

Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

1. Overall summary of the scientific evaluation of Glimepirida Parke-Davis and associated names (see Annex I)

Glimepiride is a second generation sulphonylurea anti-hyperglycaemic agent used 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 authorised in the EU since 1996. The Applicant submitted a marketing authorisation application for Glimepirida Parke-Davis, based on claims of essential similarity to the marketed reference product. The Applicant therefore only performed the required bioequivalence studies. However, concerns were raised regarding the evidence of bioequivalence, considering the study conducted with the 1 mg tablet to be insufficient to provide evidence of bioequivalence for the higher strengths, as bioequivalence studies for substances with low solubility should be conducted at the highest strength according to the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), unless the active substance is highly soluble or if there are safety/tolerability reasons.

A procedure under Article 29(4) was therefore triggered in June 2012. The CHMP assessed the open label, randomized, comparative bioavailability study of glimepiride 1 mg tablets under fasting conditions and the Applicant justifications for the design of the study.

The Applicant stated that it considered the ethical concerns linked to the risk of hypoglycaemia in healthy adults when designing the bioequivalence study. Having reviewed the available literature, the Applicant concluded that fasting studies involving glimepiride appeared to be associated with a considerable risk of hypoglycaemia, even with the 1 mg dose. The Applicant subsequently explored the acceptability of conducting a study using the 1 mg tablet in order to waive studies using the higher strengths. The Applicant investigated the solubility of drug substance across the physiological pH range and confirmed the very low solubility of glimepiride. With such a low rate of dissolution, the Applicant considered that even the 1 mg strength possesses enough sensitivity to detect formulation differences. The Applicant also considered that the observed decrease in drug dissolution could be solely attributed to the inherent characteristics of glimepiride and not to formulation differences. Regarding the drug substance particle size, the Applicant stated that a micronized grade of glimepiride is used, ensuring that 95% of the particles are below 10µm and 50% of the particles are below 4µm. 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, the Applicant stated that glimepiride exhibits linear pharmacokinetic properties.

The CHMP assessed the Applicant justifications and agreed that glimepiride is associated with a risk of hypoglycaemic reactions, in particular in healthy subjects, including at the lowest 1 mg dose. The CHMP also reviewed the biopharmaceutical data and agreed that the proposed and the reference products have similar dissolution profiles, when comparing the 1 mg and the 4 mg strengths separately. 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 fact that the particle size of the active substance is controlled to be reassuring. The CHMP was therefore of the view that differences between the different strengths with regard to the *in vivo* rate of drug release are very unlikely. Regarding the risk for incomplete dissolution, the CHMP considered that the test and reference formulations exhibited a similar performance, indicating a similar risk for all formulations. In addition, 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 C_{max} and AUC. 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.

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 test and reference formulations, while ensuring the safety of the study subjects. The CHMP also considered that the presented 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. The CHMP considered that a further bioequivalence study using the 4 mg dose is not anticipated to provide significantly better discriminatory power between the different formulations, given the biopharmaceutical features of this glimepiride formulation and that such a study would therefore be unnecessary and ethically unacceptable, given the risk of hypoglycaemia.

The CHMP was therefore of the opinion that the benefit-risk ratio of Glimepirida Parke-Davis and associated names is favourable.

2. Grounds for positive opinion

Whereas

- the CHMP reviewed the available data and the justifications submitted by the Applicant,
- the CHMP considered the conducted bioequivalence study to be adequate to demonstrate bioequivalence between the proposed and the reference products,
- the CHMP considered the requested biowaiver for the 2, 3 and 4 mg strengths to be acceptable,

the CHMP has recommended the granting of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Glimepirida Parke-Davis and associated names (see Annex I).