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EU Warns Flurbiprofen Can Potentially Mask Infection Symptoms

by Tom Gallen

Popular OTC sore throat treatment flurbiprofen can possibly mask the symptoms of infection and lead to treatment delays, according to EU medicines regulators. Products sold in the EU containing flurbiprofen will soon be required to carry information warning patients and healthcare professionals about this risk.

OTC and Rx presentations of flurbiprofen sold in Europe will soon be required to carry a warning that the drug can mask the symptoms of infection.

Following a safety review of the nonsteroidal anti-inflammatory drug, topical flurbiprofen products must also flag up the risks of use during pregnancy.

Changes to the product information for flurbiprofen have been ordered by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) after it endorsed the recommendations of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee.

Based on periodic safety update reports from marketing authorization holders, PRAC said a new warning was required on the possible masking effect of flurbiprofen (systemic, oromucosal formulations and transdermal patches) for the symptoms of infection, with consequent delay in the initiation of appropriate treatment and worsening of the infection.

CMDh has asked member states to ensure marketing authorization holders of all flurbiprofen products with systemic and oromucosal formulations and transdermal patches submit a variation to update the Summary of Product Characteristics.

Flurbiprofen In EU

Under section 4.4 of the SmPC "Special warnings and precautions for use" the following text must be added:

Masking of symptoms of underlying infections

Epidemiological studies suggest that systemic non-steroidal anti-inflammatory drugs (NSAIDs) can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When <product name> is administered while the patient suffers from fever or pain in relation to infection, monitoring of infection is advised.

CMDh also set out amendments to the patient-focused package leaflet, specifically for section 2, which covers what users need to know before taking a particular drug.

Flurbiprofen products are approved at a national level across the EU, with oromucosal formulations widely available OTC for the treatment of sore throat in adults and children.

According to AESGP data, flurbiprofen lozenges are marketed without prescription in virtually all European countries, with France a notable exception.

Reckitt's flurbiprofen brand Strefen is sold in numerous markets including Norway, Spain and Sweden, while Viatris' Froben is available in Italy and Estonia and Sanofi's Lizifen in Spain. Other manufacturers marketing lozenges include Bayer, Sandoz and Alfasigma.

Over 300 flurbiprofen products, both OTC and Rx, are national authorized in Europe.

The leaflet must advise patients to talk to their doctor or pharmacist before taking flurbiprofen if they have an infection. The following text must be included:

Infections

Non-steroidal anti-inflammatory drugs (NSAIDs) may hide signs of infections such as fever and pain. This may delay appropriate treatment of infection, which may lead to an increased risk of complications. If you take this medicine while you have an infection and your symptoms of the infection persist or worsen, consult a doctor or pharmacist without delay.

Under section 3 of the package leaflet – which informs patients how to take the product – MAHs must add the message:

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms. If

you have an infection, consult a doctor or pharmacist without delay if symptoms (such as fever and pain) persist or worsen (see section 2).

Flurbiprofen is not the first NSAID required by the EU authorities to flag up risks related to infections. In 2020, a warning about masking the symptoms of underlying infections was added to ibuprofen and ketoprofen-containing products. (Also see "*EMA Committee Warns Ibuprofen Can Seriously Exacerbate Infections*" - HBW Insight, 13 May, 2020.)

This was triggered by a French medicines agency review of adverse events related to ibuprofen and ketoprofen use by patients suffering from a range of mild infections which developed into more serious infections. (Also see "*France Warns Of Serious Complications Related To OTC Ibuprofen Use*" - HBW Insight, 25 Apr, 2019.)

Fears over the safety of NSAIDs led the French medicines agency, ANSM, to reverse-switch from OTC to prescription-only status flurbiprofen back in 2019. (Also see "*France Reverse-Switches Flurbiprofen Against Backdrop Of NSAID Concerns*" - HBW Insight, 28 May, 2019.)

Pregnancy Advice

In addition to the new infection warnings, MAHs of all flurbiprofen products with oromucosal formulations and transdermal patches must review the product information wording around use during pregnancy.

The SmPC Section 4.6 – covering use of the product during pregnancy – must be updated to add the following:

There are no clinical data from the use of [product name] during pregnancy. Even if systemic exposure is lower compared with oral administration, it is not known if the systemic [product name] exposure reached after topical administration can be harmful to an embryo/fetus. During the first and second trimester of pregnancy, [product name] should not be used unless clearly necessary. If used, the dose should be kept as low and duration of treatment as short as possible. During the third trimester of pregnancy, systemic use of prostaglandin synthetase inhibitors including [product name] may induce cardiopulmonary and renal toxicity in the fetus. At the end of the pregnancy prolonged bleeding time in both mother and child may occur, and labour can be delayed. Therefore, [product name] is contraindicated during the last trimester of pregnancy (see section 4.3)

The package leaflet must include the warning:

Oral forms (e.g. tablets) of flurbiprofen can cause adverse effects in your unborn baby. It is not known if the same risk applies to [product name]. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Do not use [product name] if you are in the last 3 months of pregnancy. You should not use

[product name] during the first 6 months of pregnancy unless clearly necessary and advised by your doctor. If you need treatment during this period, the lowest dose for the shortest time possible should be used.

CMDh advises that in cases where the product information already includes similar or stricter advice on use in pregnancy, such advice continues to be valid and should remain.

These changes were communicated to EU member states – as well as Norway, Iceland and Liechtenstein – on 3 September with CMDh setting a deadline for implementation of 2 November 2023.

Subject to these proposed product information changes, CMDh said it was satisfied that the benefit-risk balance of medicinal products containing flurbiprofen is unchanged.