Annex II

Scientific conclusions

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Cyproterone is a synthetic progesterone derivative with anti-androgenic properties.

In monotherapy, cyproterone acetate is available in dosages of 10, 50 and 100 mg for oral administration and 300mg/3ml in depot formulation.

Approved indications for cyproterone containing products differ between the different strengths and between the different countries in which these products are authorised. Cyproterone products in 10 mg and 50 mg strengths are authorised mainly for signs of androgenisation in women, while formulations dosed at 50 mg, 100 mg and 300 mg/3 ml formulation are authorised for reduction of drive in sexual deviations in men, and prostate carcinoma.

Cyproterone is also authorised in low dose (1-2 mg) in combination with either ethinylestradiol (35 mcg) or estradiol valerate (1-2 mg). These products are indicated for moderate to severe acne related to androgen-sensitivity (Cyproterone acetate 2 mg/ethinylestradiol 35 mcg), hormonal contraception (cyproterone acetate 1-2 mg/estradiol valerate 1-2 mg) and hormone replacement therapy (cyproterone acetate 1 mg/estradiol valerate 2 mg).

Meningioma is a rare brain tumour which forms from the meninges. The vast majority are considered benign. They arise in intracranial (90%) or intraspinal (10%) locations. The incidence of meningiomas increases with age, with a median age at diagnosis of 65 years. The European age-standardized annual IR ranges from 3.71 to 6.85 per 100,000 persons in women and from 1.8 to 3.01 in men (Swedish National Cancer registry), indicating a female: male ratio of 2:1. Although most meningiomas grow slow over many years without symptoms in 75% of patients, their intracranial location may lead to symptoms due to compression to adjacent tissues.

The association of high dose (50 mg/day) cyproterone acetate (CPA) with meningioma was first described in a case series published by Froelich et al. in 2008[1] of 9 female patients with meningiomas treated with CPA 50 mg/day for a time period ranging from 10 to 20 years. In addition, information from the spontaneous reporting system raised the hypothesis of an increased risk of meningioma in patients treated with dosages of 25 mg per day and above. The former CHMP Pharmacovigilance Working Party (PhVWP) evaluated these data in 2009 and concluded that the administration of CPA at doses of 25 mg and more for a long time period (i.e. years) could at least be possibly causally related with the occurrence of (multiple) meningiomas whereas there is substantially less evidence for such an association with dosage forms of 2 mg or less. In the product information (PI) of CPA 10, 25, 100 mg or more this association is included (SmPC sections 4.3, 4.4, 4.8). [Minutes PhVWP November 2009]

Recently, a French pharmacoepidemiological study was conducted by Weill et al to estimate the number of cases of meningioma in France attributable to prolonged exposure in women to CPA 50 and 100 mg between 2007 and 2015[2], based on the French health Insurance (CNAM). A further overview was conducted by the French Agency ANSM which evaluated French cases of meningioma in which the use of CPA was reported.

On 02 July 2019, the ANSM triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of cyproterone-containing products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

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[1] Froelich S, Dali-Youcef N, Boyer P, et al. Does cyproterone acetate promote multiple meningiomas? Endocrine Abstracts. 2008; 16: P158

[2] 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

Overall summary of the scientific evaluation by the PRAC

The risk of meningiomas with the use of CPA has been recognised and is reflected in the CPA product information since the previous review by the PhVWP. The data that became available since the previous review confirm the conclusion that occurrence of (multiple) meningiomas has been reported in association with longer term use (years) of cyproterone acetate at doses of 25 mg/day and above. The data also show that the absolute risk of meningiomas with CPA use remains low.

The study by Weill adds to this knowledge that in women, the risk of meningioma increases with higher cumulative doses of CPA-only (table 1).

Table 1 Incidence, relative risk and adjusted hazard ratio for meningioma, by cyproterone acetate exposure – study by Weill et al (2019).

	PY	**Cases**	**Incidence per 100,000 PY**	**RR** [95%CI]	**HRa** [95%CI] [a]
Slightly exp. (< 3 g)	439,949	20	4.5	Ref.	Ref.
Exposed (>= 3 g)	289,544	69	23.8	5.2 [3.2–8.6]	6.6 [4.0–11.1]
By cumulative dose					
[3 g; 6 g]	53,744	2	3.7	0.8 [0.2–3.5]	1.1 [0.3–4.9]
[6 g; 12 g]	79,202	6	7.6	1.7 [0.7–4.1]	2.2 [0.9–5.6]
[12 g; 36 g]	115,594	30	26.0	5.7 [3.2–10.1]	6.4 [3.6–11.5]
[36 g; 60 g]	29,390	16	54.4	12.0 [6.2–23.1]	11.3 [5.8–22.2]
60 g and over	11,615	15	129.1	28.4 [14.5–55.5]	21.7 [10.8–43.5]

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

The aHR of 6.6 (95% CI: 4.0-11.1)) is comparable with the results of the 2 previous observational studies of Gil et al, (aIRR 11.4 (95% CI 4.3-30.8)) and Cea-Soriano et al. (aOR 6.30; CI: 1.37–28.94). The study of Weill et al is the first study with sufficient statistical power to stratify the exposure on cumulative dose. The stratified analysis showed the highest increase in risk for cumulative doses $\geq$ 60 g CPA, which represents CPA treatment of 5 years of 50 mg/day for 20 days a month. However, increased risks were also measured after cumulative doses between 12 and 36 g and after cumulative doses between 36 and 60 g CPA. As the authors only stratified on cumulative doses and not on treatment duration, no conclusions can be drawn on the exposure period after which meningioma can develop.

