Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

PUBLIC ASSESSMENT REPORT
Scientific Discussion

DIAMICRON 60 mg, modified release tablet
GLICLAZIDE BIOGARAN 60 mg, modified release tablet
(gliclazide)

FR/H/171/02/DC
FR/H/172/02/DC

Applicant: LES LABORATOIRES SERVIER

Date of the PAR: September 2010

Information about the initial procedure:

Application/Legal Basis	Decentralised Procedure/8.3
Active substance	Gliclazide
Pharmaceutical form	modified release tablet
Strength	60 mg
Applicant	Les Laboratoires Servier
EU-Procedure number	FR/H/171/02/DC FR/H/172/02/DC
End of procedure	27th October 2009

1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the decentralised procedure for Diamicron 60 mg, modified release tablet (MRT) and Gliclazide Biogaran 60 mg, modified release tablet from Les Laboratoires Servier was approved on 27th October 2009 for the following 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".*

A comprehensive description of the indications and doses is given in the SPC.

This application is a decentralised procedure (DCP), with France acting as Reference Member State (RMS), and involved:

- For Diamicron 60 mg, MRT: Austria, Belgium, Bulgaria, Germany, Cyprus, Czech Republic, Denmark, Estonia, Spain, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherland, Poland, Portugal, Roumania, Slovenia, Slovak Republic and United Kingdom as Concerned Member State (CMS).

- For Gliclazide Biogaran 60 mg, MRT: Austria, Belgium, Germany, Czech Republic, Denmark, Estonia, Spain, Hungary, Ireland, Italy, Latvia, Lithuania, Netherland, Poland, Portugal, Slovenia, Slovak Republic and United Kingdom as CMS.

This is an informed consent application for registration of a 60 mg gliclazide dosage as a line extension of Diamicron 30 mg, MR formulation already marketed and worldwide used with a possibility of breakability. The breakability of a 60 mg gliclazide MRT was developed and justified by the need to improve convenience of use by covering the entire daily dose range that may vary from a half tablet to two tablets. Indeed, the daily dose of gliclazide could vary from 30 to 120 mg.

The development of Diamicron/Gliclazide 60 mg, MRT included two pharmacokinetic (PK) studies in healthy volunteers (HV):
- Study PKH-05762-001 compared the PK profiles of one tablet of the gliclazide 60mg formulation versus two tablets of the gliclazide 30mg MR formulation in order to demonstrate the bioequivalence between the two formulations;
- Study PKE-05762-002 compared the PK profiles of two half tablets of gliclazide 60mg versus one tablet of gliclazide 60 mg in order to validate the breakability of the S 5762 tablet.

At Day 70, potential serious risks to public health concerns were raised by the RMS and endorsed by all CMS regarding the quality part (lack of validation of the process at industrial scale) and the pharmacokinetic part of the dossier.

This issue was adequately solved by the applicant by providing two additional studies: a Steady State Bioequivalence Study and a Bioequivalence Study in fed conditions. See section 4.3 for details.

Thus, the procedure was ended positively and a Marketing Authorisation (MA) was granted by all CMS.

2. QUALITY ASPECTS

2.1 Introduction

The medicinal product is presented in the form of a modified release tablet containing 60 mg of gliclazide. The excipients are lactose monohydrate, maltodextrin, hypromellose, magnesium stearate and silica colloidal anhydrous.
The medicinal product is packed in a transparent PVC/aluminium blisters packed in cardboard boxes.

2.2 Drug substance

Gliclazide has a monograph in the Eur. Ph. and the manufacturer holds a certificate of suitability of the European Pharmacopoeia.
Gliclazide is a white or almost white powder which is practically insoluble in water.
The specifications to control gliclazide are those of the European Pharmacopoeia monograph "Gliclazide" with additional tests. The methods used are compendial.
The retest period has been assessed as part of the certification procedure and is given in the certificate.

2.3 Medicinal product

The medicinal product is formulated using excipients described in the current Eur. Ph.
All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).
The development is sufficiently described in accordance with the relevant European guidelines. Most of the excipients are already present in the currently marketed 30 mg MR formulation.
Comparative in vitro dissolution profiles of the currently marketed 30 mg tablet strength and the proposed 60 mg tablet strength have been provided.
The manufacturing process has been sufficiently described and critical steps identified.
Results from the process validation studies at industrial scale confirm that the process is under control and ensure both batch-to-batch reproducibility and compliance with the product specification.
The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed. The data support the shelf life claimed in the SPC, 3 years with no special storage precautions.

3. NON-CLINICAL ASPECTS

3.1 Discussion on the non-clinical aspects

This product is a line extension of Diamicron 30 mg, MRT, already marketed in Europe. Thus, no new preclinical data have been submitted and no preclinical assessment has been performed and this is justified.

