

23 April 2015
EMA/445102/2015

Assessment report

Pursuant to Article 29(4) of Directive 2001/83/EC

Merisone and associated names

International Non-proprietary Names: tolperisone

Procedure no: EMEA/H/A-29/1411

Note:

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

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List of abbreviations

AUC : Area Under the Curve

BCS : Biopharmaceutics Classification System

CHMP : Committee for Medicinal Products for Human Use

CI : Confidence Interval

C_{max} : Maximum Concentration

CMDh : Co-ordination group for mutual recognition and decentralised procedures - human

CMS : Concerned Member State

MAA : Marketing Authorisation Application

MAH : Marketing Authorisation Holder

MRP : Mutual recognition procedure

PK : Pharmacokinetics

PKWP : Pharmacokinetics Working Party

RMS : Reference Member State

SmPC : Summary of Product Characteristics

1. Background information on the procedure

1.1. *Mutual recognition procedure (MRP) and CMDh 60 day procedure*

Meditop Pharmaceutical Co. Ltd. submitted an application for mutual recognition of Merisone and associated names (50 mg and 150 mg film coated tablets), on the basis of the marketing authorisation granted by the Reference Member State (RMS) Hungary on 19 January 2012.

The application was submitted to the concerned Member State (CMS): Germany

The names and MAHs of this medicinal product currently authorised following previous MRPs are listed in Annex I.

The mutual recognition procedure HU/H/0373/001-002/MR started on 8 July 2014.

On day 90, major issues on bioequivalence, raised by Germany, remained unresolved; hence the procedure was referred to the CMDh¹, under Article 29 paragraph 1 of Directive 2001/83/EC, Hungary on 6 October 2014. The CMDh 60 day procedure was initiated on 25 October 2014.

Day 60 of the CMDh procedure was on 23 December 2014, 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 Hungary on 24 December 2014. Germany raised public health objections related to the need for further bioequivalence studies.

2. Scientific discussion during the referral procedure

2.1. *Introduction*

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 referral²:

¹ Co-ordination group for mutual recognition and decentralised procedures - human

² Following the outcome of an Article 31 referral procedure on tolperisone-containing medicinal products, for which a Commission decision was adopted in January 2013.

Section 4.2

“The medicine should be taken after meals with a glass of water. Insufficient food intake may decrease the bioavailability of tolperisone.”

Section 5.2

“High-fat meal increases the bioavailability of orally administered tolperisone by approx. 100% and increases the peak plasma concentration by approx. 45% as compared with fasting condition, delaying time to peak by approx. 30 minutes.”

The above 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 food effect was therefore considered to be a characteristic of the active substance and not dependent on the formulation.

However the objecting Member State 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 studies submitted with the 50 and 150 mg tolperisone tablets under fasting conditions were not sufficient, and that bioequivalence should be demonstrated under fed conditions.

In addition, the argument that this product could be a candidate for a BCS-based biowaiver was not agreed by the objecting Member State because of the presence of the excipients mannitol and betaine in the product subject to the referral, which are not found in the reference medicinal product. This argument is furthermore not relevant for the present discussion because this is a mutual recognition procedure (MRP) and the national approval was based on the bioequivalence studies, and no request for a biowaiver was submitted by the applicant.

During the CMDh referral procedure that followed the 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 Article 29(4) referral procedure.

2.2. Critical evaluation

Bioequivalence

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% (See Table 1 below).

Table 1 Summary statistics of the two submitted bioequivalence studies

Study No	Strength (mg)	PK Parameter	GMR ratio	Confidence Interval
MDTP-T20091B	50	AUC _{0-T}	1.00	88-114%
		C _{max}	1.07	92-125.49%
MDTP-T2010B	150	AUC _{0-T}	100.71%	92.68-109.44%
		C _{max}	109.99%	98.33-123.03%

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%.

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.

Physico-chemical characteristics

It has been shown that the solubility of tolperisone is high as defined in the Guideline on the investigation of the bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). In addition its absorption is not limited by slow permeability through the cell membranes.

