Direct Healthcare Professional Communication

16 April 2020

Restrictions in use of cyproterone acetate due to risk of meningioma

Dear Healthcare professional,

Bayer plc, Cipla (EU) Limited, Fannin (UK) Limited, Generics (UK) Limited, Stragen UK Ltd., and Wockhardt UK Ltd are in agreement with the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- **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 of meningioma increases with increasing cumulative doses.**
- **Use of cyproterone acetate is contraindicated in patients with a meningioma or a history of meningioma.**
- **Patients should be monitored for meningiomas in accordance with clinical practice.**
- **If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment must be permanently stopped.**
- **For control of libido in severe hypersexuality and/or sexual deviation in the adult male, cyproterone acetate should only be used when other interventions are considered inappropriate.**
- **The use of cyproterone acetate in the management of patients with prostate cancer remains unchanged.**

Background on the safety concern

Therapeutic indications in men (50 mg and 100 mg) include **management of patients with prostatic cancer (1) to suppress "flare" with initial 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** and reduction of the sex drive in hypersexuality and / or sexual deviation.

Meningioma is a rare tumour which forms from the meninges. Clinical signs and symptoms of meningioma may be unspecific and may 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.

The association of high dose (50 mg/day) cyproterone acetate (CPA) with meningioma was first described in 2008 and the product information for CPA-containing products with a strength of 10 mg and above was updated to include a contraindication of (a history) of meningioma and a warning regarding the risk of meningioma. Recently, results from a French epidemiological cohort study showed a cumulative dose-dependent association between CPA and meningioma.[1] This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg CPA tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose CPA (cumulative dose ≥3 g) and women who were slightly exposed to CPA (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

Incidence and risk of meningioma with different cumulative doses of CPA

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	HR_{adj} (95% CI) [a]
Slightly exposed (<3 g)	4.5/100,000	Ref.
Exposed to ≥3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60g	54.4/100,000	11.3 [5.8-22.2]
more than 60 g	129.1/100,000	21.7 [10.8-43.5]

[a] Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 36 g for example can correspond with one year of treatment with 100 mg/day.

In view of these data, treatment with CPA 50 mg or 100 mg should be restricted to situations where alternative treatments or interventions are unavailable or considered inappropriate in all indications except prostate carcinoma. Also, the lowest possible effective dose should be used.

CPA (1 and 2 mg) in combination with ethinylestradiol (EE) is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age. No new safety concern regarding a risk of meningioma associated with the use of low dose CPA/EE products could be identified. However, as the risk of meningioma increases with increasing cumulative doses of CPA, low dose combination products are now contraindicated in patients with meningioma or history of meningioma.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those

that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

It is easiest and quickest to report ADRs online via the Yellow Card website - https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store.

Alternatively, prepaid Yellow Cards for reporting are available:
- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800-731-6789
- by downloading and printing a form from the Yellow Card website (see link above)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Company contact point

UK Company	**Product Name**	**Email**	**Phone**
Bayer plc	Androcur 50 mg tablets Cyprostat 50 mg tablets Cyprostat 100 mg tablets	medical.information@bayer.co.uk	0118 2063000
Cipla (EU) Limited	Cyproterone Acetate Cipla (Eu)	drugsafety@cipla.com	0800 0472144
Fannin (UK) Limited	Cyproterone Acetate Fannin (UK)	Medical@Kent-Athlone.com	0800 220280
Generics [UK] Limited	Cyproterone Acetate Generics UK	Info.uk@mylan.co.uk	01707 853000
Stragen UK Limited	Cyproterone Acetate 50mg Tablet	info@stragenuk.com	01737 735029
Wockhardt UK Limited	Cyproterone Acetate 50mg Tablets Cyproterone Acetate 100mg Tablets	drug.safety@wockhardt.co.uk	01978 669272

Yours faithfully,

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Head of Medical Affairs
Generics [UK] Limited t/a Mylan UK Healthcare Limited

Dr. Annie-Claude Benichou
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List of literature references

1. Weill A et al. (2019 Jun). Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Paris: ANSM. https://www.ansm.sante.fr/var/ansm_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf