EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

INN/active substance: cyproterone

Procedure number: EMEA/H/A-31/1488

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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Table of contents

1. Information on the procedure

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.

2. Scientific discussion

2.1. Introduction

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. Overall, cyproterone in monotherapy is approved for the following indications in Europe:

Cyproterone 10 mg tablets:

[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

Moderately severe signs of androgenisation in the woman, e.g.
- moderately severe hirsutism
- moderately severe androgenetic alopecia
- severe and moderately severe forms of acne and seborrhoea.

In moderately severe forms of acne and seborrhoea supplementary administration of cyproterone tablets is indicated in cases where the clinical picture is refractory to other treatments and no satisfactory results have been achieved with cyproterone 2mg/ethinylestradiol 35 mg alone.

Cyproterone 50 mg tablets - indications targeting the female population:

In most EU countries cyproterone 50 mg tablets is indicated for:

- Severe signs of androgenisation, e.g. very severe hirsutism, severe androgenetic alopecia, often attended by severe forms of acne and/or seborrhoea.

In France and Sweden the indication is different.

In France cyproterone 50 mg tablets are indicated for:

- Major hirsutism in women, of non-tumoural origin (idiopathic, polycystic ovary syndrome), when it has serious repercussions on psycho-affective and social life.

In Sweden cyproterone 50 mg tablets are indicated for:

- Pronounced hirsutism in women of childbearing age

Cyproterone 50 mg tablets - indications targeting the male population:

In most countries cyproterone 50 mg tablets is indicated for:

- Reduction of drive in sexual deviations in men.

- Antiandrogen treatment in inoperable carcinoma of the prostate.

In addition to the indications listed above, in the UK[3] and NL cyproterone 50 mg tablets are also indicated for:

- the treatment of "hot flushes" seborrhoea during treatment with GnRH-agonists or after orchidectomy)

- 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.

In France the indication of cyproterone 50 mg tablets is for:

- Palliative anti-androgenic treatment of prostate cancer

Cyproterone 100 mg tablets - indication targeting the male population:

In most countries cyproterone 100 mg tablets is indicated for:

- Antiandrogen treatment in inoperable carcinoma of the prostate.

In addition to the indication listed above, in France and Ireland cyproterone 100 mg tablets are also indicated for:

[3] 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.

- Reduction of drive in sexual deviations

In the UK, the indication of cyproterone 100 mg tablets is described as:

- 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.

Cyproterone 300 mg/3ml solution for injection:

In most countries cyproterone 300 mg/3ml solution for injection is indicated for:

- Reduction of drive in sexual deviations in men
- Antiandrogen treatment in inoperable carcinoma of the prostate.

In addition to the indications listed above, in Germany cyproterone 300 mg/3ml is also indicated for:

- Initially to mitigate the flare phenomenon at the beginning of treatment with LHRH agonists through the initial increase in serum testosterone can be caused (only in Germany).
In the Netherlands the indication is restricted to:

- Reduction of sex drive in hypersexuality and sexual deviations in men.

In Italy the indication is restricted to:

- Antiandrogen treatment in inoperable carcinoma of the prostate.

Cyproterone is also authorised in combination therapy as follows:

Cyproterone acetate 2 mg/ethinylestradiol 35 mcg

Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age. For the treatment of acne, <Product> should only be used after topical therapy or systemic antibiotic treatments have failed. Since <product> is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3)

Cyproterone acetate 1-2 mg/estradiol valerate 1-2 mg

Hormonal contraception.

Cyproterone acetate 1 mg/estradiol valerate 2 mg

Hormone replacement therapy.

Exposure figures for cyproterone-only products
The estimated cumulative patient exposure to cyproterone-only products is estimated to be 1,014,986 patient years for all MAHs. The Member State with the largest patient exposure to cyproterone containing products is France with a patient exposure of 400,437 patient years, representing 39% of the total cumulative exposure of cyproterone in Europe. The highest overall cumulative patient exposure has been reported for the innovator product Androcur which is estimated to be 820,097 patient years.

The cumulative patient exposure stratified for the different cyproterone formulations of the innovator product Androcur is estimated to be:

- Cyproterone 10 mg tablets: 204,198 patient years
- Cyproterone 50 mg tablets - female indication: 217,487 patient years
- Cyproterone 50 mg tablets - male indication: 266,250 patient years
- Cyproterone 100 mg tablets: 98,854 patient years
- Cyproterone 300 mg/3ml solution for injection: 33,308 patient years.

The cumulative patient exposure to the 50 mg Androcur tablets represented 59% of the cumulative patient exposure for all formulations available in the EU. It should be noted that while the cyproterone 50 mg tablets are marketed throughout the EU, the 10 and 100 mg cyproterone tablets and 300 mg/3ml solution for injection are marketed in a smaller number of countries. In the countries in which the 10 mg tablets are marketed for the female indications, the cumulative patient exposure to the 50 mg tablets is substantially lower compared to the 10 mg tablets.

Exposure figures for cyproterone combined with ethinylestradiol/estradiol valerate
The estimated cumulative patient exposure to cyproterone combined with ethinylestradiol/estradiol valerate is estimated to be 105,194,744 patient years for all marketing authorisation holders. The highest overall cumulative patient exposure has been reported for the innovator product Diane-35 and is estimated to be over 90 million treatment years since marketing authorisation.

2.1.1. Meningioma

Meningiomas are the most common intracranial neoplasia and are generally benign. The incidence of meningiomas increases with age, with a median age at diagnosis of 65 years. The European age-standardized annual incidence rate (IR) ranges from 3.71 to 6.85 per 100,000 persons in women and from 1.8 to 3.01 in men (over the years 1980-2017, Swedish National Cancer registry), and indicating a female to male ratio of 2:1.

Approximately three-quarters of meningiomas are asymptomatic; symptoms of meningiomas are often non-specific and dependent on tumour location. The symptoms are due to compression to adjacent tissues. Based on the European standard population, the age-standardized mortality rate is 0.3 per 100,000 person-years in both men and women. Diagnosis of meningioma is mainly made by magnetic resonance imaging (MRI). Therapeutic options for asymptomatic meningiomas can be observation only by using clinical and MRI tests (without histological diagnosis), and for symptomatic meningiomas, major or minor surgical resection, radiotherapy, radiation therapy or, if these options are not possible, systemic chemotherapy.

As to histologic origin, meningioma cells arise from the arachnoid cap cells which form the outer layer of the arachnoid mater. Meningiomas are categorized into 3 WHO grades, of which WHO grade I represents 90% of all meningiomas.

As to genetics, meningiomas can originate spontaneously or be part of hereditary syndromes such as neurofibromatosis type 2.

With regard to hormone receptor expression, in meningioma tissue functional progesterone receptors are found (ca. 90%) as well as androgen and oestrogen receptors. However, the functional significance of this receptor expression is not clear as also in normal meningeal tissue hormone receptors are found. As to possible influence of progestins and other steroids on meningioma growth, in some tumour cell cultures stimulation of growth by progesterone has been described. This effect of progesterone could be inhibited by mifepristone (a steroidal antiprogestogen) in vitro, but a phase III

study with mifepristone to treat patients with unresectable meningioma showed no benefit over placebo. In two studies, oestrogen receptor inhibition with tamoxifen showed no evidence of clinical activity. Androgen receptor inhibition in a small number of patients did not show clinical activity. An increased growth of meningiomas during pregnancy was observed and has long been attributed to progesterone and oestrogen stimulation. However, also other factors may be involved like the reversible hemodynamic changes, but the exact cause of the increased meningioma growth during pregnancy is not clear.

Further, in vitro experiments showed that antiandrogens can inhibit meningioma cell growth. The role of oestrogen receptors (ERs) in the pathogenesis of meningioma is less clear; recent data however indicated that ER-positive meningiomas proliferate more rapidly than ER-negative tumours. Although these data support the general concept that proliferation of meningiomas is influenced by endogenous and exogenous sex hormones, they also indicate the complexity as the different hormones, including CPA, may have counteracting effects of inhibition versus proliferation of meningiomas.

Several risk factors for meningiomas have been described:

- Ionizing radiation is one of the few well-established risk factors for meningioma development leading to a 6- to 10-fold increase in risk. Patients who receive cranial irradiation for head and neck cancers or acute lymphoblastic leukaemia also have an increased risk of meningiomas in a radiation dose-dependent manner. Radiation-associated meningiomas are more likely to be atypical or malignant and multifocal than sporadic meningiomas.
- Some genetic mutations are associated with meningiomas, e.g. inherited nervous system disorder, such as neurofibromatosis 2.
- Data up to now support a role of sex hormones in the development of meningiomas, based on the presence of progesterone-, oestrogen-, and androgen receptors in meningiomas, and the reported increase in risk of meningioma in pregnancy. However, the exact mechanism and role of the different sex hormones is not elucidated, and up to now studies evaluating treatments that inhibit sex hormone receptors in patients with meningiomas did not show positive results.
- Suggested associations in epidemiological studies (e.g. head trauma, smoking, and cell phone use) have not been consistently shown.

