

Public Assessment Report

Scientific discussion

**Glivasol
6 mg tablets**

Glimepiride

DK/H/0864/005/MR

This module reflects the scientific discussion for the approval of Glivasol. The procedure was finalised on 4 August 2009. 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 Glivasol 6 mg tablets, from Stada Arzneimittel AG. The product was authorised in Denmark on 19 April 2007. The product is indicated for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate.

Glimepiride is a long-acting sulfonylurea, the primary mechanism of action of which appears to be dependent on stimulating the release of insulin from functioning pancreatic cells. This effect is based on an increase in responsiveness of the pancreatic beta cells to the physiological glucose stimulus.

This mutual recognition procedure concerns a generic application claiming essential similarity with the reference product Amaryl 6 mg tablets marketed by Sanofi-aventis. Amaryl was approved nationally in Denmark as 1 mg, 2 mg, 3 mg and 4 mg tablets on 23 October 1995 following the MRP NL/H/0101/001-004, whereas tablets of 6 mg were approved on 14 April 2003 following the MRP NL/H/0101/005. In 2007 this strength was withdrawn in Denmark.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

Amaryl 2 mg tablets, Aventis Pharma Deutschland GmbH from the German market, has been used as reference product in the bioequivalence study.

II. QUALITY ASPECTS

II.1 Introduction

Each tablet contains 6 mg glimepiride.

The tablets are orange, flat, oblong tablets (10 x 5 mm) with bevelled edges and a score on one side and marked with "G" on the other side. The tablet can be divided into equal halves.

The tablets are packed in PVC/Aluminium blisters in pack sizes of 10, 20, 30, 50, 60, 90 and 120 tablets. However, not all pack sizes may be marketed.

The excipients in the tablet are: Lactosemonohydrate; sodium starch glycolate (type A); magnesium stearate; microcrystalline cellulose; povidone K 29-32 and pigment blend PB-23103 consisting of lactose monohydrate and yellow and red iron oxide (E172).

Compliance with Good Manufacturing Practice

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 product contains glimepiride as active substance which is monographed in the Ph.Eur.

INN: Glimepiride

Compendial names: Glimepiride (Ph.Eur., BAN & USAN)

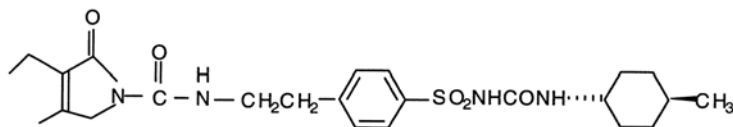
Chemical names: a) 1*H*-Pyrrole-1-carboxamide,3-ethyl-2,5-dihydro-4-methyl-*N*-[2-[4-[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-,*trans*-;
b) 1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]

phenyl]sulfonyl]-3-(trans-4-methylcyclohexyl)urea

Molecular formula: C₂₄H₃₄N₄O₅S

Molecular mass: 490.62

Structural formula:



Glimperide is a white crystalline powder, which is soluble in dimethyl formamide and dimethyl sulphoxide, slightly soluble in acetone and very slightly soluble in methanol, acetonitrile and ethyl acetate. It is insoluble in water and dilute NaOH (pH 12.76) and slightly soluble in 0.1N HCl (pH 1.24).

Two diastereoisomer forms exist: cis and trans. The active substance is the trans form.

The applicant sources the substance from two suppliers; one presenting a European Drug Master File/Active Substance Master File (DMF) and the other holding a Certificate of Suitability from EDQM, a copy of which has been provided in the file.

The applicant specification for glimepiride is acceptable and complies with general ICH for drug substance specifications, with the Ph.Eur. monograph and covers additional tests as described in the EDMF and CEP. All necessary analysis methods and validations are provided.

A retest period of 24 months and 4 years, respectively, has been set for the active substance.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained.

Excipients are those commonly used in tablet manufacture. The packaging materials are standard and shown suitable by the presented stability studies.

