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Restrictions on use of medicines containing ergot derivatives

CHMP confirms its recommendations for dihydroergotoxine following a re-examination

On 27 June 2013, the EMA's Committee for Medicinal Products for Human Use (CHMP) recommended restricting the use of medicines containing ergot derivatives. These medicines should no longer be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications. This is based on a review of data showing an increased risk of fibrosis (formation of excess connective tissue that can damage organs and body structures) and ergotism (symptoms of ergot poisoning, such as spasms and obstructed blood circulation) with these medicines.

At the request of a manufacturer of medicines containing dihydroergotoxine, one of the ergot derivatives, the CHMP carried out a re-examination of its opinion on this medicine. The re-examination concluded on 24 October 2013 with the Committee maintaining its previous recommendation, which will now be sent to the European Commission.

The European Commission has already endorsed the CHMP opinion for 4 other ergot derivatives (dihydroergocristine, dihydroergotamine, nicergoline dihydroergocryptine), adopting a final legally binding decision on 27 September 2013.

Ergot derivatives that are only indicated for these conditions will have their marketing authorisations suspended across the EU. In some EU Member States, ergot derivatives are also authorised for other indications such as treatment of dementia, including Alzheimer's disease, and treatment (as opposed to prevention) of acute migraine headache. They will remain authorised for use by patients in those indications.

In its review, the CHMP considered all available data on the benefits and risks of ergot derivatives, including data from clinical studies, post-marketing safety reports and the published literature. The review was initiated due to concerns identified by the French National Agency for the Safety of Medicine and Health Products (ANSM) in a national pharmacovigilance review in 2011.

Fibrosis can be a serious, sometimes fatal disease, which is often difficult to diagnose because of delayed symptoms and may be irreversible. The CHMP noted that there is a plausible mechanism by which ergot-derivatives could cause fibrosis and ergotism. Given that the evidence for these medicines'



benefits in these indications was very limited, the CHMP concluded that the benefits in the concerned indications did not outweigh the risk of fibrosis and ergotism.

Information to patients

- Medicines containing substances known as ergot derivatives can have serious side effects, called fibrosis and ergotism. As a result, they should no longer be used in the EU to treat a number of conditions involving blood circulation problems (that usually affect elderly patients) or problems with memory and sensation, or to prevent migraine headaches, as the risks outweigh the benefits.
- You should make a non-urgent appointment with your doctor if you are taking a medicine containing any of these substances: dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine. Your doctor will confirm whether you should change to another treatment.
- If you are unsure whether you are affected, or if you have any questions, speak with your doctor or pharmacist.

Information to healthcare professionals

- Healthcare professionals should stop prescribing medicines containing dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine, for any of the following indications:
 - Symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in the elderly (excluding Alzheimer's disease and other dementia);
 - Ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD Stage II);
 - Ancillary treatment of Raynaud's syndrome;
 - Ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin;
 - Acute retinopathies of vascular origin;
 - Prophylaxis of migraine headache;
 - Orthostatic hypotension;
 - Symptomatic treatment of veno-lymphatic insufficiency.
- Patients currently taking these medicines for any of the above indications should have their treatment reviewed at a routine (non-urgent) medical appointment.
- Some ergot derivatives are approved in some EU Member States for use in other therapeutic indications, including other circulatory disorders, treatment of dementia (including Alzheimer's disease) and treatment of acute migraine. These indications were not included in the CHMP review; therefore these products will remain authorised and may continue to be used in those indications.

The CHMP opinion follows a review of available safety and efficacy data on ergot derivatives in the above indications, including clinical studies, post-marketing data in Europe and the published literature:

- Fibrosis was most frequently reported with dihydroergotamine, including retroperitoneal, cardiac, pulmonary and pleural fibrosis. There were fewer reports of fibrotic reactions with the other ergot

derivatives. The CHMP noted the difficulty of diagnosing fibrosis (due to delayed onset of symptoms) and the probability of under-reporting of fibrotic reactions.

- Ergot derivatives are recognised as being capable of inducing fibrosis, in particular heart valve fibrosis, through serotonergic receptor activation, which is extensively described in the literature. The varying affinity for serotonergic receptors of the different ergot derivatives, and the therapeutic doses used, may explain the differences observed in reporting frequencies for the fibrotic reactions.
- Cases of ergotism or potentially related symptoms were most frequently reported with dihydroergotamine. Patients were young (mean age 41 years-old), with a short time to onset after starting dihydroergotamine (less than 2 months, mean: 2 days). The severity of such adverse effects and their possible fatal outcome was underlined. Several cases of ergotism or symptoms potentially related to ergotism (including severe cases of symptoms of constriction of peripheral blood vessels) were also identified with the other ergot derivatives.
- The available efficacy data for the described indications were considered to be very limited. In addition, scientific advisory groups held in December 2012 and October 2013 did not consider there was evidence of a therapeutic need for ergot derivatives in the indications covered by the review.

More about the medicine

Ergot derivatives are substances derived from a group of fungi commonly known as ergot. Five ergot derivatives were considered in the CHMP review: dihydroergocristine, dihydroergotamine, dihydroergotamine, nicergoline and the combination of dihydroergocryptine with caffeine.

Medicines containing ergot derivatives have an effect on blood circulation and they have been used for decades to treat conditions involving circulatory problems. Certain ergot derivatives have been used to treat conditions usually affecting elderly patients, such as peripheral arterial occlusive disease (PAOD, where the body's large arteries become obstructed) causing pain when walking, and Raynaud's syndrome (where the blood supply is blocked to the extremities, usually the fingers and toes), as well as eyesight disturbances due to blood circulation problems. They have also been used for treating chronic pathological cognitive and neurosensorial impairment (problems with memory and sensation) and for preventing migraine headaches. In some EU countries, certain ergot derivatives are also authorised for other indications not covered by the CHMP review, including other circulatory disorders, treatment of dementia (including Alzheimer's disease) and treatment of acute migraine.

In the EU, medicines containing ergot derivatives have been authorised by national procedures and have been marketed under various trade names. The pharmaceutical forms and the approved indications, strengths and doses vary in different EU countries.

More about the procedure

The review of ergot derivatives was initiated on 18 January 2012 at the request of France, under Article 31 of Directive 2001/83/EC. The French medicines agency asked the CHMP to carry out an assessment of the benefit-risk balance and to issue an opinion on whether the marketing authorisations for these medicines should be maintained, varied, suspended or withdrawn across the European Union.

The procedure for 4 ergot derivatives (dihydroergocristine, dihydroergotamine, nicergoline dihydroergocryptine) has concluded, with the European Commission endorsing the CHMP opinion and adopting a final legally binding decision on 27 September 2013.

The CHMP opinion on dihydroergotoxine will now be forwarded to the European Commission, which will issue a final decision in due course.

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