Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions

The CMDh, having considered the PRAC recommendation dated 6 March 2014 with regards to zolpidem-containing medicinal products, agrees with the recommendation therein as stated below:

Overall summary of the scientific evaluation by PRAC

In February 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) discussed the results of the search in EudraVigilance (EV) of cases of impaired driving ability as well as road traffic accidents associated with zolpidem, performed by the Italian Competent Authority (AIFA). Following this, the PRAC requested the MAH of the reference medicinal product for zolpidem to submit a cumulative review of spontaneous cases, clinical studies and published literature of 'impaired driving ability', 'Road traffic accidents' and 'Somnambulism' associated with zolpidem.

In light of the data provided in the cumulative review performed by the MAH, and taking into consideration the recent Food and Drug Administration (FDA) approved label changes specifying new dosing recommendations for zolpidem-containing medicinal products, AIFA considered that it was in the interest of the EU to refer the matter to the PRAC for a benefit-risk review of zolpidem-containing medicinal products. Therefore in July 2013, AIFA requested the PRAC to give a recommendation under Article 31 of Directive 2001/83/EC on whether marketing authorisation of these products should be maintained, varied, suspended, or withdrawn.

The PRAC reviewed the safety and efficacy data relating to the risk of impaired driving and somnambulism following treatment with zolpidem.

The analysis of the submitted individual case reports of driving ability and somnambulism showed that whatever the age and gender category, most of the cases of impaired driving were reported at a 10mg daily dose for both events. Amongst the risk factors for impaired driving and somnambulism were, concomitant intake of other CNS depressants, sleep-deprivation and alcohol or illicit drugs consumption. Discrepancies about drug-drug interactions information were observed in different product information of zolpidem containing products, notably on the interaction of zolpidem with CNS depressant. Based on evidence from the literature, it was considered necessary to amend and harmonise the 'Interaction with other medicinal products' section of the product information.

Some studies showed an association between impaired driving performance on the next morning and middle of the night intake of zolpidem. It was therefore considered by the PRAC that the dosing recommendation should include instructions that Zolpidem is to be taken in a single intake immediately at bedtime and should not be re-administered during the same night.

Considering that the effect of zolpidem may last for at least 8 hours and in view of the above referred risk factors, the PRAC also recommended to include warnings indicating that the risk of impaired driving is increased if zolpidem is taken within less than 8 hours before performing activities that require mental alertness, if zolpidem is taken in a higher than the recommended dose, and/or co-administered with other CNS depressants, and/or alcohol or illicit drugs.

With regards to the effects on the ability to drive and use machines, the PRAC recommended that vehicle drivers and machine operators are warned that in addition to the possible risk of drowsiness, prolonged reaction time and impaired driving the morning after therapy, there is also the possibility of dizziness, sleepiness, blurred/double vision and reduced alertness. The product information was amended accordingly.

Finally and in view of further minimising the risks of impaired driving and somnambulism, a potential lowering of the recommended dose for adults was discussed by the PRAC. However, on a population level, the randomised trials only showed convincing evidence of efficacy of the 10mg dose of zolpidem. The provided data did not consistently show that a lower dose would be effective or that a lower dose would significantly reduce the risk of impaired driving and somnambulism, and it was considered that reducing the daily recommended dose would likely result in in-effective doses being used, in turn resulting in additional doses being taken in the middle of the night and in an increased risk of accidents the following day.

The PRAC therefore agreed that the recommended daily dose of zolpidem should not be reduced for adults. It was however acknowledged that in some patients a lower dose of 5mg could be effective. The currently recommended daily dose in the elderly and in patients with hepatic impairment is 5mg, and this dose recommendation remains unchanged in the product information.

Overall conclusion

Based on the totality of the data available on the safety and the efficacy of zolpidem, and considering all the risk minimisation measures proposed during assessment, the PRAC concluded that the benefit-risk balance of zolpidem-containing medicinal products remains favourable subject to changes to the product information.

Grounds for the PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for zolpidem-containing medicinal products;
- The PRAC reviewed all available data provided by the MAHs on the safety and efficacy of zolpidem-containing medicines with regards the risk of impaired driving ability and somnambulism following treatment with zolpidem;
- The PRAC considered that the data from post-marketing spontaneous case reports, clinical trials, published literature and other available information have shown that the use of zolpidem-containing products is associated with an increased risk of impaired driving and somnambulism;
- The PRAC also reviewed the available data on the efficacy of zolpidem in order to determine whether amendments to the posology would help to minimise the risks but agreed that the available efficacy data do not provide robust evidence that a lower dose would be effective on a population level;
- The PRAC considered that the above-mentioned risks of impaired driving ability and somnambulism could be mitigated by changes to the product information of zolpidem-containing medicines, in particular that zolpidem should be taken as a single intake immediately at bedtime and not exceed the recommended dose, without being re-administered during the same night, as well as highlighting the risks regarding impaired driving and somnambulism, warnings and precautions aimed at decreasing this risk and also the risks of co-administration with CNS depressants and alcohol, and/ or illicit drugs;

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing zolpidem identified in Annex I remains favourable, subject to the changes to the product information set out in Annex III.

CMDh position

The CMDh, having considered the PRAC recommendation dated 6 March 2014 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached a position on the variation of the marketing authorisations of zolpidem containing medicinal products for which the amendments to the product information are set out in annex III.