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SCIENCE MEDICINES HEALTH

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Restrictions in use of cyproterone due to meningioma risk

On 13 February 2020, EMA's safety committee (PRAC) recommended that medicines with daily doses of 10 mg or more of cyproterone should only be used for androgen-dependent conditions such as hirsutism (excessive hair growth), alopecia (hair loss), acne and seborrhoea (excessively oily skin) once other treatment options, including treatment with lower doses, have failed. Once higher doses have started working, the dose should be gradually reduced to the lowest effective dose.

The medicines should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable.

There is no change in use of the medicines in men for prostate cancer.

The recommendations follow a review of the risk of the rare tumour meningioma with cyproterone. Overall, this side effect is rare: it may affect between 1 and 10 in 10,000 people, depending on the dose and duration of treatment. The risk increases with increasing cumulative doses (the total amount of medicine a patient has taken over time).

Available data do not indicate a risk for low-dose cyproterone medicines containing 1 or 2 milligrams cyproterone in combination with ethinylestradiol or estradiol valerate and used for acne, hirsutism, contraception, or hormone replacement therapy. However, as a precaution, they should not be used in people who have or have had a meningioma. This restriction is already in place for the higher dose medicines.

Doctors should monitor patients for symptoms of meningioma, which can include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches, memory loss, seizures or weakness in arms and legs. If a patient is diagnosed with meningioma, treatment with cyproterone medicines must be stopped permanently.

As part of the ongoing surveillance of the safety of the medicines, companies marketing medicines containing 10 mg or more of cyproterone will be required to carry out a study to assess doctors' awareness of the risk of meningioma and how to avoid it.

Meningioma is a rare tumour of the membranes covering the brain and spinal cord. It is usually non-malignant and is not considered to be a cancer, but due to their location in and around the brain and spinal cord, meningiomas can cause serious problems.

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The PRAC recommendation was adopted by the CMDh[1] by consensus and will be implemented directly at national level.

Information for patients

- There is a risk of meningioma (a non-cancerous brain tumour) from medicines containing cyproterone. The risk, which is very low, occurs especially when the medicines are taken at high doses (25 mg daily or more).
- For some uses – excess hair growth, hair loss, acne and oily skin – medicines containing 10 mg or more cyproterone should only be given when other treatment options, including lower-dose cyproterone medicines, have not worked or cannot be used. Once they have started working, the dose should be gradually reduced to the lowest dose that works.
- Cyproterone medicines should only be used to reduce sex drive in sexual deviations in men when other options for treatment are not suitable.
- Although there is no evidence of a risk for low-dose products containing cyproterone in combination with ethinylestradiol or estradiol valerate, as a precaution, these medicines should not be used in people who have or have had a meningioma. Higher-dose cyproterone-containing medicines already have this restriction not to use with meningioma.
- There is no change in the use of cyproterone medicines for prostate cancer.
- If you are taking a cyproterone medicine and have any questions about your treatment, talk to your doctor or pharmacist.

Information for healthcare professionals

- The occurrence of meningiomas (single and multiple) has been reported in association with the use of cyproterone acetate, primarily at doses of 25 mg/day and above.
- The risk increases with increasing cumulative doses of cyproterone acetate. Most cases have been reported after prolonged exposure (several years) to high doses of cyproterone (25 mg a day and above).
- Medicines containing 10 mg or more of cyproterone should only be used for hirsutism, androgenic alopecia, acne and seborrhoea once other treatment options, which could include low-dose cyproterone-containing medicines such as cyproterone acetate 2 mg/ethinylestradiol 35 micrograms, have not worked. After clinical improvement, the dose should be gradually reduced to the lowest effective dose.
- Cyproterone medicines should only be used in men for reduction of sex drive in sexual deviations when other treatments are not appropriate.
- Healthcare professionals should monitor patients for clinical signs and symptoms of meningioma in line with clinical practice. Symptoms may be unspecific and include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures or weakness in extremities.
- If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped.

[1] Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

- Cyproterone acetate (1 and 2 mg) in combination with ethinylestradiol or estradiol valerate will be contraindicated in patients with a meningioma or history of meningioma. Higher-dose cyproterone medicines already have this contraindication.
- There is no change in the use of cyproterone medicines for prostate cancer. These medicines are used as antiandrogen treatment in inoperable prostate cancer, including for prevention of the initial flare-up in treatment with luteinizing hormone-releasing hormone (LHRH) agonists.
- The association of cyproterone acetate with meningioma was first added to the product information for medicines with cyproterone daily doses of 10 mg or more in 2009, with a contraindication for people with a history of meningioma.
- This review included recent results from a French epidemiological study showing a cumulative dose-dependent association between cyproterone acetate and meningioma (Weill et al) and an analysis by the French medicines agency ANSM of cases of meningioma with cyproterone use in France. Recent published literature and analysis of the EU database of adverse events, EudraVigilance, were also included.

A direct healthcare professional communication (DHPC) will be sent to healthcare professionals prescribing, dispensing or administering the medicine in due course. The DHPC will also be published on a dedicated page on the EMA website.

More about the medicine

Cyproterone is an antiandrogen medicine, meaning that it blocks the action of androgens, a type of sex hormone found in both men and women, and it also acts in the same way as another sex hormone called progesterone. Medicines containing cyproterone are available as tablets (10 mg, 50 mg, 100 mg) and solution for injection (300 mg/3 ml). Cyproterone medicines are used to treat various androgen-dependent conditions such as hirsutism (excessive hair growth), alopecia (hair loss), acne, prostate cancer and reduction of sex drive in sexual deviations in men. They are also used as contraception and in hormone replacement therapy. Cyproterone medicines contain either cyproterone alone or cyproterone at a lower dose in combination with an oestrogen (a third type of sex hormone).

Cyproterone has been authorised in the EU via national procedures since the 1970s and is available on prescription under various trade names.

More about the procedure

The review of cyproterone-containing medicines was initiated on 11 July 2019 at the request of France, under Article 31 of Directive 2001/83/EC.

The review was first carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendation was sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted it by consensus on 26 March 2020. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures.

The PRAC recommendation will now be implemented by EU Member States, Iceland, Lichtenstein, Norway and the United Kingdom[2].

[2] As of 1 February 2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period.