, France, given as 1 and ½

tablets) has been investigated in this study under fed conditions. The 90% confidence intervals of the ratio AUC_t, AUC_i and C_{max} were within the accepted range of 0.80 - 1.25 for gliclazide, thus bioequivalence can be concluded.

Test name	Parameter	Test value (test/reference)	Lower CL	Upper CL
Classic 90% CI	AUC_t	103.88%	100.19%	107.71%
Classic 90% CI	AUC_i	103.12%	99.39%	107.00%
Classic 90% CI	C_{max}	108.93%	103.07%	115.12%

Study KRKA 14-416 (multiple doses, fed conditions)

Bioequivalence of the test product (Gliclazide 90 mg prolonged release tablets) with the reference product (Diaprel 60 mg modified release tablets by Laboratoires Servier, France, given as 1 and ½ tablets) has been investigated in this study under multiple dose and fed conditions.

The 90% confidence interval for the primary parameters AUC_{thau}, C_{max} and C_{min} were within the acceptance range of 80.00 to 125.00%, thus permitting to conclude for bioequivalence.

Test name	Parameter	Test value (test/reference)	Lower CL	Upper CL
Classic 90% CI	AUC_{thau}	103.16%	100.49%	105.91%
Classic 90% CI	C_{max}	101.86%	98.60%	105.23%
Classic 90% CI	C_{min}	101.60%	95.56%	108.02%

Analytical studies

The EMA/CHMP/600958/2010/Corr.* Appendix IV of the Guideline on the Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1): Presentation of Biopharmaceutical and Bioanalytical Data in Module 2.7.1 was followed.

Determinations of gliclazide were performed by HPLC-MS/MS. Blank plasma was kept frozen, at or below -20 °C, until use. The validation method was developed in accordance with the guideline EMEA/CHMP/EWP/192217/2009. GLP compliance is stated. The information given in the bioanalytical study report confirms that the analytical method is validated and suitable to determine gliclacide in human plasma in an accurate, precise and reproducible manner.

Safety

Gliclazide 90 mg modified release tablet was well tolerated in all three submitted bioequivalence studies. The reported adverse events were graded mild or moderate and no new unexpected adverse events had been observed. No relevant differences in safety profiles were observed between test and reference, particularly with respect to the number of subjects experiencing adverse events.

Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future 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 provided an updated RMP version 2.2 for gliclazide containing products. The RMP covers one product. Data lock point for the updated RMP is 31.08.2015; date of the final sign off is 12.10.2015.

The MAH provided the following summary of safety concerns:

Important identified risks	Hypoglycaemia
	Severe cutaneous adverse reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis)
	Changes in haematology (including anaemia, leukopenia, thrombocytopenia, granulocytopenia)
	Hepatic disorders including hepatitis
	Drug interaction with miconazole
Important potential risks	Haemolytic anaemia
Missing information	Use in paediatric population

The applicant considers routine pharmacovigilance and routine risk minimisation measures sufficient. This is agreed.

However, the applicant was requested to update the RMP and the applicant did so sufficiently.
The RMP is acceptable now.

Periodic Safety Update Report (PSUR)

For MAA with a substance not listed in the published EURD list, please use the below statement.

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

Common renewal date
A common renewal date of 5 years after finalisation of the procedure was accepted.

Legal status
Medicinal product subject to medical prescription.

User Test
The applicant has justified waiving user consultation for the medicinal product Gliclazide 90 mg modified release tablets in accordance to the recent Guidance/Guidelines.
The applicant has submitted a Bridging Report for the readability testing of the Package Leaflet (PL)

Name of the product: Parent PL: Gliclazide 60 mg modified-release tablets,
Daughter PL: Gliclazide 90 mg modified-release tablets

It is conclusive from the Bridging Report that the format, design and layout of the proposed PL for Gliclazide 90 mg modified release tablets, and the already approved PL for Gliclazide 60 mg modified release tablets are identical. There are differences in text between the daughter PL and parent Pl, which may however not have an impact on the patients understanding. The PL proposed for the 90 mg modified release tablets is nearly identical with the PL for the originator.
The Bridging Report is adequate and acceptable.

IV. BENEFIT RISK ASSESSMENT

Quality view
From a quality point of view approval for Gliclada 90 mg/ Glibemat 90 mg modified release tablets is recommended.

Non-clinical and clinical view
The application contains an adequate review of published pre-clinical and clinical data. The pharmacodynamics and pharmacokinetic characteristics of gliclazide are well known. The efficacy and safety of gliclazide in the proposed indication is established in clinical use.
Although not available for the reference product, the 90 mg dose strength applied for is within the therapeutic dose range for gliclazide and therefore reasonable and acceptable.
Bioequivalence has been demonstrated for Gliclazide 90 mg prolonged release tablets with the reference product Diaprel MR 60 mg modified release tablets, (by Laboratoires Servier, Industrie, France, given as 1 and ½ tablets).
No issues have been identified regarding GCP compliance.
The bioequivalence studies were designed and conducted in accordance with the CHMP"Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)" and "Guideline on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**)".
Both formulations were well tolerated in the studies.
No death, serious or severe adverse events or new safety concerns related to the administrated formulations occurred during studies. No differences in the safety profiles were observed between the formulations test and reference.

RMP
The RMP is acceptable. With regard to RMP approval for Gliclada 90 mg/ Glibemat 90 mg Tabletten mit veränderter Wirkstofffreisetzung is recommended.

The application is approved. For intermediate amendments see current product information.

V. PROPOSED CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 Final list of recommendations not falling under Article 21a/22 of Directive 2001/83 / positive benefit risk assessment

In this section post approval commitments **not** falling under Article 21a or 22 should be included, e.g. as follows:	
Description	**Due date**
The process validation for the maximal batch size will be carried out on three consecutive industrial scale batches according to the validation protocol provided in the MAA documentation before placing the product on the market.	Before placing the product on the market.