COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Gliclazide Retard Mylan 30 mg, modified release tablets
# (gliclazide)

# NL/H/4947/001/DC

# Date: 7 February 2023

**This module reflects the scientific discussion for the approval of Gliclazide Retard Mylan 30 mg, modified release tablets. The procedure was finalised on 13 December 2007 in Germany (DE/H/0893/001/DC). After a transfer on 30 September 2019, the current RMS is the Netherlands. 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 |
| RMS | Reference Member State |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |

# INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gliclazide Retard Mylan 30 mg, modified release tablets, from Mylan Pharmaceuticals Limited.

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 product Diamicron ® 30 mg. The Originator product for a prolonged release formulation of gliclazide was first authorised in France (at that time approved as “modified release” tablets), 2000-03-29, (Diamicron ® 30 mg, marketing authorisation holder Les Laboratories Servier, France.) and gained approval via MRP in the EU in October 2000. The reference medicinal product authorised in Germany is Diamicron UNO® 30 mg, referring to the French MA also approved as “modified release” tablets, marketing authorisation holder is Servier Deutschland GmbH.

The dossier was submitted in full accordance to Common Technical Document (CTD) requirements.

The reference member state (RMS) of the initial procedure was Germany and the concerned member states (CMS) were France, Italy and the Netherlands. The role of RMS was transferred to the Netherlands on 30 September 2019.

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

# I. QUALITY ASPECTS

## I.1 Introduction

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 prior to authorisation.

The RMS has accepted copies of current drug product manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

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

The bioequivalence studies were carried out according to GCP.

## I.2 Drug Substance

The active substance in Gliclada 30 mg is gliclazide, a 'second generation' sulfonylurea, an oral antidiabetic agent which differs from other related compounds. Gliclazide was introduced in France in 1971 as Diamicron 80 mg tablet. The immediate release formulation Diamicron 80 mg tablet was registered in Germany in 1978. Gliclazide has subsequently received marketing approval in approximately 100 countries worldwide.

A new pharmaceutical formulation, a 30 mg tablet with prolonged release form of gliclazide was developed with the aim to limit plasma concentration fluctuations and to allow a once daily dosing regimen. The once daily intake of gliclazide was thought to improve treatment compliance. The Originator product for a prolonged release formulation of gliclazide was first authorised in France (at that time approved as "modified release" tablets), 2000-03-29, (Diamicron® 30 mg, marketing authorisation holder Les Laboratories Servier, France.) and gained approval via MRP in the EU in October 2000. The reference medicinal product authorised in Germany is Diamicron UNO® 30 mg, referring to the French MA also approved as "modified release" tablets, marketing authorisation holder is Servier Deutschland GmbH.

Diamicron UNO® 30 mg, is approved for the therapeutic indication: "Non-insulin-dependent diabetes (type 2) in adults when dietary measures, physical exercise and weight loss alone are not sufficient to control blood glucose."

The generic formulation of Gliclada 30mg tablets is claimed to be essentially similar to the European originator product Diamicron® 30 mg.

## I.3 Medicinal Product

Development Programme
The objective of the development programme was to formulate a robust, stable, acceptable formulation of gliclazide 30 mg tablets, comparable in performance to Diamicron UNO 30 mg.

Quality aspects
Information, amendments and supplements suggest that the drug product's quality resulting from the proposed route of manufacturing leads to a drug product in accordance with the set specifications consistently from batch to batch. Both drug substance sources, for which CEPs have been provided, have been shown to be suitable. Control of the drug product is considered sufficient based on the specifications and methods.

From the point of view of pharmaceutical quality the drug products are "prolonged release" tablets. Even so, due to formal/administrative requirements the drug products will be approved as "modified release" tablets since this Standard Term has been used for the originator product at the time of approval.

# II. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of gliclazide are well known. As gliclazide is a widely used, well-known active substance, no own non-clinical studies were required and the applicant provided none.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology was considered adequate.

# III. CLINICAL ASPECTS

## III.1 Pharmacokinetics, pharmacodynamics, clinical efficacy and safety

The active substance is gliclazide, a 'second generation' sulfonylurea, an oral antidiabetic agent which differs from other related compounds. It has an N-containing heterocyclic ring with an endocyclic bond. Gliclazide reduces blood glucose levels by stimulating insulin secretion from the ß-cells of the islets of Langerhans. Studies have also shown that therapy with gliclazide could improve the insulin sensitivity of peripheral tissues (muscle and liver) suppress the hepatic production of glucose and enhance insulin-stimulated glucose metabolism by potentiating insulin action on skeletal and muscle glycogen synthetase. Pharmacodynamics, pharmacokinetics, efficacy and safety of gliclazide are well known. Gliclazide as immediate release formulation has been used for more than three decades. A prolonged release formulation (Diamicron® 30 mg) has been used for 6 years.

