30 May 2013
EMA/321395/2013

European Medicines Agency recommends restricting Trobalt to last-line therapy in partial epilepsy

Benefit-risk balance remains positive for patients who cannot use alternatives; restricted use is recommended due to risk of retinal pigmentation

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of the anti-epileptic medicine Trobalt (retigabine) only to those patients for whom other anti-epileptic medicines have proved inadequate or have not been tolerated. This follows a careful evaluation of cases of pigmentation (abnormal colouring) of the skin, nails, lips and eye tissues, including the retina (the light sensitive layer at the back of the eye) reported in patients taking part in long-term studies.

The CHMP recommended that patients currently being treated with Trobalt should be reviewed at a routine (non-urgent) appointment. The balance of benefits and risks should be re-evaluated, and patients should be informed of the latest safety information. The CHMP also recommended that a comprehensive eye examination should be performed at the start of treatment (for new patients) and at least every six months during treatment. If retinal pigment or vision changes are detected, treatment with Trobalt should only be continued after a careful re-assessment of the balance of benefits and risks.

Among the 55 patients who had received Trobalt in the long-term studies and who have been examined so far, 15 had retinal pigmentation. Around one third of the 15 patients with retinal pigmentation also had impaired vision, although this was mild in all but one patient. It is currently uncertain if this impairment was present before starting Trobalt treatment, or whether it was in any way related to the pigmentation. In addition, 51 cases of blue-grey pigmentation of the nails, lips and skin have been reported in the long-term studies. At present, the nature of the colour changes and how the medicine could cause them is still being clarified.

In its assessment, the CHMP took into account not only the importance of retinal pigmentation, as it could possibly result in impaired vision, but also considered that uncontrolled epilepsy is a serious condition which may be life-threatening if left untreated. The CHMP therefore concluded that Trobalt remains a valuable alternative option for patients whose epilepsy cannot be controlled by other medicines.

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

Information to patients

- You should note that changes in colour of the retina (the light sensitive layer at the back of the eye) have been observed in some patients following long-term treatment with the anti-epileptic Trobalt. Since this might lead to eyesight problems, Trobalt should now only be used by patients who cannot be treated with other anti-epileptic medicines.
- Do not stop your treatment without talking to your doctor. Stopping anti-epileptic medication may put you at risk of seizures (fits).
- If you are currently being treated with Trobalt, your doctor may consider switching you to an alternative treatment.
- During treatment with Trobalt, your doctor will request an eye examination for you at least every six months. If you experience changes in vision, talk to your doctor.
- If retinal or vision changes are detected, the benefits and risks of continuing treatment with Trobalt will need to be re-assessed with your doctor.
- Some patients taking Trobalt have also had a blue-grey pigmentation of their nails, lips, or skin. If you notice such changes while taking the medicine, speak to your doctor.
- If you have any questions, speak to your doctor or pharmacist.

Information to healthcare professionals

- In light of the risk of retinal pigmentation, healthcare professionals should only prescribe Trobalt to adult patients with drug-resistant partial onset seizures with or without secondary generalisation for whom other appropriate combinations have proved inadequate or have not been tolerated.
- Patients currently receiving Trobalt should be reviewed at a routine (non-urgent) appointment. The balance of benefits and risks should be re-evaluated, and patients should be informed of the risk of pigmentation with long-term treatment.
- Healthcare professionals should request a comprehensive eye examination at the start of treatment and at least every six months while treatment with Trobalt is ongoing. Patients already treated with Trobalt should have an appointment scheduled for an eye examination.
- If retinal pigmentation or vision changes are detected, Trobalt should be discontinued unless no other suitable treatment options are available. If continued, the patient should be monitored more closely and the potential risks weighed against the benefits of continuing treatment with Trobalt.
- Retinal pigmentation has occurred in a high proportion of patients treated long-term with Trobalt: 15 out of the 55 patients participating in the ongoing long-term clinical studies who have been examined so far. Almost all cases of retinal pigmentation occurred after 2 years of treatment. This may explain why no cases of pigmentation have been reported post marketing, since the medicine was only authorised 2 years ago.
- In some of these 15 cases, patients had impaired vision (including reduction in visual acuity and in the visual field). At present it is not known whether this was due to the retinal pigmentation.
- In patients who develop a blue-grey pigmentation of the nails, lips or skin, treatment with Trobalt should only continue after a careful assessment of the benefits and risks.
- Taking this safety concern into account but also acknowledging that Trobalt has a different mechanism of action to other medicines and could be of benefit to some patients with uncontrolled

epilepsy, the CHMP concluded that Trobalt continues to have a role in the treatment of patients for whom alternative treatment is inadequate or is not tolerated.

More about the medicine

Trobalt (retigabine) was authorised in the EU on 28 March 2011 as add-on treatment in adults with partial-onset seizures (epileptic fits). This is a type of epilepsy where too much electrical activity in one part of the brain causes symptoms such as sudden, jerky movements of one part of the body, distorted hearing, sense of smell or vision, numbness or a sudden sense of fear. The medicine is available as tablets in the following Member States: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

Epilepsy is caused by excessive electrical activity in the nerve cells of the brain. Trobalt has an effect on the potassium channels located on the nerve cells of the brain. These are pores that let potassium move in and out of the cell and play a role in terminating electrical impulses. Trobalt acts by helping to keep the potassium channels open. This may stop further transmission of electrical impulses thereby preventing epileptic seizures.

More about the assessment

The company that markets Trobalt, Glaxo Group Ltd., submitted a variation application in December 2012 to update the product information for Trobalt following cases of pigmentation of nails, lips, skin and retina observed in patients taking part in ongoing long-term studies with the medicine.

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has now finalised its assessment and recommended changes to the prescribing information for Trobalt. The CHMP opinion will be sent to the European Commission, which will issue a legally binding decision.