Environmental risk. As gliclazide is a well-known substance, an evaluation of the environmental risk with this new dosage is deemed unnecessary.

4. CLINICAL ASPECTS

4.1 Introduction

Gliclazide is a sulphonylurea oral hypoglycaemic agent. It is a well-known active substance with established efficacy and tolerability.

It was introduced in France in 1971 as Diamicron 80 mg and has subsequently received marketing approval in approximately 100 countries worldwide. The efficacy and the safety of this oral

antidiabetic agent are well established either in monotherapy or in combination with other antidiabetic drugs such as metformin, acarbose or insulin. No safety issue was raised either in clinical trials or in post-marketing data after more than 30 years of marketing.

Gliclazide exerts its hypoglycaemic effect by stimulating insulin release. It acts *via* sulfonylurea receptors. Besides the ability of gliclazide to stimulate or potentiate glucose-mediated insulin secretion, studies have shown that therapy with gliclazide could improve the insulin sensitivity of peripheral tissues (muscle and liver). Studies have also suggested that gliclazide could reduce the hepatic production of glucose and enhance insulin-stimulated glucose metabolism by potentiating insulin action on skeletal muscle glycogen synthetase.

Before the authorization of the 30 mg, MRT in the EU in October 2000, there were two major marketed pharmaceutical formulations of gliclazide (corresponding to Diamicron 80 mg: formulation I marketed in France and formulation II marketed in United Kingdom). With both formulations, substantial inter-patient variability in pharmacokinetic parameters, as well as in peak-to-trough fluctuations at steady-state, were observed. The development of the new pharmaceutical formulation (MRT) aimed at reducing plasma concentration fluctuations and allowing a once daily dose regimen. The once daily intake of gliclazide is thought to improve treatment compliance. Gliclazide 30 mg (Diamicron 30 mg), modified release (MR) subsequently received marketing approvals in 122 countries worldwide, including 24 EU countries and 98 non EU countries.

4.2 Discussion on the clinical aspects

Diamicron/Gliclazide 60 mg, MRT is a line extension of the already approved 30 mg strength. The development of Diamicron/Gliclazide 60mg, MRT was initially based on two pharmacokinetic (PK) studies in healthy volunteers (HV) : Study PKH-05762-001 compared the PK profiles of one tablet of the gliclazide 60 mg formulation versus two tablets of the gliclazide 30 mg, MR formulation in order to demonstrate the bioequivalence between the two formulations; and Study PKE-05762-002 compared the PK profiles of two half tablets of gliclazide 60 mg versus one tablet of gliclazide 60 mg in order to validate the breakability of the S 5762 tablet.

Nevertheless, when the formulations of the two strengths (30 and 60 mg) were considered and compared, it appears clearly that both formulations differ with regard to rate controlling agent and other excipients.

Considering that the products under review are monolithic modified release formulations, according to the relevant note for guidance on the modified release pharmaceutical forms, the biopharmaceutical development should include the following BE demonstrations:

- single-dose under fasting conditions,
- steady-state under fasting conditions,
- and food-effect testing.

Thus, two additional studies were submitted by the applicant to address these issues:

- Study PKH-05762-006/Steady State Bioequivalence Study in diabetic patients
- Study PKH-05762-003/ Bioequivalence Study in fed conditions,

which have confirmed the bioequivalence of the 60 mg MR strength to two tablets of the already approved 30 mg MR strength.

4.3 Pharmacokinetics

The development of Diamicron/Gliclazide 60 mg, MR included four pharmacokinetic (PK) studies, three single dose studies in healthy volunteers (HV) and one steady state study in diabetic patients:

- Study PKH-05762-001 compared the pharmacokinetic profiles of one tablet of the gliclazide 60 mg MR formulation versus two tablets of the gliclazide 30 mg MR formulation in order to demonstrate the bioequivalence between the two formulations;

- Study PKE-05762-002 compared the pharmacokinetic profiles of two half tablets of gliclazide 60 mg versus one tablet of gliclazide 60 mg in order to validate the breakability of the S 5762 tablet.

- **Study PKH-05762-003** compared the pharmacokinetic profiles of one tablet of 60 mg gliclazide MR versus two tablets of 30 mg gliclazide MR after single oral administration in fed condition in order to demonstrate the bioequivalence between the two formulations in fed condition;

- Study PKH-05762-006 Steady State Bioequivalence Study in diabetic patients assessed the bioequivalence between one tablet of 60 mg gliclazide MR and two tablets of 30 mg gliclazide MR after repeated oral administration.

The studies performed during the development of the 60 mg formulation followed European Good Laboratory Practices and Good Clinical Practice guidelines.

