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Questions and answers on the suspension of buflomedil-containing medicines

Outcome of a procedure under Article 107 of Directive 2001/83/EC

The European Medicines Agency has completed a review of the safety and effectiveness of buflomedil-containing medicines, both oral and injectable, due to serious side effects seen with buflomedil. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of buflomedil do not outweigh its risks, and has recommended that all marketing authorisations for medicines containing buflomedil should be suspended throughout the European Union (EU).

What is buflomedil?

Buflomedil is a vasoactive agent, a medicine which has an effect on blood circulation. Buflomedil increases the blood flow to the brain and other parts of the body by widening the blood vessels. It is used to treat the symptoms of peripheral arterial occlusive disease (PAOD), a condition where the body's large arteries become obstructed causing symptoms such as pain and weakness, particularly in the legs. Buflomedil is used in patients with stage II PAOD, which means that they experience severe pain when walking relatively short distances.

Buflomedil-containing medicines have been authorised in the EU since the 1970s via national procedures. Buflomedil is authorised in Austria, Belgium, Cyprus, France, Germany, Greece, Italy, Luxembourg, the Netherlands, Poland, Portugal and Spain, under the invented name Loftyl and other trade names. Buflomedil is available in the form of tablets, an oral solution or a solution for injection.

Why was buflomedil reviewed?

In February 2011, the French medicines regulatory agency suspended the marketing authorisations for buflomedil-containing medicines because of serious and sometimes fatal side effects seen with these medicines. These included neurological disorders such as convulsions and *status epilepticus* (a dangerous condition where the brain is in a persistent state of seizure), and cardiac disorders such as accelerated heart rate and cardiac arrest. These side effects mainly occurred in elderly patients or in patients with kidney problems who did not receive the appropriately reduced dose and whose kidney function was not suitably monitored. Buflomedil can build up in the body and there is only a small difference between the treating dose and the dose that can harm certain patients, such as those with

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kidney problems. Patients with PAOD are likely to have kidney problems due to the nature of the condition.

Measures to minimise the risks with buflomedil had already been taken in some of the Member States where the medicine is marketed. These included changes to the packaging and product information, recommendations on adjusting the dose for patients with kidney problems and restrictions on the medicines' use in certain patients (for instance patients with epilepsy). France had previously taken such measures in 1998 and 2006, but concluded in February 2011 that these had not been sufficient to prevent serious side effects from occurring in France.

As required by Article 107, France informed the CHMP of its latest action to suspend the marketing authorisations in France, so that the Committee could prepare an opinion on whether the marketing authorisations for products containing buflomedil should be maintained, changed, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

The CHMP considered the benefit-risk assessments previously carried out, including by France in 2010-2011, as well as information requested from the companies that market buflomedil-containing medicines in the EU. This included data from clinical trials with buflomedil, post-marketing surveillance and the published literature, as well as from poison control centres in Europe on cases of severe poisoning with buflomedil.

What are the conclusions of the CHMP?

The CHMP noted that there was a risk of serious neurological and cardiac side effects in patients when buflomedil is used normally, due to the small difference between the treating dose and the dose that can harm elderly patients or people with certain conditions such as kidney problems, which are common in patients with PAOD. In spite of measures put in place by regulatory authorities to minimise the risks, serious side effects continue to be reported. The CHMP also noted that the medicine had only been shown to have a limited benefit for patients, measured in terms of walking distance, and that the studies also had a number of methodological weaknesses.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP concluded that the benefits of buflomedil-containing medicines do not outweigh their risks, and recommended that all marketing authorisations for medicines containing buflomedil should be suspended throughout the EU.

What are the recommendations for patients and prescribers?

- Doctors should stop prescribing buflomedil and consider alternative treatment options. These include managing underlying health problems which can increase the risk of PAOD, such as diabetes, high cholesterol, high blood pressure as well as smoking.
- Patients currently using buflomedil-containing medicines should speak to their doctor to review their treatment.
- Patients who have any questions should speak to their doctor or pharmacist.

The European Commission issued a decision on 13 February 2012.