19 November 2012
EMA/CHMP/686344/2012
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Glimepirida Parke-Davis and associated names

Glimepiride

**Procedure no:** EMEA/H/A-29/1338

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
**Telephone** +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7051
**E-mail** info@ema.europa.eu **Website** www.ema.europa.eu

# Table of contents

# 1. Background information on the procedure

## 1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Parke-Davis - Produtos Farmaceuticos, Lda submitted an application for decentralised procedure of Glimepirida Parke-Davis and associated names, 2, 3 and 4 mg tablets on 14 March 2011.

The application was submitted to the reference Member State (RMS): PT and the concerned Member States (CMS): AT*, BE*, CY, CZ*, DE, DK*, EE*, EL*, ES*, FI*, FR, HU*, IE*, IT, LT*, LU*, LV*, MT*, NL*, NO*, RO*, SE, SK*, UK.
(*) Note: CMS withdrawn with the response to day 195 comments, including Ireland and the Netherlands, who had raised objections regarding the methodology used to demonstrate bioequivalence.

The decentralised procedure PT/H/0602/002-004/DC started on 18 April 2011.

On day 210, Ireland's and the Netherlands' major issues on bioequivalence remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC by Portugal on 8 March 2012. The CMD(h) 60 Day procedure was initiated on 1 April 2012.

Day 60 of the CMD(h) procedure was on 31 May 2012, and since there could be no agreement, the procedure was referred to the CHMP.

## 1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC to the CHMP was made by Portugal on 31 May 2012. Ireland and the Netherlands raised public health objections regarding the methodology used to demonstrate bioequivalence between the proposed product and the reference product.

# 2. Scientific discussion during the referral procedure

## 2.1. Introduction

Glimepiride is a second generation sulphonylurea anti-hyperglycaemic agent that may be given in a single daily dose. It acts by stimulating insulin release from pancreatic β-cells and possibly also via extra-pancreatic mechanisms. Glimepiride may be considered an alternative to other sulphonylureas for use as monotherapy in patients with type 2 diabetes mellitus insufficiently controlled by diet and exercise alone or in combination with insulin in patients in whom diet and exercise plus oral anti-hyperglycaemic therapy have failed to control blood glucose. Glimepiride has been found to be effective in reducing fasting plasma glucose, post-prandial plasma glucose and glycosylated haemoglobin (HgbA1c) levels and has a good safety profile. Benefits of glimepiride include rapid and complete absorption and possible once-daily dosing. Glimepiride was first authorised in the US in 1995 and has been authorised in the EU since 1996.

The Applicant submitted a marketing authorisation application through the decentralised procedure for Glimepirida Parke-Davis, based on claims of essential similarity to the marketed reference product Amaryl, available in Europe as 1 mg, 2 mg, 3 mg and 4 mg tablets. The Applicant cross-referenced to

the non-clinical and clinical data supporting the authorisation of Amaryl and did therefore not perform any further studies, apart from the required bioequivalence studies. While the reference member state considered the application to be approvable, the objecting concerned member states raised concerns regarding the methodology used to demonstrate the bioequivalence of the proposed products, considering the study conducted with the 1 mg tablet to be insufficient to provide evidence of bioequivalence for the higher strengths.

The CHMP assessed bioequivalence study 182-10, conducted by the Applicant, which was an open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioavailability study of 1 mg glimepiride tablets, administered in 28 healthy adult under fasting conditions. The CHMP also reviewed the Applicant justifications for not using the highest (4 mg) strength to demonstrate bioequivalence, despite the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), which states that for substances with linear pharmacokinetics, bioequivalence should in general be established with the highest strengths, which are the most sensitive to identify a possible difference between formulations, unless the active substance is highly soluble or if there are safety/tolerability reasons.

