COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Glimepiride Accord 6 mg, tablets

(glimepiride)

NL/H/3505/005/DC

Date: 12 September 2019

This module reflects the scientific discussion for the approval of Glimepiride Accord 6 mg, tablets. The procedure was finalised at 22 November 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Glimepiride Accord 6 mg, tablets from Accord Healthcare Ltd.

The product is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.
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 Amaryl 6 mg tablets (NL License RVG 17847) which has been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 20 June 1995 (original product).

The proposed product is a line extension of Glimepiride Accord 1 mg, 2 mg, 3 mg, and 4 mg, tablets (NL/H/3505/001-4/DC).

The concerned member states (CMS) involved in this procedure were Germany, Poland and Romania.

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

II. QUALITY ASPECTS

II.1 Introduction

Glimepiride Accord is a white to off white, oval shaped, uncoated tablets debossed with "HA1" on one side and with a score line on other side. The tablet can be divided into equal doses. Each tablet contains 6 mg of glimepiride.

The tablets are packed in clear PVC-PVdC/Aluminium blisters.

The excipients are: lactose monohydrate, sodium starch glycolate (Type A), povidone K-30 and magnesium stearate.

II.2 Drug Substance

The active substance is glimepiride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder. Glimepiride is

practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, and very slightly soluble in methanol. Polymorphic form I is manufactured.

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.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The formulation development and manufacturing process development is in line with the other strengths. Process optimization has adequately been studied.The 6 mg tablets bear a score line. Results have been provided that demonstrate the halved tablets comply with the dissolution specification, also over 6 months storage in the blister packaging.

One bioequivalence study is conducted under fasting condition to compare pharmacokinetic profile of Glimepiride Accord 6 mg tablets and Amaryl 6 mg tablets.

Manufacturing process
A description and flow chart of the straightforward wet granulation, blending, lubrication and tablet compression manufacturing process has been provided. Adequate process validation is performed on three batches. The additional batch size is within 10 fold of the validation batches. A commitment is made to perform process validation of additional higher batch size. The process validation protocol for additional batch size is appropriate.

Control of excipients
The excipients are the same as approved for the other tablet strengths. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight, identification, resistance to crushing, loss on drying, dissolution, uniformity of dosage units, related substances, assay, subdivision, microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Results of stability studies, 18 months data from normal (25°C/60% RH), 12 months intermediate (30°C/65% RH), and 6 months from accelerated (40°C/75% RH) storage conditions, have been submitted. All results meet the current shelf-life specifications. Additionally, results of testing dissolution on compliance with the dissolution specification 'NLT 85% (Q) after 20 minutes' over 23 months storage at long-term storage conditions have been provided for the three validation batches. The results comply and are consistent. In view of that, the proposed shelf-life of 2 years and storage condition 'Do not store above 25°C' are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Glimepiride Accord 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 Glimepiride Accord 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 Amaryl 6 mg tablets 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

Glimepiride 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Glimepiride Accord 6 mg, tablets (Accord Healthcare Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Amaryl 6 mg tablets (Sanofi-Aventis S.p.A., Germany).

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.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 63 healthy male subjects, aged 33.0±7.4 years. Each subject received a single dose (6 mg) of one of the two glimepiride formulations. The tablet was orally administered with 240 ml of drinking water containing 20% glucose at room temperature. The subjects were provided 60 ml of water containing 20% glucose at every 15 minutes till four hours post-dose to prevent hypoglycaemia. There were two dosing periods, separated by a washout period of four days.

Blood samples were collected at 0 hours (pre-dose) and at 0.33, 0.67, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 10, 12, 16, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. The overall design of the study is acceptable. The evaluation of bioequivalence is based upon measured concentrations of the parent compound, in accordance with the guideline.
Sampling period and sampling scheme are adequate as well as the washout period between periods. The administration of the formulations in combination with water containing 20% glucose is acceptable as it has been chosen to increase safety of the volunteers. In addition, it is not expected to influence absorption of glimepiride.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of six subjects discontinued on their own accord (one pre-dosing, replaced; five during period 2). One subject was discontinued due to emesis (period 1) and one subject was discontinued on medical grounds (period 1, generalized body ache). Therefore, 57 subjects were eligible for pharmacokinetic analysis.

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

Treatment N_{test}=56 $N_{reference}$=57	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	3017 ± 2006	3129 ± 2301	351.0 ± 128.1	3.0 (1.5 - 12)
Reference	3242 ± 2617	3387 ± 3067	350.3 ± 117.5	3.7 (1.25 - 16)
***Ratio (90% CI)**	1.00 (0.96 - 1.04)	1.00 (0.97 - 1.04)	1.01 (0.94 - 1.08)	--

$AUC_{0-\infty}$	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 five adverse events (AEs) were reported by five subjects during the conduct of the study. Three AEs were reported in the first period and two AEs in the second. Three AEs were reported in the subjects after administration of the test formulation, two AEs were reported after administration of reference formulation.

All the AEs were mild in nature and all the subjects were followed up until resolution of their AEs. The causality assessment was judged as unlikely related for three AEs and as possibly related for two AEs. The subjects were treated appropriately and followed up until resolution of AEs. The causality assessment was judged as unlikely related for one AE and as possibly related for the other AE.

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Glimepiride Accord 6 mg is considered bioequivalent with Amaryl 6 mg.

The MEB has been assured that the bioequivalence study 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.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 Glimepiride Accord.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hypoglycaemia • Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
Important potential risks	• Use in patients with G6PD-deficiency with sulfonylurea agents can lead to haemolytic anaemia
Missing information	• Use in pregnancy and lactating women • Use in children and adolescents

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 Amaryl. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference for the content to Glivasol 6 mg tablets (DK/H/0864/005/MR) and for the lay-out to Solifenacin succinate 5 mg and 10 mg film-coated tablets (DK/H/2339/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Glimepiride Accord 6 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Amaryl 6 mg tablets. Amaryl 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 Glimepiride Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 November 2018.

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/3505 /IA/033/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Replacement or addition of a site where batch control/testing takes place. Replacement or addition of a manufacturer responsible for importation and/or batch release	--	20-4-2019	Approval	--