Restrictions in use of cyproterone acetate due to risk of meningioma

Dear Healthcare Professional,

<Name of marketing authorisation holders> in agreement with the European Medicines Agency and the <National Competent 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 <indications in women as per national SmPC>, cyproterone acetate <10 mg>/<50 mg> are indicated when no satisfactory results have been achieved with lower dose cyproterone-containing products or with other treatment options.**
- **For <indication of reduction of drive in sexual deviations in men as per national SmPC> cyproterone acetate <50 mg>/<100 mg>/<300 mg/3 ml> can be used when other interventions are considered inappropriate.**
- **The use of cyproterone acetate for the following indications remain unchanged: <indications inoperable prostate cancer and LHRH flare as per national SmPC>**

Background on the safety concern

*<<**The wording of the indication varies between EU countries. Indication details to be amended on national level as needed:***>*

Therapeutic indications for cyproterone acetate (CPA) monotherapy in a dose of <10 mg> <and> <50 mg> in women include moderately severe to severe signs of androgenisation, e.g. hirsutism, androgenetic alopecia, acne and seborrhoea. Therapeutic indications in men (<50 mg>, <100 mg> <and> <300 mg/3ml>) 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 <10 mg>, <50 mg>, <100 mg> <or> <300 mg/3 ml> 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 ethinylestradiol (EE)/estradiol valerate (EV) is indicated for: <<The wording of the indication varies between EU countries. Indication details to be amended on national level>. 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

Healthcare professionals are encouraged to report adverse events in patients taking CPA-containing products to [NCA] <in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

Company contact point

<A table of Marketing authorisation holders and contact points>

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

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Medicinal products containing only cyproterone
Marketing authorisation holder(s)	All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all relevant medicinal products authorised in that Member State.
Safety concern and purpose of the communication	Restrictions in use of cyproterone acetate due to risk of meningioma
DHPC recipients	Dermatologists, endocrinologists, gynaecologists, general practitioners, urologists, oncologists involved in treatment of prostate cancer, and psychiatrists involved in treatment of hypersexuality/ reduction of drive in sexual deviations and any other target groups as agreed at national level.
Member States where the DHPC will be distributed	AT, BE, BG, HR, CZ, DK, EE, FI, FR, DE, EL, HU, IS, IE, IT, LV, LT, LU, MT, NL, NO, PL, PT, RO, SK, SI, ES, SE, UK[1].

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	13 February 2020
DHPC and communication plan (in English) agreed by CMDh	26 March 2020
Submission of translated DHPCs to the national competent authorities for review	CMDh position/EC decision (as applicable) + 5 calendar days
Agreement of translations by national competent authorities	CMDh position/EC decision (as applicable) + 14 calendar days
Dissemination of DHPC	CMDh position/EC decision (as applicable) + 21 calendar days

[1] As of 1.2.2020, the UK is no longer an EU Member State. However, EU law still applies to the UK during the transition period.