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Committee for Medicinal Products for Human Use (CHMP)

Thymanax

Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

International non-proprietary name: agomelatine

Procedure No. EMEA/H/C/000916/PSUV/0021

Period covered by the PSUR: 20 February 2013 – 19 February 2014

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Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for Thymanax, and further discussions at the CHMP, the scientific conclusions are as follows:

The CHMP considers that the benefit risk balance for the product remains positive. However, hepatotoxicity remains an important safety concern with agomelatine. The severity and incidence of hepatic ADRs reported during this PSUR period are of the same magnitude as in the previous PSUR period and there seems to be a considerable level of non-compliance with the recommended liver transaminases monitoring programme in clinical practice despite the measures already in place. This is supported by the results of a recent analysis based on the observational cohort study evaluating the safety of agomelatine in medical practice (CLE-068), indicating that baseline monitoring was documented for only 65% of the patients while a baseline value and at least one post baseline value, was documented for 55%. Still, there are indications of an improvement in transaminases monitoring over time and the effectiveness of the last DHPC (October 2013), in which prescribers were reminded of the importance of transaminase monitoring, cannot be fully evaluated in this PSUR.

The CHMP recommends that the product information is amended to clarify the monitoring requirements for the liver function, in particular the necessity for LFTs to be performed *before* starting treatment, and that the following additional risk minimization measures and pharmacovigilance activities should be introduced in an updated version of the RMP to increase the compliance of the regime and its monitoring: 1) Physicians guide to prescribing, 2) Patient booklet with recommendations regarding liver adverse reactions, 3) a post-authorisation safety category 3 study to evaluate the adherence to the monitoring regime and the compliance to relevant contraindications (date for submission of interim/final reports should be December 2016).

Hepatic impairment should be considered deleted from the missing information in the RMP. As hepatotoxicity is an important identified risk, hepatic impairment is a contraindication for the product, and detailed recommendations for monitoring of hepatic function is already included in the SmPC and PIL.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for Thymanax, the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing the active substance agomelatine is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.