Product manufacture is standard. Satisfactory validation data are provided for the minimum scale batches.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Limits have been appropriately justified. Batch analysis data on one lab scale and two pilot scale batches are provided showing compliance with the release requirements and confirming consistency of product manufacture.

Stability data are provided for one lab scale and two pilot scale batches stored in the proposed market packaging. A shelf-life of 2 years with the storage condition “do not store above 30°C” is approved.

III. NON-CLINICAL ASPECTS

This product is a generic formulation of Amaryl 6 mg tablets, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application

Environmental risk assessment

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 glimepiride 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

Glimepiride is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Glivasol 2 mg tablets is compared with the pharmacokinetic profile of the reference product Amaryl 2 mg tablets, Aventis Pharma Deutschland GmbH from the German market.

From a pharmaceutical viewpoint, the selection of the 2 mg strength for the bioequivalence study is justified on the basis that:

- All tablet strengths (1 mg, 2 mg, 3 mg, 4 mg and 6 mg) are manufactured by the same manufacturer at the same site and using the same process,
- The compositions of all strengths are practically identical (apart from colourants) and each tablet strength contains a low concentration of the active substance (< 5 % of total tablet weight),
- The dissolution profiles for the 2 mg and 6 mg tablets are similar under identical conditions.

From a clinical aspect, 2 mg is chosen as the pharmacokinetic of glimepiride is linear, and higher strengths would expose healthy volunteers to an unacceptable degree of hypoglycaemia.

The study was an open label, laboratory blind, randomised, single dose, two-way cross-over study conducted under fasting conditions with a wash out period of 7 days between the two administrations. A single dose of 1 x 2 mg was administered in each period with 240 ml water.

Blood sampling was performed predosing and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 15.0, 18.0, 22.0, 26.0 and 32.0 hours post administration.

32 healthy volunteers were enrolled in the study. All 32 completed the study.

The pharmacokinetic parameters calculated were AUC_{0-t} , $AUC_{0-\infty}$, $AUC_{0-t}/AUC_{0-\infty}$, C_{max} , t_{max} and K_{el} . Primary variables were AUC_{0-t} and C_{max} .

90% geometric intervals for AUC_{0-t} and C_{max} should be within 80-125% in order to conclude bioequivalence.

Results

Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} median, range):

N=30

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test (S.D.)	729.7 (651.04)	809.4 (846.15)	105.8 (48.55)	2.75 (1.00-12.00)	7.01 (2.61)
Reference (S.D.)	707.0 (612.48)	757.8 (759.56)	107.2 (41.36)	2.00 (1.00-12.00)	6.865 (2.63)
*Ratio (90% CI)	103.1% (97.6-109.0%)	105.5% (100.8-110.4%)	96.8% (84.1-111.4%)	0.01 to 1.01	-
CV (%)	12.6	10.1	32.9	-	-

The 90% confidence intervals are within the 80-125% limit as required by current guidelines. Based on the study Glivasol 6 mg tablets are considered bioequivalent with Amaryl 6 mg tablets, Aventis Pharma.

The RMS 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.2 Risk management plan & Pharmacovigilance system

Glimepiride was first approved in 1995 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of glimepiride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet

The content of the SmPC and package leaflet approved during the mutual recognition procedure is in accordance with that accepted for the reference product Amaryl tablets marketed by Aventis Pharma.

Readability test

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

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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Glivasol 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 MAH 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 glimepiride 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 Glivasol with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised on 4 August 2009.

A European harmonised birth date has been allocated (1995-06-20) and subsequently the first data lock point for glimepiride is 2009-06, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 9 May 2010.

The following post-approval commitments have been made during the procedure:

- The Applicant confirms that method transfer and cross-validation will be performed at each site before any batches are tested and released at the respective site.
- The Applicant confirms that stability studies shall be performed on the first three batches of the maximum batch size.