

## **Annex II**

*Scientific conclusions and grounds for positive opinion*

## Scientific conclusions

The active substance of Merisone is tolperisone hydrochloride, which is a centrally acting muscle relaxant indicated for the symptomatic treatment of post-stroke spasticity in adults. The marketing authorisation application (MAA) for Merisone was submitted under Article 10(1) of Directive 2001/83/EC (i.e. a generic application), *vis-à-vis* the reference medicinal product Mydeton (Gedeon Richter Plc).

The applicant highlighted that, at the time the bioequivalence studies were performed, the summary of product characteristics (SmPC) of the reference medicinal product did not make any recommendations regarding food and did not mention that the food effect was significant. However more recently the effect of food on the bioavailability of tolperisone has been established to be significant and was reflected accordingly in the SmPC of the reference medicinal product at the time of submission of the MAA subject to this referral<sup>1</sup>. The information that was introduced in the SmPC of tolperisone was based on two well-designed studies conducted with different formulations of tablets, which showed that compared to the fasting state, fat-rich food increases the bioavailability of tolperisone by about 100%.

The objecting concerned member state (CMS) was of the view that a similar extent of the food effect that was shown for the two different products referred to above, does not have to hold true for this generic formulation since it has not been proven that the food effect is a characteristic of the active substance and not a formulation related factor. Furthermore it was argued that serious concerns remained as to whether the test product in this case (that is advised to be taken concomitantly with food), would be bioequivalent under fed conditions, given that the results of the bioequivalence studies under fasted conditions were borderline. Therefore the objecting member state was of the view that the two bioequivalence submitted with the 50 and 150mg tolperisone tablets under fasting conditions were not sufficient, and that bioequivalence should be demonstrated under fed conditions.

During the CMDh<sup>2</sup> referral procedure that followed the mutual recognition procedure (MRP), no consensus could be reached as the objecting member state maintained its objection, which was thought to represent a potential serious risk to public health. The CMDh therefore referred the matter to the CHMP through an Art 29(4) referral procedure.

Since the summary of product characteristics (SmPC) of the reference medicinal product did not make any recommendations regarding food and did not mention a food effect, the MAA that was submitted for Merisone included two bioequivalence studies with 50 and 150 mg tolperisone film-coated tablets conducted under fasting conditions with 52 volunteers each. Bioequivalence was demonstrated with regard to the primary pharmacokinetic parameters, i.e. AUC and  $C_{max}$ , in the study with the 150 mg tablet, as the 90% CIs were within the required 80-125% limits. In the study with the 50 mg tablet, bioequivalence was not demonstrated as the upper limit of the  $C_{max}$  was outside the upper band, i.e. 125.49%.

Although the results of the bioequivalence studies were considered to be borderline by the objecting CMS, the applicant argued that the second bioequivalence study was a replicate design study where it was shown that tolperisone is a highly variable drug - the within-subject variability of the reference medicinal product  $C_{max}$  was 46.99%. Because the within-subject coefficient of variation is higher than 30%, the applicant was of the view that according to the current bioequivalence guideline extended limits could have been used to show bioequivalence, which would have been in this case 71.25% – 140.35%.

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<sup>1</sup> Following the outcome of an Article 31 referral procedure on tolperisone-containing medicinal products, for which a Commission decision was adopted in January 2013.

<sup>2</sup> Co-ordination group for mutual recognition and decentralised procedures - human

Therefore based on the results of the submitted bioequivalence studies, the CHMP members agreed that Merisone 50 and 150 mg tablets are bioequivalent to the reference medicinal product Mydeton 50 and 150-mg tablets (Gedeon Richter Plc) under fasting conditions.

The CHMP also noted that the excipients mannitol and betaine found in the product subject to the referral but not in the reference medicinal product, had no effect on the bioequivalence of these products in fasting state.

Taking into account that the MAH had submitted data which showed that tolperisone is a highly soluble and highly permeable active substance, neither solubility nor dissolution was considered to be a limiting factor in terms of *in vivo* absorption. The majority of the CHMP members agreed that *in vivo* dissolution differences between formulations are likely to be less apparent and more difficult to observe in fed conditions since gastric emptying time is longer in the fed state than in the fasting state. Therefore it was considered that fasting bioequivalence studies are expected to be more sensitive to detect formulation differences.

The CHMP noted that the excipients mannitol and betaine found in the product subject to the referral but not in the reference medicinal product, had no effect on the bioequivalence of these products in fasting state. Since the effect of these excipients would be diluted in the presence of food, it was considered unlikely that excipients such as mannitol would be larger in fed conditions compared to fasting conditions, given that the effect of mannitol is based on its osmotic effect.

The Pharmacokinetics Working Party (PKWP) was also consulted to seek their view on whether there is any scientific reasoning that tolperisone (classified as a highly variable drug as the within-subject variability of the C<sub>max</sub> of the reference medicinal product was 46.99%) may have the option of showing bioequivalence in either the fasted or fed state. As there is no evidence that the food-effect is formulation dependent and the formulation is a conventional one, some of the PKWP members considered that a bioequivalence study in the fasting state was acceptable in this case. Other PKWP members were of the view that a fed study would not have been required only if the effects of food were known to be solely hepatic, which however was considered to be insufficiently supported, and since the food effect for tolperisone was considered to be significantly high, a study in a fed state should have been performed.

Taking into account all the evidence and arguments presented, the majority of the CHMP noted that that bioequivalence had been demonstrated in the fasting state for tolperisone, which is highly soluble and highly permeable active substance, demonstrating high within-subject variability. As there is no evidence that the food-effect is formulation dependent, the majority of the CHMP concluded that the bioequivalence studies conducted in the fasting state, which is considered to be the most sensitive condition, would give sufficient evidence to conclude on the bioequivalence in both the fasting and fed states in this particular case.

### ***Grounds for positive opinion***

Whereas

- The Committee considered the notification of the referral triggered by Hungary under Article 29(4) of Directive 2001/83/EC where Germany raised objections that were considered to be a potential serious risk to public health;
- The Committee reviewed the responses submitted by the applicant to address the issues raised with regard to the bioequivalence of Merisone with respect to the reference medicinal product;
- The Committee was of the view that results of the submitted bioequivalence studies showed that Merisone 50 and 150 mg tablets was bioequivalent to the reference medicinal product Mydeton 50 and 150-mg tablets under fasting conditions;
- Therefore, the Committee concluded by majority that the bioequivalence studies conducted in the fasting state give sufficient evidence to conclude on the bioequivalence also in the fed state since Merisone contains a highly soluble and highly permeable active substance, and pharmacokinetic principles and convincing experimental evidence suggest that the food effect of this active substance is formulation independent.

The CHMP has recommended the granting of the marketing authorisation for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group, for Merisone and associated names (see Annex I).