13 September 2013
EMA/563900/2013

Restrictions in the use of flupirtine-containing medicines

On 26 June 2013, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed by majority new recommendations to restrict the use of oral flupirtine medicines and suppositories. These medicines should only be used for treating acute (short-term) pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drug (NSAIDs) and weak opioids, and treatment should not last longer than 2 weeks.

In addition, patients' liver function should be checked after each full week of treatment and treatment should be stopped if the patient has any signs of liver problems. Flupirtine must also not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.

The recommendations follow a review by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) which looked into reported liver problems with flupirtine, ranging from high liver-enzyme levels to liver failure. The PRAC evaluated the available data on liver safety, noting that there were no cases of liver failure or liver transplantation reported in patients who took the medicine for 2 weeks or less. The PRAC also reviewed the available data on the benefits of flupirtine and concluded that, while there were data from studies in the treatment of acute pain, there were insufficient data to support its use in the treatment of long-term pain.

In addition to oral medicines and suppositories, this review also covered injectable flupirtine medicines which were being given as a single injection for pain following surgery. The PRAC concluded that the benefits of injectable flupirtine continue to outweigh their risks when used in this way. Doctors using the injectable flupirtine should also follow relevant advice to minimise risk to patients.

The CMDh agreed with the PRAC's conclusions and endorsed the PRAC's recommendations on the use of flupirtine-containing medicines. The CMDh position was sent to the European Commission, which endorsed it and adopted a final legally binding decision valid throughout the EU on 5 September 2013.

Information to patients

- Oral flupirtine medicines and suppositories should only be used to treat acute (short-term) pain in adults who cannot use other painkillers (such as NSAIDs and weak opioids). If you are taking flupirtine, your treatment should not last longer than 2 weeks.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

© European Medicines Agency, 2013. Reproduction is authorised provided the source is acknowledged.

- You should not take flupiritine as a long-term treatment for chronic pain. If you have been taking flupirtine for longer than 2 weeks you will need to get your treatment reviewed by your doctor or pharmacists.
- Because flupirtine may have effects on the liver in some patients, your doctor will test your liver function during treatment and stop treatment if there are any signs of liver problems.
- If you are being treated with flupirtine and have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information to healthcare professionals

A review of the safety data from the EU adverse reaction database revealed 330 cases of adverse liver events suspected to be linked to flupirtine. The events ranged from asymptomatic increases in liver enzymes to liver failure. No cases of liver failure or liver transplantation were reported in patients who took the medicine for 2 weeks or less.

With regard to the evidence of efficacy, the review highlighted a lack of sufficient data on the benefits of flupirtine in chronic pain. In particular, there was a lack of efficacy data on the use of flupirtine for longer than 8 weeks.

Based on the findings of this review, healthcare professionals in the EU are advised of the following updated recommendations:

- Oral flupirtine medicines and suppositories should only be used to treat adults with acute pain and only if treatment with other painkillers (such as NSAIDs and weak opioids) is contraindicated.
- The duration of treatment with flupirtine should not exceed 2 weeks and patients' liver function should be checked after each full week of treatment.
- Treatment must be stopped in any patient with abnormal liver function tests results or symptoms of liver disease.
- Flupirtine must not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.
- Healthcare professionals should review the treatment of patients taking flupirtine taking into account the recommendations above.

More about the medicine

Flupirtine is a non-opioid painkiller that has been used to treat pain, such as pain associated with muscle tension, cancer pain, menstrual pain and pain following orthopaedic surgery or injuries.

Flupirtine-containing medicines have been authorised since the 1980s and are currently available in the following EU Member States: Bulgaria, Estonia, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania and Slovakia.

Flupirtine is available as 100-mg immediate-release capsules, 400-mg extended-release tablets, 75-mg and 150-mg suppositories and as a solution for injection (100 mg). The 100-mg immediate-release capsules are available in the 11 EU Member States listed above. The other dosages and pharmaceutical forms are only available in Germany.

Flupirtine was first introduced as an alternative painkiller to opioids and NSAIDs. Subsequently, multiple other actions such as muscle relaxation were identified. Flupirtine works as a 'selective

neuronal-potassium-channel opener'. This means that it opens specific pores on the surface of nerve cells called potassium channels. The opening of these channels reduces the excessive electrical activity that leads to many pain states.

More about the procedure

The review of flupirtine-containing medicines was initiated in March 2013 at the request of Germany, under Article 107i of Directive 2001/83/EC. It followed the procedural steps laid out in Article 107i of Directive 2001/83, also known as the urgent Union procedure.

A review of these data was first conducted by the PRAC. The PRAC recommendations were sent to the CMDh, which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by majority it was sent to the European Commission, which endorsed it and adopted a final legally binding decision valid throughout the EU.

Contact our press officers

Monika Benstetter or Martin Harvey

Tel. +44 (0)20 7418 8427

E-mail: press@ema.europa.eu