## *2.2. Critical evaluation*

*Applicant responses*

The Applicant stated that it considered the ethical concerns linked to the investigation of anti-diabetic drugs in healthy volunteers, in particular the risk of hypoglycaemia, which has the potential to lead to a medical emergency, when designing the study. The Applicant therefore reviewed the available literature on glimepiride to support the design of the protocol for the bioequivalence study. In particular, the Applicant reviewed studies by Malerczyk et al (1994), Jovanovic et al (2006) and Pistos et al (2005) as well as a synopsis of fasting and fed bioequivalence studies conducted by Ranbaxy Labs Ltd. using the 1 mg strength. The Applicant also reviewed the SmPC of the reference product, noting that hypoglycaemia is mentioned under adverse reactions. The Applicant noted that studies in healthy human volunteers have been conducted world-wide on all approved strengths of glimepiride i.e. 1, 2, 3, 4 & 6 mg. However, as the fasting studies conducted with strengths higher than 1 mg did not provide detailed discussions of the measures used to avoid hypoglycaemia, a thorough safety assessment was not possible. The Applicant also noted that in the Ranbaxy studies, hypoglycaemia associated with the 1 mg strength was observed in several volunteers, despite oral supplements of glucose being given at regular intervals. The SmPC of the reference product also recommends starting new patients on the 1 mg dose with a stepwise dose increase as needed. The Applicant considered that since the SmPC of the reference product states that the product can be taken shortly before a breakfast, the fasting condition would be the most sensitive condition to detect potential difference between formulations. However, fasting studies involving glimepiride appeared to be associated with a considerable risk of hypoglycaemia, even with the 1 mg dose.

The Applicant therefore explored the acceptability of conducting a bio-equivalence study using the 1 mg tablet in order to waive studies using the higher strengths. Regarding the solubility of the drug substance, the Applicant stated that glimepiride exhibits very low solubility across the physiological pH range and provided data on dissolution profiles of the 1 mg and 4 mg strengths of the proposed and the reference products in different dissolution media (0.1N hydrochloric acid (HCl), pH 4.5 acetate buffer and pH 6.8 phosphate buffer) over time points ranging from 5 to 45 minutes. Due to very low solubility (e.g. <0.0005 mg/ml) of glimepiride in 0.1N HCl and pH 4.5 buffer, less than 5% of the drug substance was dissolved for the 1 mg and the 4 mg strengths of the proposed and the reference products, even after 45 minutes. Given this low rate of dissolution, the Applicant considered that the 1 mg strength possesses enough sensitivity to detect formulation differences. The data using the pH-6.8

buffer also revealed similar dissolution profiles for the proposed and the reference products, when comparing the 1 mg and the 4 mg strengths separately. The Applicant also carried out additional comparisons between the dissolution profiles of the 1 mg and the 4 mg tablets, for both the proposed and the reference products, noting that the extent of drug dissolution was significantly lower for the 4 mg strength (35% dissolved in 45 minutes) compared to the 1 mg strength (70% dissolved in 45 minutes). The Applicant considered this difference to be solely attributable to the lack of sink conditions due to the inherent characteristics of glimepiride and not due to formulation differences between the strengths. The Applicant noted that the current note for guidance allows biowaivers despite non-similar dissolution profiles, provided that the non-similarity is purely due to drug substance characteristics (i.e. sink conditions) and not formulation related.

Regarding the drug substance particle size, which is one of the parameter which may impact on the absorption of drug substances with low aqueous solubility, the Applicant stated that the proposed product uses a micronized grade of glimepiride, with particle size being controlled over a narrow range to ensure that 95% of the particles are below 10 µm and 50% of the particles are below 4 µm. This provides reassurances regarding a potential negative impact due to differences in particle size distribution.

The Applicant also stated that the proposed tablets are developed as look-alike formulations. As a result, all tablet strengths have the same average weight (170 mg) and identical qualitative and quantitative composition in terms of functional excipients, with the exception of small differences in the quantity of the filler lactose monohydrate, which is used proportionally to compensate for the differences in the active substance content (less than 5 % of the total tablet weight) resulting from the range of tablet strengths. This implies that the composition of the different strengths will have the same impact on the in vivo absorption.

Finally, regarding the pharmacokinetics of the drug, the Applicant stated that glimepiride does not exhibit complicated pharmacokinetic properties, as evidenced by the rapid and complete absorption from the gastrointestinal tract, with a linear increase in Cmax and AUC over the entire dosage range.

*CHMP assessment*

The CHMP assessed the Applicant justifications and agreed that glimepiride is associated with a risk of hypoglycaemic reactions, even at the 1 mg dose, in particular in healthy subjects. The CHMP was therefore of the opinion that the exceptional conditions relating to safety described in the *Guideline on the Investigation of Bioequivalence* were applicable in this particular situation, despite the established low solubility of glimepiride.

The CHMP also reviewed the biopharmaceutical data obtained across the physiologically relevant pH range and agreed that the dissolution profile of glimepiride is similar for all strengths, independently of the dissolution medium used, both in sinking and in non-sinking conditions. The CHMP considered that the dissolution studies confirmed that the low dissolution of glimepiride is related to the drug substance rather than to the formulation and that all strengths of the proposed product have similar qualitative and quantitative compositions, leading to similar in vivo absorption. The CHMP also considered the control of the particle size of the active substance through micronization to be reassuring. The CHMP therefore agreed that the identical composition of all strengths and the low concentration of the active substance make differences between the different strengths with regard to the *in vivo* rate of drug release very unlikely.

