

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REFUSAL

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MYDERISON

Tolperisone is a centrally acting muscle relaxant indicated in the spasticity of the skeletal muscles. The originator medicinal product is Mydeton and it was developed by Gedeon Richter, Ltd.

This procedure concerns a bibliographic application of tolperisone film-coated tablets with Hungary as the Reference Member State in the Mutual Recognition Procedure (MRP). The Marketing Authorisation Holder, Meditop Pharmaceutical Co. Ltd., was applying for marketing authorisations for Myderison in Czech Republic, Germany, Lithuania, Poland, Romania and Slovakia.

The Marketing Application of Myderison had been submitted under the WEU (well established use) legal basis.

A Potential Serious Risk for Public Health was raised by the Czech Republic, Lithuania and Slovakia. The CHMP addressed a list of questions and a further list of outstanding issues to the Marketing Authorisation Holder to clarify its concerns regarding: efficacy (including therapeutic indication and the optimal daily dose), safety (drug interactions), kinetic properties, and extent of use of tolperisone.

To further justify the data submitted, the MAH referred to the SPC of the authorised originator product (Mydeton). The publications were grouped in three chapters according to the indications:

- a./ increased tone and spasticity of the skeletal muscles due to organic neurological disorders.
- b./ muscular hypertension and muscular spasm accompanying locomotors diseases
- c./ rehabilitation after orthopaedic and traumatological surgery.

Question 1 – The MAH was asked to demonstrate efficacy and safety in the claimed indication.

The MAH submitted six abstracts of selected publications to support the claimed indication *increased tone and spasticity of the skeletal muscles due to organic neurological disorders*. From these 6 papers only one (Stamenova et al. 2005) was published in an international peer reviewed journal. The trial was a placebo controlled, randomised, double blind dose-titration study of high standard. The article has scientific merit and seems to support the efficacy of tolperisone in decreasing of spasticity of the skeletal muscles due to post-cerebral stroke. However in this trial the majority of the patients had taken tolperisone in higher dose than recommended in the SPC of the originator product. The other papers only refer to observational studies, congress-reports or reviews (published in Hungarian) having limited scientific value.

In addition, to further support the claimed indication the MAH submitted a number of publications on the originator. The MAH presented 15 abstracts on the indication “*muscular hypertension and muscular spasm accompanying locomotors diseases*”. From these 15 publications only one (Pratzel et al 1996) was published in an international peer reviewed journal that had acceptable standard and scientific value (double blind, randomised, placebo controlled).

In this trial tolperisone in dose of 300 mg daily proved to be significantly superior to placebo in treatment of painful reflex muscle spasm, in patients with diseases of the spine column or proximal joints. However there was no significant difference in the mobility of patients treated with tolperisone or placebo.

Out of the other publications six reported on the results of comparative, but open studies, and tolperisone was used added on to a very complex (medicinal and physical) combined therapy. The other papers contain results of various observational studies, congress reports, and surveys (published in Hungarian).

The third indication of Mydeton, *rehabilitation after orthopaedic and traumatological surgery*, is supported only by two observational studies. The scientific value of these papers is rather limited.

The safety profile of tolperisone was not analysed in detail by the MAH. Some information on the safety

of tolperisone can only be collected from the publications submitted to support the use of tolperisone in selected indications, mentioned above. These data show that tolperisone was well tolerated in clinical use, and the side effects (generalized body weakness, fatigue, and dizziness) observed in these clinical trials were usually mild or moderate and did not necessitate the discontinuation of the treatment.

Thirteen cases of more serious side effects (allergic/hypersensitivity reactions) have also been published in the literature; the detailed analysis of the safety profile of tolperisone, including these serious adverse reactions, is missing from the documentation submitted. No data of epidemiological studies on the safety of tolperisone in clinical use have been provided.

Based on the submitted data it can not be ignored that tolperisone might represent an effective and relatively safe treatment option of spasticity and painful reflex spasm due to organic neurological disorders or accompanying locomotor diseases but the poor quality of the clinical trials and data presentations make it difficult to give a general recommendation on the proper use of tolperisone in the indication claimed by the MAH.

The CHMP is of the opinion that the documentation submitted by the MAH is not sufficient to demonstrate the efficacy and safety of tolperisone.

Question 2 - The MAH had to provide sufficient information on pharmacokinetics of tolperisone hydrochloride and comment on the relevance of bibliographic data submitted which concern a product different from Myderison.

The MAH presented a new study report, MDTP-T20091B, which was a PK study sponsored by Meditop performed in 48 healthy volunteers. This study, according to the MAH, confirmed the PK parameters of the relevant publications. The PK parameters have been compared to the innovator product however the results of the PK study had not been included.

