IRISH MEDICINES BOARD

16th September 2013

Safety Information following an EU safety review of flupirtine containing medicines (not licensed in Ireland)

Restriction of target population and limitation of treatment duration for flupirtine containing medicinal products following assessment of hepatotoxicity risk

Dear Pharmacist,

The IMB would like to inform you of the outcome of an EU safety review that was recently completed for flupirtine containing medicinal products, following safety concerns of hepatotoxicity and the lack of proof of efficacy for chronic pain.

While flupirtine is not authorised in Ireland, the IMB is aware of a low level of usage of exempt (unlicensed) products and has requested that we highlight the new restrictions to the indication and duration of use to be implemented to licenses in Member States where the product is licensed.

While there have been notifications of exempt use in Ireland, a comprehensive list of prescribers is not available. For this reason, we would greatly appreciate your cooperation in highlighting the outcome of the safety review to other healthcare professionals of which you are aware, that are involved in the care of patients treated with flupirtine.

Further information on the outcome of the review is available on the website of the European Medicines Agency (EMA) at the following link; European Medicines Agency - News and Events - Restrictions in the use of flupirtine-containing medicines - CMDh endorses PRAC recommendation

Summary of the recommendations of the EU review:

- **Assessment of spontaneous reports of hepatic disorders associated with the use of flupirtine, which ranged from asymptomatic increase of liver enzymes to liver failure, has led to the update of prescribing information for flupirtine containing medicinal products.**

- **Flupirtine should now only be used in the treatment of acute pain in adults if treatment with other analgesics (e.g. non-steroidal anti-inflammatory drugs, weak opioids) is contraindicated.**

- **The duration of treatment for oral formulations must not exceed 2 weeks.**

- **Contraindications now include patients with pre-existing liver disease or alcohol abuse, as well as concomitant use of flupirtine with other drugs known to cause drug induced liver injury.**

- **Liver function tests must be performed at weekly intervals during treatment and if abnormal liver function tests or clinical symptoms consistent with liver disease occur, treatment must be discontinued.**

- **If any symptoms compatible with hepatic damage occur, treatment must be immediately discontinued.**

- **Doctors should review patients on Flupirtine containing products in line with these recommendations at their next scheduled appointment.**

Further information on the safety concern and recommendations

This assessment was triggered following an increasing number of reports of liver problems associated with the use of flupirtine, which ranged from asymptomatic increase of liver enzymes to liver failure. A review of reports in the European Union adverse reaction database identified a total of 800 individual case safety reports with flupirtine reported as a suspect or interacting medicinal product. Of these, there were 332 cases reported that related to the SOC *Hepatobiliary disorders*. All but four of these were cases from Germany. Twenty-four of the cases resulted in a fatal outcome, 17 of which involved hepatotoxicity.

Flupirtine has been authorised since the 1980s and was first introduced as an alternative analgesic to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation were identified.

Patient exposure to flupirtine has increased steadily and a growing number of reports of probably idiosyncratic liver toxicity associated with flupirtine have been observed. Reactions ranged from asymptomatic liver enzyme elevation to fatal liver failure or liver transplantation. Three more recent clinical trials also reported elevated transaminases in patients treated with flupirtine and additional cases have been described in the literature.

The conclusions of the assessment indicate that the major safety concern of hepatotoxicity and the lack of proof of efficacy for chronic pain limit the indications of flupirtine to treatment of acute pain and restrict the duration of treatment to 2 weeks. The benefit-risk balance of flupirtine is considered to be favourable in the revised recommended therapeutic indication and if the warnings, precautions for use, and contra-indications are implemented.

Call for reporting of adverse reactions

Healthcare professionals should report any adverse reactions suspected to be associated with the use of any medicine or vaccine to the Irish Medicines Board using the online reporting system, or downloadable report forms at *www.imb.ie* , or through the post-paid yellow card option which can be obtained from the Irish Medicines Board. Adverse reactions can also be reported to the Irish Medicines Board by calling on (01) 676 4971.

Yours Sincerely,

Joan Gilvarry

Dr. Joan Gilvarry, MB, FRCPI

Director of Human Medicines