2.1.2. Information on meningioma in the product information

All cyproterone-only containing products dose at 10 mg or higher currently have information in the summary of product characteristics reflecting that meningiomas have been reported in association with long-term use (several years) of cyproterone acetate at doses of 25 mg/day and above. This is accordance with the conclusions of the 2009 Pharmacovigilance Working Party review.

The current SmPC text is as follows:

Section 4.3 Contra-indications

Meningioma or a history of meningioma.

Section 4.4 Special warnings and precautions for use

Meningiomas: The 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. If a patient treated with <product> is diagnosed with meningioma, treatment with <product> must be stopped (see section 4.3).

Section 4.8 Undesirable effects

Not known:

The 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.

No information on the risk of meningioma is currently found in the PI of combination products containing low dose cyproterone acetate.

In February 2019, the French authority ANSM requested an update of the product information of all authorised cyproterone containing products in France to include recommendations on MRI brain imaging before and during use of cyproterone 50 and 100 mg tablets. As a consequence, the French PI for the 50 and 100 mg tablets differs from other countries and includes the below:

Section 4.2 Posology and method of administration (included as a boxed warning):

Because of the risk of meningioma, ACETATE CYPROTERONE 50 mg tablet should be prescribed and dispensed subject to the collection of patient information certificate that must be renewed annually (see sections 4.3 and 4.4).

The interest of the prescription must be reviewed annually taking into account the benefit /risk for each individual patient and the evolution of the symptoms. To the extent that the risk of meningioma increases with the dose and duration of use, prolonged use of high doses should be avoided.
…
"Prolonged use (several years) of 50 ACETATE CYPROTERONE 50 mg tablet should be avoided (see section 4.4)."
…

Section 4.3 Contra-indications for use

Existence or history of meningioma: Conduct a brain imaging with MRI in early treatment to eliminate the existence of a meningioma (see section 4.4).

Section 4.4 Special warnings and precautions for use

Cases of meningiomas (simple and multiple) have been reported in case of prolonged use (several years) of cyproterone acetate at doses of 25 mg per day and more.
If a meningioma is diagnosed in a patient treated with ACETATE CYPROTERONE 50 mg scored tablet, treatment should be permanently discontinued and neurosurgical opinion will be required (see section 4.3).
Conduct a brain imaging with MRI in early treatment to eliminate the existence of a meningioma (see section 4.3). If the treatment is continued for several years, brain imaging with MRI should be

performed no later than 5 years after the first imaging, then every 2 years if MRI at 5 years is normal. The prescriber must ensure that the patient was informed of the risk of meningioma and their symptoms such as headaches, blurred vision, speech, memory and hearing, nausea, dizziness, convulsions, loss smell and weakness, paralysis.
The prescriber should also ensure that the patient has been informed of the necessary supervision and has acknowledged understanding of information (annual information statement co-signed by the prescriber and the patient).

2.2. Risk of meningioma in association with cyproterone use

No cases of meningioma could be identified in clinical trials performed with cyproterone-containing medicinal products. The absence of meningioma cases is not unexpected, considering the rarity of the event, the size and duration of the clinical trials and the fact that meningiomas are normally very slowly growing.

The assessment of all relevant safety data on this risk (pharmacoepidemiological data, literature review and spontaneous reports) can be found below.

2.2.1. Pharmacoepidemiological study by Weill et al

The objective of this study was to estimate the number of cases of meningioma attributable to prolonged exposure to cyproterone acetate 50 and 100 mg in women in France between 2007 and 2015. Only a draft version of this study was provided within this referral procedure and this study has not been published in a scientific journal at the time of this assessment report was drafted.

