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Questions and answers on the suspension of oral buflomedil-containing medicines

The European Medicines Agency is reviewing the safety and effectiveness of buflomedil-containing medicines, both oral and injectable. The Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended that the benefits of oral buflomedil do not outweigh its risks, and that the supply of these medicines should be suspended throughout the European Union (EU). The CHMP is still reviewing injectable buflomedil, and will adopt an opinion at the end of the full review[1].

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 available in the form of tablets or an oral solution 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 also authorised in some Member States as a solution for injection. The benefit-risk balance of injectable buflomedil is also being reviewed by the CHMP and an opinion will be adopted at the end of the full review.

Why is buflomedil being 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. This mainly occurred due to an accidental or intentional overdose, or in patients with kidney problems who did not receive the appropriately reduced dose.

[1] Outcome of a procedure under Article 107 of Directive 2001/83/EC.

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Measures to minimise the risks with buflomedil, in particular the risk of overdose, had already been taken in some of the Member States where the medicine is marketed. These included changes to the packaging, 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 in France these had not been sufficient to prevent overdoses and serious side effects from occurring.

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 overdose and severe poisoning with buflomedil.

What are the recommendations of the CHMP?

The CHMP noted that there was a risk of serious neurological and cardiac side effects in patients taking oral buflomedil, particularly due to overdose. 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 the studies assessed had a number of 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 in the form of tablets or an oral solution do not outweigh their risks, and recommended that the supply of oral buflomedil-containing medicines should be suspended throughout the EU.

The Committee is currently finalising the review of injectable buflomedil and will make recommendations at the end of the full review.

What are the recommendations for patients and prescribers?

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