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Direct Healthcare Professional Communication (DHPC)

Restrictions in use of cyproterone acetate due to risk of meningioma

Dear Healthcare professional,

Bayer Limited Ireland, Bayer Plc United Kingdom, Central Procurement & Supplies Unit, Wockhardt UK Limited in agreement with the European Medicines Agency and the Malta Medicines Authority 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 indication of reduction of drive in sexual deviations in men, cyproterone acetate 50 mg/100 mg can be used when other interventions are considered inappropriate**
- **The use of cyproterone acetate for the following indications remain unchanged: inoperable prostate cancer and LHRH flare.**

Background on the safety concern

Therapeutic indications in men (50 mg and 100 mg) include antiandrogen treatment in inoperable carcinoma of the prostate or palliative anti-androgenic treatment of prostate cancer and reduction of the sex drive in hypersexuality and sexual aberrations.

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) CPA with meningioma was first described in 2008 and the SmPC of CPA-containing products with a strength of 10 mg and above was updated with 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 cyproterone acetate 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 cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose <3 g). A cumulative dose-response relationship was demonstrated.

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 12 g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

In view of these data, treatment with cyproterone acetate, 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.

Cyproterone acetate (1 and 2 mg) in combination with estradiol valerate (EV) is indicated for:

- Hormone Replacement Therapy (HRT) and symptoms of postmenopausal oestrogen deficiency
- Prevention of osteoporosis in postmenopausal women who are at high risk of fractures and who have an intolerance or contraindication to other drugs approved for the prevention of osteoporosis.

No new safety concern regarding a risk of meningioma associated to the use of low dose CPA/EE and CPA/EV products could be identified. However, as the risk of meningioma increases with increasing cumulative doses of cyproterone acetate, low dose combination products are now contraindicated in patients with meningioma or history of meningioma.

Call for reporting

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with cyproterone-containing products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt.

Company contact point

Should you have any questions or require additional information, please call Medical Information at:

Company	Product Name	Email	Phone
Bayer Limited Ireland	Androcur 100mg Tablets	acurmi@alfredgera.com	+ 356 99474162
Bayer Plc United Kingdom	Androcur 50mg Tablets	acurmi@alfredgera.com	+356 99474162
Central Procurement & Supplies Unit	Climen coated Tablets 2mg; 2mg/1mg	info.cpsu@gov.mt	+356 2540 4000
	Cyproterone Acetate 50mg Tablets		
Wockhardt UK Limited	Cyproterone Acetate 50mg Tablets	drug.safety@wockhardt.co.uk	+44 (0)1978 669 272

Yours faithfully,

Post-Licensing Directorate

Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Bayer Limited Ireland, Bayer Plc United Kingdom, Central Procurement & Supplies Unit, Wockhardt UK Limited

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