To further clarify the relationship between prolonged use of CPA of 50 mg and 100 mg and risk of meningioma, the French Health Insurance (CNAM) conducted a pharmacoepidemiological study on 253,777 women (aged 7-70 years) exposed to medicines containing 50 or 100 mg cyproterone between January 2007 and December 2014). The study was performed using data from the French National Health Data System (SNDS). The SNDS contains data on all reimbursements for healthcare expenditure (medical procedures, drugs, laboratory tests etc.) dating back to 2006. In this study, data from the SNDS was combined with the PMSI (French hospital discharge database), which provides medical information for all hospitalised patients, including ICD-10 diagnostic codes and medical procedures. Women were considered to be "exposed" if they had received an initial supply of CPA-only between 1 January 2007 and 31 December 2014 and received a cumulative dose of 3 g or more (equal to ≥ 3 boxes of 20 tablets containing 50mg CPA), during the first six months following the initial supply. This group of "exposed" women was compared to a group of "very slightly exposed" women, who received an initial supply of CPA-only between 1 January 2007 and 31 December 2014 and quickly discontinued the treatment, having received a cumulative dose of less than 3 g (equal to 1 or 2 boxes of 20 tablets containing 50-mg CPA).

The primary analysis on this "incident cohort" consisted of the comparison of women exposed to high-dose CPA-only (defined as ≥ 3 g within six months after the first dispensing) with those exposed to a low dose (defined as < 3 g within six months after the first dispensing). A schematic representation of the study design (composed by MAH Bayer) is presented below:

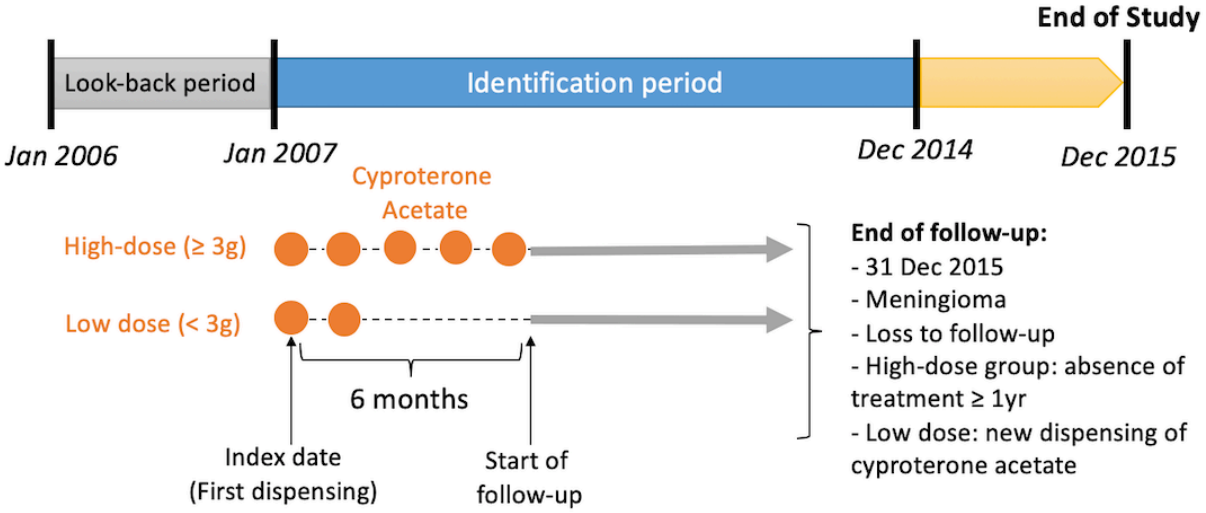

Figure 1 Schematic representation of the study design

Weill and colleagues found that exposure to high-dose cyproterone acetate (cumulative dose of ≥ 3 g of CPA) was strongly associated with a risk of meningioma treated with neurosurgery or radiotherapy (aHR 6.6 (95% CI: 4.0-11.1)), adjusted for age and oestrogen use. A strong dose-effect relationship was found as the risk of meningioma increased substantially with higher cumulative doses, see table 1 with the main results of the study.

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

An additional analysis (of a "prevalent" cohort) which involved women already exposed to cyproterone acetate in 2006 (the earliest year available in the SNDS database), with follow-up to the end of 2015 was performed as subanalysis. In this prevalent cohort, the women already exposed in 2006 and who continued treatment with more than 60 g of cyproterone acetate from 2006 onwards had an absolute risk of meningioma of around 4 per 1000 patient-years, which represents a 30-fold increase in the risk. The majority of women with an exposure time between 10 and 30 years were found in this "prevalent"

cohort of women, the absolute risk of 4 per 1000 years represents the risk in women with >10 years cyproterone exposure. The number of cases of meningioma attributable to exposure to cyproterone acetate in France was estimated at 550 in the 9-year study period (on average 62 cases per year).

