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Restrictions on the use of methysergide-containing medicines

On 20 February 2014, the European Medicines Agency recommended restricting the use of methysergide due to concerns that it could cause fibrosis, a condition in which fibrous (scar) tissue accumulates in the body's organs potentially damaging them. Methysergide medicines are now only to be used for preventing severe intractable migraines and cluster headaches (a type of severe, recurring headache on one side of the head, usually around the eye) when standard medicines have failed.

In addition, treatment should only be started and supervised by a specialist doctor with experience in treating migraine and cluster headaches. Patients should also be screened for fibrosis at the start of treatment and should have additional screenings every 6 months. Treatment must be discontinued if symptoms of fibrosis occur.

The Agency's Committee for Medicinal Products for Human Use (CHMP), which conducted the review, noted that these recommendations were necessary due to the reports of fibrosis seen with methysergide and other medicines of the same class (ergot derivatives). The symptoms of fibrosis often take some time to appear and without screening the diagnosis may come too late to prevent severe (and potentially life-threatening) damage to organs .

Regarding the benefits, the Committee noted that there is some evidence of a clinically relevant effect of methysergide when used for prevention in patients who regularly get migraines and cluster headaches and for whom treatment options are limited. Methysergide has also been used for treating diarrhoea caused by carcinoid disease (a slow-growing tumour that commonly affects the gut). However, there were no data to support this use and Methysergide should therefore no longer be used in carcinoid disease.

The prescribing information for physicians and information in the patients' information leaflet has been updated. The CHMP recommendations were sent to the European Commission, which has endorsed them and issued a final legally-binding decision that is valid throughout the EU.

Information to patients

- Methysergide-containing medicines may cause a potentially serious condition known as fibrosis, in which scar tissue accumulates in some of the body's organs. As a result of this, the use of these

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

medicines is being restricted to the prevention of severe intractable migraines and cluster headaches when standard medicines have failed.

- Methysergide should no longer be used for treating diarrhoea caused by carcinoid disease (a type of slow-growing tumour). If you are being treated for this purpose, please contact your doctor to discuss alternative treatment.
- If you are using methysergide to prevent migraines and cluster headaches, your doctor will check on a regular basis whether you are developing any signs or symptoms of fibrosis. Your doctor will stop your treatment if fibrosis is suspected.
- Your doctor will also regularly re-assess the need for you to continue treatment with methysergide by seeing if your symptoms return after periodic breaks in treatment.
- Patients who have any questions should speak to their doctor or pharmacist.

Information to healthcare professionals

- Methysergide should no longer be used for treating diarrhoea caused by carcinoid disease.
- Following the review of methysergide-containing medicines, methysergide should now only be used for:
  - Prophylactic treatment of severe intractable migraine (with or without aura) with functional disability in adults, when treatment with standard medicines has failed. Previous treatment must have included treatment with medicines of other classes for at least 4 months at the maximum tolerated dose;
  - Prophylactic treatment of episodic and chronic cluster headache in adults when treatment with standard medicines has failed. Previous treatment must have included treatment with medicines of at least 2 classes for a minimum of 2 months.
- Treatment with methysergide should only be started and supervised by specialised physicians with experience in treating migraine and cluster headaches.
- Patients should be screened for fibrosis at baseline and at least every 6 months thereafter. Screening investigations may include heart ultrasound, abdominal MRI and lung function tests. Treatment must be stopped if a patient develops symptoms suggestive of fibrosis unless an alternative cause is confirmed.
- Treatment must not begin until after the patient has been examined for any pre-existing fibrotic conditions. Once treatment is started the patient must be examined for occurrence of fibrosis at 6-monthly intervals. This examination should include a re-assessment of the benefit-risk balance in the individual patient.
- During treatment with methysergide, a treatment-free period of at least 4 weeks must be allowed between treatment courses at least every 6 months.

The Agency's recommendations are based on available data on the benefits and risks of methysergide, from clinical studies, post-marketing safety reports and the scientific literature. Based on these data a potential causal association between methysergide and fibrosis seems likely. The mechanism by which methysergide could cause fibrosis through serotoninergic-receptor activation is widely described in the literature.

More about the medicine

Methysergide is a medicine that belongs to the class 'ergot alkaloids' that has been used in the EU for preventing migraines (with or without aura) and other types of throbbing headaches. It was also used to treat diarrhoea caused by carcinoid disease.

In the EU, medicines containing methysergide 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 methysergide was initiated on 24 May 2012 at the request of the French medicines agency ANSM under Article 31 of Directive 2001/83/EC following concerns about serious cases of fibrosis identified by the French agency.

The CHMP opinion was sent to the European Commission, which endorsed it and issued a final legally binding decision on 28 April 2014.

Contact our press officers

Monika Benstetter or Martin Harvey

Tel. +44 (0)20 7418 8427

E-mail: press@ema.europa.eu