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Withdrawal of pain medicine flupirtine endorsed

Serious liver problems continued to be reported despite previous restrictions in use

The CMDh[1] has endorsed EMA's recommendation to withdraw the marketing authorisation for the pain medicine flupirtine, because of the risk of serious liver injury. This means that the medicine will no longer be available.

The EMA recommendation was the outcome of a review of flupirtine medicines which was started because liver problems continued to be reported even after measures were introduced in 2013 to manage this risk. These measures had included limiting flupirtine use to no more than 2 weeks in patients with acute pain who could not use other painkillers, and carrying out weekly tests of liver function during treatment.

The review, carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), looked at the available data including studies evaluating whether the 2013 restrictions were followed in clinical practice. It also assessed cases of serious liver damage reported since the 2013 review.

The CMDh agreed with the PRAC conclusion that the restrictions introduced in 2013 have not been sufficiently followed, and cases of serious liver injury, including liver failure, still occurred. In addition, no further measures to increase adherence to the restrictions nor adequately reduce the risk of liver problems could be identified.

The CMDh therefore agreed that patients taking flupirtine-containing medicines continue to be exposed to serious risks which outweigh the benefits of these medicines. In order to protect public health, the CMDh endorsed the PRAC recommendation to withdraw the marketing authorisations of flupirtine-containing medicines.

Information for patients

- Flupirtine-containing medicines have been used to treat acute (short-term) pain for up to two weeks in adults who cannot use other painkillers (such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids).
- These medicines are being taken off the market in the EU because of a risk of serious liver injury.

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

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- Strict measures to try to reduce this risk were introduced in 2013 but have not been put into practice widely enough, and liver injury has continued to be reported. In addition, no further measures to reduce the risk of liver problems could be identified.
- Since 2013, cases of serious liver injury, including 23 cases of acute liver failure (sudden loss of liver function), some of which were fatal or led to transplantation have been reported following flupirtine use. [2]
- Alternative treatment options are available.
- Patients with any questions should speak to their healthcare professional.

Information for healthcare professionals

- Flupirtine-containing medicines are being taken off the market in the EU because of the risk of serious liver injury.
- Restrictions introduced in 2013, which included limiting flupirtine use to two weeks and regular monitoring of liver function tests, have not been sufficiently followed in clinical practice. While the use of flupirtine-containing products has decreased, the measures implemented have not been effective at minimising the risk.
- In addition, no further measures to increase adherence to the restrictions nor adequately reduce the risk of liver problems could be identified.
- Healthcare professionals should consider alternative treatments for patients.
- Healthcare professionals in the EU countries where flupirtine is marketed will receive a letter with detailed information on the appropriate actions to be taken, including when the medicine will become unavailable.
- Since 2013, cases of serious liver injury, including 23 cases of acute liver failure, some of which were fatal or led to transplantation have been reported following flupirtine use.[2] The reactions are unpredictable and the exact mechanism by which flupirtine causes liver injury is not known.
- Six observational studies showed a lack of compliance with the measures that were introduced to minimise the risk of hepatotoxicity.

More about the medicine

Flupirtine is a medicine used to treat acute (short-lived) pain for up to 2 weeks, in patients who cannot use other painkillers such as opioids or nonsteroidal anti-inflammatory medicines (NSAIDs). Flupirtine works as a 'selective neuronal potassium channel opener'. This means that it opens specific pores on nerve cells called potassium channels. The opening of these channels reduces the excessive electrical activity that leads to many pain states.

Flupirtine-containing medicines have been authorised since the 1980s and are currently available in the following EU Member States: Estonia, Germany, Latvia, Lithuania, Luxembourg, Poland, Portugal, and Slovakia. They are available under several trade names and in different formulations.

[2] These cases have been reported in the European database of suspected adverse drug reaction reports (Eudravigilance) between April 2013 and December 2017

More about the procedure

The review of flupirtine was initiated on 26 October 2017 at the request of Germany, under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a position on 21 March 2018. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

Since the CMDh adopted its position by consensus, it will be directly implemented by the Member States where the medicines are authorised, according to an agreed timetable.