

## Cyproterone medicines: use restricted due to meningioma risk

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### Information on Cyproterone medicines

- Cyproterone is an antiandrogen medicine, which act in same way as progesterone, a sex hormone. Cyproterone acts by blocking the action of androgens, sex hormones found in both men and women
- Cyproterone-containing medicines are available as tablets (10 mg, 50 mg, 100 mg) and solution for injection (300 mg/3 ml).
- Cyproterone-containing medicines are used to treat various androgens-dependent conditions such as hirsutism (excessive hair growth), alopecia (hair loss), acne, prostate cancer and reduction of sex drive in sexual deviations in men. These medicines are also used as contraceptives and hormone replacement therapy
- Cyproterone-containing medicines can contain either cyproterone alone or cyproterone in combination with oestrogen (a third type of sex hormone).

In Malta the following products are authorised through national procedures

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number	MAH/license holder
Cyproterone Acetate 100 milligram(s)	Androcur 100mg Tablets	Tablet	POM	MA639/01402	Bayer Limited
Cyproterone Acetate 50 milligram(s)	Androcur 50mg Tablets	Tablet	POM	MA513/03601	Bayer Public Limited Company
Estradiol Valerate 2 milligram(s)   Estradiol Valerate 2 milligram(s)   Cyproterone Acetate 1 milligram(s)	Climen coated Tablets 2mg; 2mg/1mg	Coated Tablet	POM	AA565/56501	Central Procurement & Supplies Unit
Cyproterone Acetate 50 milligram(s)	Cyproterone Acetate 50mg Tablets	Tablet	POM	AA565/26901	Central Procurement & Supplies Unit
Cyproterone Acetate 50 milligram(s)	Cyproterone Acetate Tablets 50m	Tablet	POM	AA729/17901	Cherubino Limited
Cyproterone Acetate 50 Milligram(S)	Cyproterone Acetate	Tablet	POM	MA154/01001	Wockhardt UK Limited

## **Information from the EMA about risk of meningioma associated to Cyproterone medicines**

The Pharmacovigilance Risk Assessment Committee (PRAC) carried out a review on the risk of meningioma associated with the use of Cyproterone-containing medicines. Meningioma is a rare tumour of the membranes covering the brain and spinal cord. Although it is usually non-malignant, meningiomas can cause serious problems due to their location around the brain and spinal cord.

The review concluded that risk of meningioma is a rare side effect which 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.

Available data do not indicate a risk for low dose cyproterone medicines, containing 1 or 2 milligram cyproterone in combination with ethinylestradiol or oestradiol valerate. However, as a precaution, they should not be used in patients who have or had meningioma. PRAC's recommendations are:

- Cyproterone medicines with daily doses of 10 mg or more, 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 option, including treatment with lower doses, have failed. High doses that have started working, should be gradually reduced to the lowest effective dose
- Cyproterone should only be used for reduction of sex drive in sexual deviations in men when other treatment options are not suitable
- The indication of cyproterone in men for prostate cancer remains unchanged

The PRAC's recommendation has been forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) which adopted its consensus and will be implemented directly at national level.

## **In Malta**

### **For Healthcare Professionals**

- The occurrence of single and multiple meningiomas has been linked to the use of cyproterone acetate, primarily at the dose 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)
- Cyproterone-medicines containing 10 mg or more should only be used to treat hirsutism, androgenic alopecia, acne and seborrhoea once other treatment options, including low-dose cyproterone-containing medicines such as cyproterone acetate 2

mg/ethinylestradiol 35 micrograms, have failed. 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 meningiomas. Symptoms of meningiomas can be unspecific and 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 treated with cyproterone acetate is diagnosed with meningioma, treatment must be permanently stopped
- Cyproterone acetate 1 and 2 mg, in combination with ethinylestradiol or oestradiol valerate will be contraindicated in patients with meningioma or history of meningioma. This already applies for higher dose cyproterone medicines
- Cyproterone medicines with indication for prostate cancer will not undergo any changes. 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
- Results from a French epidemiological study were included in this review. Results show a cumulative dose-dependent association between cyproterone acetate and meningioma<sup>1</sup> 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 DHPC letter about the safety concern has been disseminated to HCPs in Malta. Archived DHPC letters are available online at <http://www.medicinesauthority.gov.mt/dhpc>.

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<sup>1</sup> Dr Alain Weill, Benjamin Cadier, Dr Pierre Nguyen, Pr Joël Coste. Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Etude pharmaco-épidémiologique de cohorte à partir des données du SNDS. [https://www.ansm.sante.fr/var/ansm\\_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf](https://www.ansm.sante.fr/var/ansm_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf) (2019, accessed 08 April 2020).

## Advice for Patients

- Cyproterone-containing medicines have been linked to risk of meningioma (non-cancerous brain tumor). The risk is very low and occurs especially when the medicines are taken at doses of 25 mg daily or more
- For certain treatments - excess hair growth, hair loss, acne and oily skin – cyproterone-containing medicines 10 mg or more, 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-containing medicines should only be used to reduce sex drive in sexual deviations in men when other treatment options are not suitable
- Low dose cyproterone-containing medicines in combination with ethinylestradiol or estradiol valerate should not be used in patients with history of meningioma. No evidence links low dose cyproterone medicines and risk of meningioma, and this is a precaution. Higher-dose cyproterone-containing medicines already have this restriction not to use with meningioma
- There is no change in the use of cyproterone-containing medicines for prostate cancer
- If you are taking a cyproterone medicine and have any questions about your treatment, talk to your doctor or pharmacist.

For more information, visit the European Medicines Agency's [Cyproterone acetate referral page](#)

## Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on cyproterone-containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form and sending it to Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or online to <http://www.medicinesauthority.gov.mt/adrportal> or to the marketing authorisation holder or their local representatives.

## Post-Licensing Directorate Medicines Authority

*Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.*

**Feedback Form**

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required)

**Feedback:**

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