The stratified analysis in the incident cohort showed a strong dose-effect relation with an aHR of 21.7 (95% CI: 10.8-43.5) for cumulative doses $\geq$ 60 g cyproterone, which represents cyproterone treatment for 5 years of 50 mg/day for 20 days a month. However, increased risks were also reported after cumulative doses between 12 and 36 g and after cumulative doses between 36 and 60 g CPA. Both 50 mg and 100 mg cyproterone products were included in the calculation of the exposure. However, no stratified risks were computed for the 50 mg and 100 mg cyproterone tablets. Furthermore, as the authors only stratified by cumulative doses and not by treatment duration, no reliable conclusions can be drawn after which exposure period meningioma can develop, as any calculation of duration from the cumulative dose will be based on an assumption of the daily dose.

Furthermore, of the 516 cases of treated meningioma in the exposed women in the "incident" and "prevalent" cohorts, 52 (10.1%) had undergone brain MRI scans 6 to 18 months before the event. However, the frequency of performing MRI scans in the underlying cohort is not presented in the study report. It could be that the increased risk of meningiomas with increasing cumulative doses is affected by frequency of performing MRI scans, i.e. patients treated for a longer time can undergo more MRIs and consequently, the chance of finding a meningioma is increased. This would lead to an overestimation of the true risk.

The PI currently reflects that meningiomas have been reported in association with long-term use (years) of cyproterone acetate at doses of 25 mg/day and above. The results obtained by Weill and colleagues confirmed the current knowledge that high doses of cyproterone were associated with the development of meningioma. This study provided additional information, as stratified results showed a strong dose-effect relation, indicating that the risk of meningioma increases with higher cumulative doses of cyproterone.

Furthermore, additional analyses showed that after discontinuation of cyproterone for at least one year, the risk of meningioma decreased remarkably, although it remained slightly higher than the background risk without previous exposure to CPA. This is in line with what is seen from case reports described in literature. Furthermore, this study showed that in 30% of the meningioma cases, women continued or resumed cyproterone acetate after receiving treatment for meningioma.

The use of the low dose combination CPA products (CPA/ethinylestradiol, CPA/estradiol valerate) was not taken into account in this study. Therefore, this study provides no information on the risk of meningioma with the use of these products.

2.2.2. Literature review

A literature review on this topic identified 3 relevant publications which are summarised below.

- The association of high dose (50 mg/day) CPA with meningioma was first described in a case series published by **Froelich et al. in 2008**, in which 9 female patients with meningiomas who were treated with CPA 50 mg/day for various indications for a time period ranging from 10 to 20 years. In addition, information from the spontaneous reporting system of the MAHs raised the hypothesis of an increased risk of meningioma in patients treated with dosages of 25 mg per day and above. The PhVWP had 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. The

outcome of this assessment is currently reflected in the PI of cyproterone-only containing products. [Minutes PhVWP November 2009].

- A cohort study by **Cea-Soriano et al**. compared patients with meningioma (n=745) identified in the THIN database in the UK and age- and sex-matched to controls (n=10,000) from the same cohort. No significantly increased risk of meningioma was found among female users of oral contraceptives (OCs) compared with non-users (OR: 1.15; CI: 0.67–1.98). There was a significantly increased risk of meningioma among male users of androgen analogues compared with non-users (OR: 19.09; CI: 2.81–129.74) and among male users of high-dose (≥ 50 mg) CPA (OR: 6.30; CI: 1.37–28.94) compared with non-users, however there were only three cases currently using CPA.
- In a retrospective cohort study by **Gil et al**. among 2,474 users of high dose CPA (50 mg) (6,663 person-years) four meningioma cases were identified, resulting in an IR of 60.0 (95% CI 16.4-153.7) per 100,000 person-years, which was significantly higher than that observed among the non-users (IR 6.6; 95% CI 6.0-7.3) and among female users of low dose cyproterone (IR 0.0, 95% CI upper limit 5.5). After adjusting for age and gender, patients exposed to high dose CPA showed an increased risk of meningioma of 11.4 (95% CI 4.3-30.8) as compared with non-users. Meningioma incidence rates were compared in patients exposed to high dose CPA (50 mg) with those non-exposed and with those exposed to low dose CPA after adjusting for age and gender.

Summarised, prior to Weill et al, 2019, two epidemiological studies estimated the IRs of meningioma. These two epidemiological studies from Gil et al. in Spain, and Cea-Soriano et al. in the UK (sponsored by the MAH Bayer) supported the hypothesis generated by Froelich et al. that the exposure to high-dose, but not low dose CPA, increases the risk of meningioma.