The applicant submitted three dissolution studies in which they compared the dissolution of the test product with the reference medicinal product Mydeton (50 and 150 mg) and Viveo 150 mg (another independently developed reference medicinal product). The similarity of the dissolution profiles ($f_2 \geq 50$) of the test product vs. the reference medicinal product in question was shown at pH= 1.2, 4.5 and 6.8 to both reference products.

The initial submission also contained two comparative dissolution studies. In one of these studies the test product (150 mg) dissolved very fast (>85%, 15 min) while the reference product (Mydeton 150 mg) dissolved markedly slower at the highest pH, although meeting the general requirements in the relevant pH range of the stomach.

In summary, in four out of the five dissolution studies the dissolution of the test product was similar to the chosen reference medicinal product. In each of the five studies, the products under question dissolved in a way which can be described as fast (>85% in less 30 minutes) or very fast (>85% in less 15 minutes).

Efficacy/safety

The CHMP noted that the excipients mannitol and betaine had no effect on the bioequivalence in fasting state for the applied product *vis-à-vis* the reference medicinal product. The applicant claimed that no evidence could be found in the literature on any pharmacokinetic effects of the excipients of

mannitol or betaine hydrochloride (at the quantities used) on absorption. Nevertheless the applicant argued that it would be physiologically incomprehensible that these excipients would have a greater effect in fed conditions compared to fasting conditions.

Since the effect of these excipients would be diluted in the presence of food, the CHMP members agreed that it would be unlikely that the effects of excipients such as mannitol would be larger in fed than fasting conditions, given that the effect of mannitol is based on its osmotic effect.

2.3. Recommendation

The submitted bioequivalence studies show 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.

Taking into account that the applicant had submitted data that 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 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 would 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, which can be classified as a highly variable drug (within-subject variability of the C_{max} 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 CHMP noted 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 CHMP concluded that the bioequivalence studies conducted in the fasting state, which is considered to be the most sensitive condition, give sufficient evidence to conclude on the bioequivalence in both the fasting and fed states in this particular case.

2.4. Conclusions and benefit risk assessment

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 recommends the granting of the marketing authorisation for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final version achieved during the Coordination group procedure for Merisone and associated names.

Appendix 1

Divergent positions to CHMP opinion

Article 29(4) of Directive 2001/83/EC

Procedure number: Merisone and associated names (50 and 150 mg tablets) - EMEA/H/A-29/1411

Divergent statement

The following CHMP members consider that approval of Merisone is not favourable based on the presented bioequivalence studies:

It is considered that fed conditions are the most appropriate to detect differences between the formulations, since food intake significantly increases the bioavailability of tolperisone (by approximately 100%) and the product is recommended to be taken under fed conditions. Bioequivalence demonstrated under fasted conditions cannot be extrapolated to the fed conditions, even in case of a BCS class I drug, as it has not been demonstrated that the food effect for tolperisone is unrelated to formulation. The mechanism(s) behind food interactions observed for BCS class I drugs is at present unclear and the food effect seen with tolperisone is substantially greater than that seen for other BCS class I drugs, increasing the likelihood that additional factors may be important. The food effect for tolperisone has not been shown to be entirely related to hepatic factors and it cannot be concluded that the effect is not formulation related.

A bioequivalence study under fed conditions is considered necessary, in line with section 4.2 of the innovator SmPC and the recommendations laid down in the Guideline on Investigation of Bioequivalence.

Bioequivalence with the reference product Mydeton is therefore not considered to be sufficiently demonstrated at the present time.

CHMP members expressing a divergent opinion:

Pierre Demolis	23 April 2015	Signature:
Alar Irs	23 April 2015	Signature:
Robert Hemmings	23 April 2015	Signature:
Romaldas Mačiulaitis	23 April 2015	Signature:
Daniela Melchiorri	23 April 2015	Signature:
Jan Mueller-Berghaus	23 April 2015	Signature:
Ondřej Slanař	23 April 2015	Signature:

Greg Markey	23 April 2015	Signature:
Hubert Leufkens	23 April 2015	Signature:
Harald Enzmann	23 April 2015	Signature:
Pieter de Graeff	23 April 2015	Signature: