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Cyproterone acetate: new advice to minimise risk of meningioma

Risk of meningioma with cyproterone acetate increases with increasing cumulative dose. Use of cyproterone is contraindicated in patients with previous or current meningioma (for all indications) and should only be considered for control of libido in severe hypersexuality or paraphilias in adult men when other interventions are inappropriate.

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Advice for healthcare professionals:

- a review has confirmed a cumulative dose-dependent association between cyproterone acetate and the known increased risk of meningioma; the risk is thought to be rare overall, but is highest for doses of 25mg per day and above
- do not use cyproterone for any indication in patients with a meningioma or a history of a meningioma
- be vigilant for symptoms and signs of meningioma (see below) in patients taking cyproterone; stop treatment permanently if a meningioma is diagnosed in a patient taking cyproterone
- only use cyproterone for control of libido in severe hypersexuality or paraphilias (sexual deviation) in adult men when other interventions are considered inappropriate
- advice on use of cyproterone in the management of patients with prostate cancer remains unchanged

- for low-dose cyproterone (2mg) in combination with ethinylestradiol, a risk of meningioma has not been demonstrated but since the risk with higher-dose products appears to be cumulative, use is now contraindicated in patients with previous or current meningioma
- report suspected adverse drug reactions associated with cyproterone to the Yellow Card Scheme (https://www.gov.uk/yellowcard)

Cyproterone acetate and risk of meningioma

Cyproterone acetate is a synthetic progestogen with anti-androgenic activity. High-dose products containing 50–100 milligram (mg) are used in the treatment of prostate cancer (Cyprostat) and hypersexuality disorders (Androcur). Low-dose products containing 2mg cyproterone acetate in combination with 35 microgram (µg) ethinylestradiol (Dianette and Co-cyprindiol) are approved for use in the treatment of acne and hirsutism (see background for full indications). There is also evidence for off-label use of high-dose cyproterone as hormone therapy in gender reassignment and in female patients for conditions related to androgen sensitivity such as acne, hirsutism, and baldness.

The association of high dose (50mg per day) cyproterone acetate with meningioma was first described in 2008 and a warning on the possible risk of meningioma together with a contraindication in patients with meningioma or a history of meningioma was added to the product information for high dose cyproterone products (see Drug Safety Update, October 2009 (https://www.gov.uk/drug-safety-update/high-dose-cyproterone-acetate-potential-risk-of-multiple-meningiomas)).

New study data for dose-dependent risk

A recent French epidemiological cohort study[1] in women demonstrated that the relationship between cyproterone and meningioma is dose-dependent, and the risk increases with increasing cumulative dose. In the study, patients with a cumulative exposure to cyproterone of between 36g and 60g had an estimated 11-times-higher risk of meningioma than patients with cumulative exposures lower than 3g (see table 1). A 36g cumulative exposure equates to a daily dose of 100mg cyproterone for 1 year.

Table 1. Incidence and risk of meningioma with cumulative dose of cyproterone

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	Adjusted hazard ratio* (95% confidence intervals)
Slightly exposed (<3g)	4.5 per 100,000	Reference
Exposed to any dose ≥3g	23.8 per 100,000	6.6 (4.0–11.1)
– 12g to 36g	26 per 100,000	6.4 (3.6–11.5)
– 36g to 60g	54.4 per 100,000	11.3 (5.8–22.2)
– more than 60g	129.1 per 100,000	21.7 (10.8–43.5)

*Hazard ratios adjusted based on age as a time-dependent variable and estrogen at inclusion

Review of new data and recommendations

A European review of the new study data (https://www.ema.europa.eu/en/medicines/human/referrals/cyproterone-containing-medicinal-products) concluded that treatment with cyproterone 50mg or 100mg should be restricted to situations in which alternative treatments or interventions are unavailable or considered inappropriate, for all indications except prostate carcinoma. The lowest possible effective dose should be used for all patients. If a

patient taking cyproterone at any dose for any indication develops a meningioma, treatment should be stopped immediately and permanently discontinued (see letter sent to healthcare professionals (https://assets.publishing.service.gov.uk/media/5ec4f317d3bf7f5d43765d63/CPA-DHPC-UK_FINAL_14Apr2020.pdf)).

Overall, the risk of meningioma is still considered to be rare (between 1 in 1,000 patients and 1 in 10,000 people, depending on the dose and duration of treatment). The risk increases with increasing cumulative doses.

Low-dose cyproterone (2mg) in combination with ethinylestradiol (Dianette, Co-cyprindiol), indicated for the treatment in women of acne and/or hirsutism (see background for full indication) has not been shown to be associated with an increased risk of meningioma. However, as an increased risk is still plausible, low-dose combination products are now contraindicated in patients with meningioma or a history of meningioma. A warning regarding the risk of meningioma has also been added to the product information for low-dose cyproterone products.

Reports in the UK

Up to 12 May 2020, there have been 10 Yellow Card reports in the UK describing meningioma, which were suspected to be associated with high-dose cyproterone used in male hypersexuality (4), gender reassignment (4), and female hirsutism (2). The mean age of these cases was 62.1 years, and all had taken cyproterone for a prolonged time (14–36 years where information was provided). There were no reports of meningioma with low-dose cyproterone acetate in combination with ethinylestradiol.

About meningiomas

Meningiomas are the most common intracranial tumours, with an annual incidence of 6 cases per 100,000 in the general population. They arise from the meningeal coverings of the brain and spinal cord and can be single or multiple. Sex hormones are likely to have a role in the development of meningiomas as approximately 70% express progestogen receptors and 30% express estrogen receptors.[2]

Meningiomas are usually benign, but as they are space occupying lesions, they can put pressure on neurological structures. This can cause a variety of symptoms including changes in vision, hearing loss or ringing in the ears (tinnitus), loss of smell, headaches that worsen with time, memory loss, seizures, or weakness in extremities. Clinicians should be vigilant for these symptoms and signs in patients taking cyproterone, but should also be aware that meningiomas can be asymptomatic.

Background – indications for cyproterone acetate

Cyproterone acetate 50–100mg (Cyprostat (https://www.medicines.org.uk/emc/product/6248/smpc), Androcur (https://www.medicines.org.uk/emc/product/1120/smpc)) is indicated for

- management of patients with prostatic cancer (1) to suppress “flare” with initial luteinising hormone-releasing hormone (LHRH) analogue therapy; (2) in long-term palliative treatment where LHRH analogues or surgery are contraindicated, not tolerated, or where oral therapy is preferred; and (3) in the treatment of hot flushes in patients under treatment with LHRH analogues or who have had orchidectomy
- control of libido in severe hypersexuality and/or sexual deviation in the adult male

Cyproterone acetate 2mg combined with ethinylestradiol 35µg (Dianette, Co-cyprindiol) is indicated for treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.

Report on a Yellow Card

Please continue to report suspected adverse drug reactions, including for cyproterone acetate to the MHRA via the Yellow Card Scheme.

You can report suspected side effects electronically via:

- the Yellow Card website (https://www.gov.uk/yellowcard/)
- the free Yellow Card app; download now from the Apple App Store (https://itunes.apple.com/us/app/apple-store/id990237487) or Google Play Store (https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&referrer=utm_source%3DEYC%26utm_medium%3Dcpc%26anid%3Dadmob)
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

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1. Weill A et al. Exposition prolongée à de fortes doses d’acétate de cyprotérone et risque de méningiome chez la femme. Paris: ANSM. 2019 Jun. ↩
2. Blitshteyn S, et al. Is There an Association Between Meningioma and Hormone Replacement Therapy? (https://ascopubs.org/doi/10.1200/JCO.2007.14.2133) J Clin Oncol 2008; 26: 279–82 ↩

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