Appendix to CMDh position

Divergent positions to CMDh position

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1363 for Flupiritine containing medicinal products

The following CMDh Members support the divergent position appended to the PRAC recommendation on flupirtine containing medicinal products dated 13 June 2013, as stated below:

CMDh members expressing a divergent position

Virginie Bacquet (FR)	26 June 2013	Signature: ……...
Anna Kalita (PL)	26 June 2013	Signature: ……...
Maria-Luisa Garcia Vaquero (ES)	26 June 2013	Signature: ……...
Kora Doorduyn (NL)	26 June 2013	Signature: ……...
Keith McDonald (UK)	26 June 2013	Signature: ……...
Sophie Colyn (BE)	26 June 2013	Signature: ……...
Laurence O'Dwyer (IE)	26 June 2013	Signature: ……...

<u>Divergent statement from PRAC members</u>

Some members of PRAC did not agree with the PRAC's Recommendation on the Article 107i referral for flupirtine containing medicinal products based on the following reasons:

- Uncertainties about the benefits in the proposed indications

From an efficacy point of view, both the data provided by the marketing authorisation holders and the published studies show very limited evidence of the efficacy of flupirtine in the proposed indications of acute pain. The few published studies on acute, mild-moderate pain have a number of deficiencies including small number of patients, lack of statistical analysis of outcomes, or lack of a placebo group. A single study with an acceptable design and well described (Überall 2012) which seems to show an equivalent efficacy with regard to tramadol, cannot be deemed as proof of efficacy since in the same study, tramadol was not superior to placebo. This suggests some

deficiencies in the study and questions data reliability. Some of the problems above described for mild-moderate acute pain, are also identified in the studies for moderate-severe acute pain.

Overall, there is an absence of well designed randomised, double blind, placebo controlled studies with clinical meaningful results to support the efficacy of flupirtine in short term (< 2 weeks) analgesic treatment.

– Uncertainties about the hepatotoxicity and the risk minimisation strategy proposed

The lack of clarity on the mechanism by which flupirtine causes hepatotoxicity is of real concern and the data indicate it is most likely idiosyncratic, and not due to accumulation, since there is no dose dependency and no clear time-relationship. This is further supported by pre-clinical experiments and liver biopsy data suggesting it is idiosyncratic in nature. Consequently the risk of hepatotoxicity with flupirtine is unpredictable, and hence cannot be excluded in short term use (up to 2 weeks).

Any risk mitigation strategy needs to be sufficiently robust and evidence driven to prevent unnecessary harm in the context of a treatment for which there are therapeutic alternatives. Given that the hepatoxic effect of flupirtine is most likely idiosyncratic this calls in to question the ability to introduce appropriate risk minimisation measures. Inclusion of a requirement for weekly liver function monitoring is considered to add an additional unnecessary burden to patients with no clear benefit in terms of risk minimisation. Furthermore they are not considered clinically feasible and hence are unlikely to be adhered to in routine clinical practice.