In terms of concerns regarding the possible incomplete dissolution of the 4 mg strength, the CHMP noted that the proposed and reference formulations exhibited similar performances in all dissolution media and that within dose range, the fraction of absorbed glimepiride is consistently described as being non-dose-dependent and close to 100%, as evidenced from the rapid and complete absorption

from the gastro-intestinal tract with linear increase in Cmax and AUC over the entire therapeutic dosage range. The CHMP was therefore of the view that absorption is not dependent or limited by *in vivo* drug dissolution and that the low solubility of glimepiride does not prevent granting a biowaiver for the 2, 3 and 4 mg strengths.

## 2.3. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

## 2.4. Recommendation

In conclusion, the CHMP was of the opinion that the exceptional conditions relating to safety referred to in the *Guideline on the Investigation of Bioequivalence* are applicable to this particular application, despite the recommendation that bio-equivalence studies should be performed with the highest strength for substances with low solubility. The CHMP therefore considered that the conducted fasting bioequivalence study using the 1 mg strength was acceptable and adequate to demonstrate bioequivalence between the proposed and the reference formulations, while ensuring the safety of the study subjects. The CHMP also considered that the available biopharmaceutical and pharmacokinetic data confirmed the adequate sensitivity of the bio-analytical method and further supported the acceptability of the requested biowaiver for the 2, 3 and 4 mg strengths. While acknowledging that bioequivalence studies have been conducted with doses up to 4 mg in healthy volunteers in the context of other applications, the CHMP considered that a further bioequivalence study using the 4 mg dose is not expected to provide significantly better discriminatory power between the different formulations and that such a study would therefore be unnecessary and ethically unacceptable, given the risk of hypoglycaemia.

## 2.5. Conclusions and benefit risk assessment

Based on:

- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the benefit/risk ratio of Glimepirida Parke-Davis and associated names is considered to be favourable. The CHMP issued a positive opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion. The divergent positions are appended to this report.

# Appendix

## *Divergent positions*

## Article 29(4) referral of Council Directive 2001/83/EC

**Procedure No: EMEA/H/A-29/1338**

**Glimepirida Parke-Davis and associated names**

**Divergent statement**

Based on the presented bioequivalence evidence in their totality, we are of the following opinion:

For the application of the 1, 2, 3 and 4 mg tablets of Glimepirida Parke-Davis only a bioequivalence study with the 1 mg formulation was submitted. For the 2, 3 and 4 mg formulations a waiver for bioequivalence studies was requested.

Glimepiride is an active substance with extremely low solubility over the entire physiological pH-range. According to the *Guideline on Investigation of Bioequivalence*, for substances with low solubility, bioequivalence studies should be conducted at the highest strength, since this is the most sensitive strength to identify a possible difference between formulations. Exceptions could be made if the product cannot be given to healthy volunteers due to safety/tolerability reasons.

We consider the waiver for the higher strengths of the products at issue not acceptable as due to the uncertainty in the extrapolation from the lowest dose to the higher dose there will be the risk for a false-positive conclusion.

The argumentation of the MAH for conducting only a study with the 1 mg tablets based on safety grounds is not endorsed. For glimepiride we do not consider that there are any major safety risks. Although there is a low risk of hypoglycaemia, it could be handled by monitoring and administration of glucose solution if necessary. A study under fed conditions could also reduce the risk of hypoglycaemia.

Therefore the CHMP opinion that the 2, 3 and 4 mg Glimepirida Parke-Davis tablets are considered to be bioequivalent with the 2, 3 and 4 mg innovator tablets is not supported.

**CHMP members expressing a divergent opinion:**

| | | |
|---|---|---|
| Barbara van Zwieten-Boot (NL) | 20 September 2012 | Signature: ..... |
| Jens Heisterberg (DK) | 20 September 2012 | Signature: ..... |
| Concepcion Prieto Yerro (ES) | 20 September 2012 | Signature: ..... |
| Walter Janssens (BE) | 20 September 2012 | Signature: ..... |

| | | |
|---|---|---|
| David Lyons (IE) | 20 September 2012 | Signature: ..... |
| Sol Ruiz (co-opted) | 20 September 2012 | Signature: ..... |
| Hubert Leufkens (co-opted) | 20 September 2012 | Signature: ..... |
| Romaldas Mačiulaitis (LT) | 20 September 2012 | Signature: ..... |