The analysis of post-marketing cases confirms that in the majority of cases reported, cyproterone was used longer than 5 years and in daily doses of 50mg and above. However, a number of cases were identified with a relatively short exposure (n=47) and in particular 4 cases were sufficiently well documented and allowed to establish an association between short term use of high daily doses cyproterone and the development of meningioma.

In view of the above, PRAC considered that these findings (higher risk with higher cumulative doses, not limited to long term use) need to be reflected in the product information of cyproterone-containing products. Treatment with high dose cyproterone should be restricted to the lowest effective dose, and in case of products authorised for severe signs of androgenisation in women, to when other treatment options are not available or not effective.

Cyproterone-containing products are also authorised in high doses (50 mg, 100 mg and 300 mg/3ml) for reduction of sexual deviations in adult males. In view of the seriousness of this condition, the need for adequate treatment, and the fact that meningiomas are generally of a benign nature and their incidence remains low, the benefit-risk balance of this indication remains favourable provided that other interventions are considered inappropriate.

For the prostate carcinoma indication, the mortality is high and disease progression is prevented by CPA. Therefore, the benefits of CPA in antiandrogen treatment in inoperable prostate cancer continue to outweigh the risk of meningiomas and the benefit-risk balance in this indication remains favourable.

No scientific literature was identified that specifically links the use of low dose cyproterone combination products to meningioma. The analysis of spontaneously reported cases also does not provide evidence of a causal association. Extrapolation of the risk seen in women who used 50 mg and 100 mg CPA to the low-dose combined CPA products indicates that for products containing 2 mg cyproterone, the theoretical duration of use to reach the hypothesized 12 g CPA cumulative dose threshold would be more than 20 years (23.8 years based on a monthly CPA exposure of 42 mg), and twice as long for the products containing 1 mg cyproterone. Considering the indications for these products, long term use for several decades is unlikely.

While no increased risk was described specifically in association to the use of low dose combination cyproterone products, it is noted that there are situations where patients may have exposure to both high and low dose products. As the risk increases with increasing cumulative dose, the product information of low dose combination products should reflect current knowledge on this issue and use of low dose products should be contraindicated in patients with previous or existing meningioma.

In view of the findings of the Weill study showing that in France in 30% of the meningioma cases, patients continued or resumed CPA after being treated for meningioma, healthcare professionals should be reminded of the contraindication in place and informed of the new restrictions in use of cyproterone via the distribution of a direct healthcare professional communication (DHPC) to be jointly disseminated by marketing authorisation holders in each Member State.

The PRAC considered the need for additional studies on the risk of meningioma in association with cyproterone use. Considering the low absolute risk of meningiomas with high doses of CPA-only, it is not expected that an additional observational study will obtain significant new information that would further characterise the risk of meningiomas in an acceptable timeframe. However the PRAC further considered that additional pharmacovigilance activities are needed to evaluate the physicians' awareness and level of knowledge of the information included in the SmPC and DHPC regarding risk of meningioma, and therefore recommended that marketing authorisation holders conduct a joint observational cross-sectional survey to assess healthcare professionals' awareness and level of knowledge of this risk.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for cyproterone-containing products.
- The PRAC reviewed the available data on risk of meningioma in association with cyproterone, in particular the epidemiological studies including the French Health Insurance (CNAM) study, post-marketing case reports and data submitted by the marketing authorisation holders.

- The PRAC concluded from the data that, while the absolute risk of meningioma in association with cyproterone use remains low, the risk increases with increasing cumulative doses of cyproterone. PRAC noted that most cases occur after prolonged exposure to high doses of cyproterone, but cases of meningioma have also been identified after short-term exposure to high doses.
- PRAC therefore recommended that in all indications except prostate carcinoma, treatment with cyproterone should be restricted to situations where alternative treatments are unavailable or considered inappropriate and that the lowest possible effective dose should be used.
- PRAC also noted that while the available data do not indicate an increased risk of meningioma in association with low dose combination products containing 2mg or less of cyproterone, these products are often used following treatment with higher dose cyproterone products or concomitantly. Given that the risk increases with increasing cumulative doses of cyproterone, the Committee recommended that low dose combination products should also be contraindicated in patients with meningioma or history of meningioma.
- The Committee further recommended other updates to the product information of cyproterone-containing products to reflect current knowledge on the risk of meningioma.
- The Committee recommended that marketing authorisation holders conduct a joint observational cross-sectional survey to assess healthcare professionals' awareness and level of knowledge of this risk.

In view of the above, the PRAC concluded that the benefit-risk balance of cyproterone-containing products remains favourable subject to changes to the product information described above.

A DHPC will be distributed to inform healthcare professionals of the updated recommendations.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for cyproterone-containing products.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

The CMDh also agreed with the content of the DHPC as proposed by PRAC and adopted an amended version of the communication plan to clarify that the requirement to disseminate the DHPC is applicable only to marketing authorisation holders of cyproterone-only containing products.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of cyproterone-containing products remains favourable subject to the amendments to the product information described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for cyproterone-containing products.