The same design was followed in the first two studies submitted (Study PKH-05762-001, Study PKE-05762-002). The studies were open label, two-treatment, two-period, two-sequence, single-dose, crossover studies with a wash out period of 7 days.

The number of subjects included was 26 in the Study PKH-05762-001, 27 in the Study PKE-05762-002.

The study PKH-05762-003 was designed according to a two-treatment, two-period, two-sequence, single-dose, crossover study with a wash out period of at least 7 days in fed state.
26 subjects were included in this study.

The plasma concentration of gliclazide was monitored over 72 h time period after drug administration in the three single dose studies.

The steady state study PKH-05762-006 was a repeated dose, open-label, randomised; two-way cross-over study performed in type 2 diabetic patients.
36 subjects were included in this study and plasma concentration was monitored over 24h post dose.

The analytical technique used for the measurement of gliclazide plasma concentrations was an LC MS-MS assay and was adequately described and validated.

The primary pharmacokinetic parameters assessed were C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$ in the single dose studies and C_{maxss}, C_{minss} , AUC_{τ} in the steady-state study.

The statistical analysis of the data was conducted according to up to date methods. The analysis consisted in an ANOVA analysis and the estimation of the 90% Confidence Interval of the ratios Test/Reference for each PK parameter of interest.

The main results of the four studies are tabulated below.

Study PKH 05762-001:

Treatment	AUC_{0-t} h.ng/ml	$AUC_{0-\infty}$ h.ng/ml	C_{max} ng/ml	t_{max} h
Test	35762	37048	1367	8.5
Reference	36316	36406	1571	5
Ratio (%) and 90% CI	98 93-105	102 98-106	87 81-94	

$AUC_{0-\infty}$ 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

Study PKE-05762-002:

Treatment	AUC_{0-t} h.ng/ml	$AUC_{0-\infty}$ h.ng/ml	C_{max} ng/ml	t_{max} h
Test	35266	35265	1462	8.9
Reference	34524	34582	1376	6.7
Ratio (%) and 90% CI	102 99-106	102 99-106	106 100-113	

$AUC_{0-\infty}$ 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

Study PKH-05762-003/ Bioequivalence Study in fed conditions.

Treatment	AUC_{0-t} h.ng/ml	$AUC_{0-\infty}$ h.ng/ml	C_{max} ng/ml	t_{max} h
Test	39019	40596	2101	7
Reference	38206	39588	2141	7
Ratio (%) and 90% CI	100 97-103	100 97-103	96 91-102	

$AUC_{0-\infty}$ 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

Study PKH-05762-006/Steady State Bioequivalence Study in diabetic patients.

Treatment	AUC_{tau} h.ng/ml	C_{maxss} ng/ml	C_{minss} ng/ml	t_{maxss} h
Test	39434	2497	969	5.5
Reference	42552	2644	1007	6
Ratio (%) and 90% CI	92.7 86.6-99.2	94.5 86.5-103.2	96.2 86.3-107.3	

AUC_{tau} area under the plasma concentration-time over the dosing interval
C_{maxss} maximum plasma concentration
C_{minss} minimum plasma concentration
T_{maxss} time for maximum concentration

Overall Pharmacokinetic conclusions

- The bioequivalence of the 60 mg, MR strength to two tablets of the already approved 30 mg MR strength is demonstrated when administered under fasted state.

- The bioequivalence of the 60 mg, MR strength to two tablets of the already approved 30 mg MR tablet is demonstrated after single dose administration under fed conditions.

- The bioequivalence of the 60 mg, MR strength to two tablets of the already approved 30 mg MR tablet is demonstrated after repeated-dose administration.

- The bioequivalence of one entire tablet of the 60 mg MR drug product under review to two halves of the same tablet is also demonstrated.

5. OVERALL DISCUSSION , BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Diamicron 60 mg, MRT is demonstrated, and it is a line extension of Diamicron 30 mg, MRT which is a well-known medicinal product with an established favourable efficacy and safety profile. Satisfactory chemical-pharmaceutical documentation has been provided, assuring consistent and sufficient quality of the product.

Based on the overall pharmacokinetic submitted studies, the bioequivalence of the 60 mg MR strength to two tablets of the already approved 30 mg MR strength has been demonstrated. Bioequivalence has been shown to be in compliance with the European guidance documents.

In conclusion, all issues being solved, the CMS mutually recognised the French evaluation of the marketing authorisation for Diamicron 60 mg, modified release tablet and Gliclazide Biogaran 60 mg, modified release tablet.

There was no discussion in the CMD(h).

The SPC, Package Leaflet (PL) and Labelling are in the agreed template. The SPC is consistent with that of the reference product.