Considering the number of tolperisone formulations on the market, the CHMP asked the MAH to elaborate on the difference in the bioavailability of tolperisone between the various manufacturing procedures. The MAH stated, after assessment of own PK data, that *no significant difference was observed in the relevant bibliographic data reviewed concerning similar products containing tolperisone.*

The MAH claimed that the PK variability occurred due to genetic polymorphism of drug metabolizing enzymes, without providing reliable data on that reasoning. The highly variable PK needs to be carefully addressed since the potential efficacy and safety implications are high.

In summary, there are no data on PK/PD relationship, no confirmation of sufficient efficacy and safety in such a variable PK and the dosing has not been properly selected, as well. The clinical relevance of inter-individual variability of tolperisone PK and the potential impact of CYP2D6 polymorphism of the drug are unknown.

In conclusion, the CHMP is of the opinion that the MAH's response is not sufficient to have reliable information about the PK characteristics of Myderison.

Question 3 - The MAH was asked to provide data from scientific literature justifying the dosing recommended in the proposed SPC.

The majority of clinical studies with tolperisone have been performed in a dose range of 150–450 mg/day. A similar range is recommended in the Product Information in most countries. The MAH did not intend to claim different dosage range and posology.

The MAH argued that no specifically designed dose-response/dose-titration study was performed for tolperisone. Still, one of the studies performed by Stamonova et al (2005) was a dose range, dose titration study.

No dose-response relationship has been established; the MAH used as main reference, in justifying the posology of Myderison, the SPC of Mydeton, DRUGDEX and other un-specified products.

The MAH emphasized the inter-individual differences in the AUC and Cmax of the drug which were variable after oral tolperisone treatment. Furthermore, the oral dose might need to be individualised within the recommended dose range 150-450 mg / day according to the clinical needs.

The MAH proposed a 3-fold higher dose than in the approved German PI for the innovator.

The CHMP acknowledged that there is a lack of reliable dose finding studies in publicly available sources but did not find enough justifications to support the claimed daily dose recommendation.

Question 4 - The MAH was asked to provide data taken from scientific literature on possible drug-drug interactions especially with drugs metabolised by CYP2D6 enzyme system.

The MAH admitted that no formal or specific drug interaction studies with tolperisone have been performed and only limited clinical reports are available from several publications.

Tolperisone is metabolised by the cytochrome P450 system in particular CYP2D6. It means that all drugs which metabolism depends on the activity of this system may potentially interact with tolperisone or vice versa. The CHMP noted that no formal or specific drug interaction studies have been performed. The MAH only presented a list of drugs used in combination or in parallel with tolperisone and stated that no report on unwanted interaction with tolperisone had been reported in the clinical trials. According to the published data, tolperisone can be co-administered with: sedatives, hypnotics, and NSAID-s with no relevant or unwanted drug interactions.

The CHMP noted that in his response the MAH refers to in vitro studies focusing on the enzymes which are involved in the metabolism of tolperisone. Regarding the metabolic profile of tolperisone the in vitro data which are discussed in the response document do not substitute for the in vivo interaction studies and do not allow conclusive on possible PK or PD drug-drug interactions.

In view of the above the CHMP considered that information to justify the proposal for section 4.5 of the SPC was missing and therefore no conclusions could be reached on this regards.

Question 5 - The MAH was asked to present the quantitative aspects of the use of the substance within the community.

The MAH presented in its response the extent of the tolperisone use in some European countries. The sources were not validated, not all the MAHs and data related to non various generic products were included.

The CHMP considered that it was not clear whether tolperisone has also been registered in other EU countries or only in the countries mentioned by the MAH.

The CHMP noted that the data provided on the extent of use of tolperisone in Europe was inconclusive.

Benefit/Risk Assessment

In the response document to CHMP list of questions, the MAH did not pursue presenting full text of scientific articles to be evaluated. The MAH decided to submit a set of abstracts with any scientific discussion related. None of the CHMP questions were sufficiently answered.

The CHMP, based on the data submitted by the MAH, concluded that the benefit/risk ratio of clinical use of tolperisone is negative.

The CHMP retained his concerns regarding: efficacy (therapeutic indication and the optimal daily dose), safety (drug interactions), kinetic properties, and extent of use of tolperisone.

The CHMP is of the opinion that the MAH's responses to the questions raised are insufficient to support the WEU application of Myderison.

GROUNDNS FOR REFUSAL

The CHMP considered that the “Well-Established” use in accordance to Article 10(a) of Directive 2001/83/EC for Myderison has not been demonstrated.

Whereas

- the documentation submitted is not sufficient to cover all aspect of the efficacy and safety assessment of tolperisone, in particular to justify the claimed therapeutic indication and posology.
- the MAH failed to explain the relevance of PK data submitted concerning a product different from Myderison.
- the information on drug-drug interaction was missing
- the MAH has not been able to clearly demonstrate that tolperisone has been extensively used.

The CHMP recommended the refusal of the granting of the Marketing Authorisation in the Concerned Member States and the revocation of the Marketing Authorisation for Myderison where the product is currently authorised.