To support essential similarity with the reference product Diamicron® 30 mg, the applicant submitted three bioequivalence studies, two single dose studies and one multiple dose study.

Bioequivalence studies

The objectives of the bioequivalence studies were to evaluate the bioequivalence of TEST formulation (Gliclazide 30 mg SR formulation KRKA, d.d. Novo Mesto, Slovenia) and REFERENCE formulation (DIAMICRON UNO® 30 mg, SERVIER GmbH-EU Market) following a single oral dose of 1 tablet each under fasting or fed conditions or following multiple doses of TEST or REFERENCE under fed conditions in healthy volunteers.

*Results study 1, single dose study, under fasting conditions:*

Bioequivalence comparison, primary parameters

| Test name | Parameter | Test value (test/reference) | Lower 90% CL | Upper 90% CL |
|---|---|---|---|---|
| Classic 90% CI | AUC0-t | 99.519 | 96.664 | 102.458 |
| Classic 90% CI | AUC0-inf | 99.939 | 96.924 | 103.047 |
| Classic 90% CI | Cmax | 97.281 | 90.894 | 104.117 |

*If the lower and upper CL lie within accepted CL (80-125) can conclude equivalence.*

| Test name | Parameter | Test value (t) | Lower t | Upper t |
|---|---|---|---|---|
| Schuirmann | AUC0-t | 1.691 | 12.684 | 13.244 |
| Schuirmann | AUC0-inf | 1.691 | 12.285 | 12.352 |
| Schuirmann | Cmax | 1.691 | 4.870 | 6.243 |

*If the lower t≥t and upper t≥t can conclude equivalence*

Secondary and additional parameters

| Parameter | Statistic Method | GLICLAZIDE |
|---|---|---|
| Tmax | WilcoxonT-test, Kruskall-Wallis | 3.32804E-01 Not significant<br>3.26640E-01 Not significant |
| Thalf | ANOVA | 6.75372E-01 Not significant |
| MRT | ANOVA | 9.35728E-01 Not significant |

*Study 2, single dose study, under fasting conditions:*

Bioequivalence comparison, primary parameters

| Test name | Parameter | Test value (test/reference) | Lower 90% CL | Upper 90% CL |
|---|---|---|---|---|
| Classic 90% CI | AUC0-t | 97.810 | 93.850 | 101.937 |
| Classic 90% CI | AUC0-inf | 98.144 | 94.150 | 102.307 |
| Classic 90% CI | Cmax | 99.248 | 93.632 | 105.201 |

*If the lower and upper CL lie within accepted CL (80-125) can conclude equivalence.*

| Test name | Parameter | Test value (t) | Lower t | Upper t |
|---|---|---|---|---|
| Schuirmann | AUC0-t | 1.692 | 8.231 | 10.045 |
| Schuirmann | AUC0-inf | 1.692 | 8.327 | 9.854 |
| Schuirmann | Cmax | 1.692 | 6.264 | 6.702 |

*If the lower t≥t and upper t≥t can conclude equivalence*

Secondary and additional parameters

| Parameter | Statistic Method | GLICLAZIDE |
|---|---|---|
| Tmax | WilcoxonT-test, Kruskall-Wallis | 2.13584E-02 *<br>1.82075E-02 * |
| Thalf | ANOVA | 5.41501E-01 Not significant |
| MRT | ANOVA | 8.40415E-01 Not significant |

*Study 3, multiple dose study, under fed conditions*

Bioequivalence comparison, primary parameters

| Test name | Parameter | Test value (test/reference) | Lower 90% CL | Upper 90% CL |
|---|---|---|---|---|
| Classic 90% CI | AUCss | 97.625 | 93.376 | 102.067 |
| Classic 90% CI | Cmaxss | 94.885 | 89.420 | 100.683 |

*If the lower and upper CL lie within accepted CL (80-125) can conclude equivalence.*

| Test name | Parameter | Test value (t) | Lower t | Upper t |
|---|---|---|---|---|
| Schuirmann test | AUCss | 1.691 | 7.566 | 9.393 |
| Schuirmann test | Cmaxss | 1.691 | 4.864 | 7.858 |

*If the lower t≥t and upper t≥t can conclude equivalence*

Secondary and additional parameters

| Parameter | Statistic Method | GLICLAZIDE |
|---|---|---|
| Tmax | Wilcoxon T-test<br>Kruskall-Wallis | 1.05968E-01 Non-Significant<br>1.00292E-01 Non Significant |

| Test name | Parameter | Test value (test/reference) | Lower 90% CL | Upper 90% CL |
|---|---|---|---|---|
| Classic 90% CI | Cminss | 101.911 | 93.977 | 110.514 |
| Classic 90% CI | %ptf | 94.569 | 90.466 | 98.858 |

| Test name | Parameter | Test value (t) | Lower t | Upper t |
|---|---|---|---|---|
| Schuirmann test | Cminss | 1.691 | 4.261 | 5.050 |
| Schuirmann test | %ptf | 1.691 | 6.378 | 10.636 |

| Parameter | Statistic Method | GLICLAZIDE |
|---|---|---|
| %Swing | ANOVA | 3.96600E-01 Non-significant |
| Caverage | ANOVA | 8.64400E-01 Non-significant |

Conclusion on bioequivalence studies:
Bioequivalence of the test products with the reference product could be shown in all three studies. The 90 % confidence intervals of the ratios for $AUC0_{-last}$ and $C_{max}$ were within the accepted limits of 0.80 and 1.25 in all three studies. The safety profiles of test and reference were similar.

## III.2 Risk Management Plan

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

A Risk Management Plan is not necessary for this generic application.

# IV. USER CONSULTATION

The SPC and PL are consistent with that of the reference product. Packaging fulfils the legal requirements. The applicant submitted a readability test on the package leaflet. The results of the test did not show any major problems. Changes and amendments proposed for the PIL by the RMS and CMS have been considered. The modified text contains the patient relevant information in a patient friendly language.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gliclazide Retard Mylan 30 mg, modified release tablets from Mylan Pharmaceuticals Limited, represent a generic form of Diamicron UNO tablets 30 mg, produced by Servier, Germany. Gliclazide is a well-known active substance with an established favourable efficacy and safety profile.

Satisfactory chemical-pharmaceutical documentation has been provided assuring adequate and consistent quality of the product.

A commitment was given by the Applicant to provide further data from stability testing of batches produced with drug substance of one of the alternative active substance manufacturer.

The application contained an adequate review of published clinical data on gliclazide-containing products. Bioequivalence studies are generally accepted as the most appropriate proof of establishing therapeutic equivalence between two chemically–derived medicinal products containing the same active substance. Bioequivalence of the test, Gliclazide with the reference, Diamicron UNO, has been demonstrated after single dose (fasting or fed conditions) and multiple doses under fed conditions. The safety profiles for test and reference were similar.

## 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 |
|---|---|---|---|---|---|
| NL/H/4947/001/IB/020 | Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product<br>- implementation of change(s) for which no new additional data is required to be submitted by the MAH. | Yes | 18-2-2021 | Approved | N/A |
| NL/H/4947/001/IB/021 | Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product<br>- to extend bulk holding time. | No | 24-3-2021 | Approved | N/A |
| NL/H/4947/001/IA/022 | Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)<br>- the activities for which the manufacturer/ importer is responsible include batch release. | Yes | 27-5-2021 | Approved | N/A |
| NL/H/4947/001/IB/023/G | - Quality changes active substance<br>- Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter).<br>- Other changes to a test procedure (including replacement or addition) for the | Yes | 15-11-2021 | Approved | N/A |

| | | | | | |
|---|---|---|---|---|---|
| | active substance or a starting material/intermediate.<br>- Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State | | | | |
| NL/H/4947/001/IB/024/G | - Minor change in the manufacturing process.<br>- Change to in-process tests or limits applied during the manufacture of the finished product. Controls frequency | No | 23-12-2021 | Approved | N/A |
| NL/H/4947/001/IB/025/G | - Change in the name and/or address of the marketing authorisation holder<br>- Change in the (invented) name of the medicinal product (in France) | Yes | 24-3-2022 | Approved | N/A |
| NL/H/4947/001/IA/026 | Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient. | Yes | 9-5-2022 | Approved | N/A |