Further to the above epidemiological studies, several additional case series were published from 2008-2019. A total of 65 case reports of meningioma associated with cyproterone were identified from the literature. Of these 65 case reports, 46 described the occurrence of meningioma in females, 5 in males, 13 in transgenders and in one case the sex was unknown. The majority of these reports confirmed the current scientific knowledge that the risk of meningioma is associated with high doses of CPA with prolonged use.

No scientific literature was identified that specifically links the use of low dose cyproterone combination products to meningioma.

2.2.3. Other post-marketing safety data

2.2.3.1. Data submitted by the marketing authorisation holders

As the majority of post marketing exposure and post marketing cases originated from the innovator, the assessment provided below is focussed on the data submitted by the innovator MAH Bayer. Post marketing cases were identified in the safety databases of generic products. However, in the data presented by the generic MAHs there might be duplicates of the 780 post marketing cases or the 65 case reports identified from literature assessed in the response of the innovator. Given the overall description of cases of the generic MAHs, no new information could be identified that adds to the assessment of cases from the innovator Bayer.

Cyproterone-only containing products

In total, 780 cases of meningioma have been reported with the use of cyproterone-only. In almost all cases cyproterone (N=763, 97.8%) was the suspect drug and almost all cases concerned female

patients (93%). Almost all cases of meningioma originated from France (92.5%) and were reported after 2018, likely as a result of media attention in France around the topic of meningioma in 2018. As almost all cases were reported in France, the cases described below represent the situation in France and not all aspects can be extrapolated to other European countries.

The overall estimated reporting rate of meningioma with the use of CPA is 11.1 cases per 100,000 person years in the EU, with a difference between male (1.4 cases/100,000) and female patients (21.5 cases/100,000), reflecting that most cases were reported in women. However, as this reporting rate is primarily driven by FR cases the reporting rate should have been calculated with exposure data from FR instead of the entire EU patient exposure. As the vast majority of cases were reported as a result of stimulated reporting it can be assumed that the extent of underreporting in France is low.

Age and other risk factors

The majority of the patients with meningioma was aged between 41 to 50 years of age. On average male cases were older (61.9 years) than female cases (46.5 years). In only 65 of 763 cases (radiotherapy (n=8), brain tumours (n=11), other tumours (n=45), genetic disorders (n=0) and pregnancy (n=1)), information on known risk factors were reported which could have confounded these cases.

Indication

In 559 cases the indication was available. In female patients, the most common indications were hirsutism (N=130), acne (N=93), contraception (N=83), alopecia (N=65), polycystic ovaries (N=63). Cyproterone is not indicated for contraception and endometriosis. With regards to the indication of ovarian cysts/polycystic ovaries, this is referring to PCOS (polycystic ovary syndrome), which often is the underlying cause of symptoms of hyperandrogenisation like hirsutism, acne and alopecia. As more than 1 indication can be reported in each case it could not be established in how many cases cyproterone was used off-label. In the cases in which CPA-only was reported to be used for the indication contraception, an approved indication, for example hirsutism, can be reported as well. In male patients, the most commonly reported indication was prostate cancer.

Cumulative dose

The majority of male and female cases were exposed to a cumulative dose of 60 g or higher (N=87%). Though information on daily doses is not available from the data presented by the MAH, a cumulative dose of 60 g can account for 50 mg for 20 days during a 30-day period for a duration of 5 years. From the stratified data on cumulative doses, a dose effect relation was seen in both the male and female cases, as the number of meningioma cases increased with higher cumulative doses.

Exposure time

Information on exposure time could be estimated for 429 of the 709 female cases (61%). In the majority of these female cases (N=393, 91.6%) meningioma was detected/diagnosed after an exposure to cyproterone of 5 years or longer. However, in 47 cases the exposure time was reported to be shorter than 5 years and in 9 cases even shorter than 1 year.

Additional analysis of the 47 cases with an exposure time ≤5 years showed that in the majority of these cases, patients were exposed to high cumulative doses of cyproterone (>12g). In one case the patient had a pre-existing meningioma and causality in this case can be excluded. In the remaining 46 cases, no risk factors or alternative explanations for the occurrence of meningioma were reported. In the majority of the remaining 46 cases a pre-existing meningioma could not be excluded and evidence for a causal association between cyproterone treatment and the development of meningioma can be considered weak. However, in 4 cases a pre-existing meningioma was excluded by cerebral imaging prior to start or during the first years of cyproterone treatment. In these 4 cases, patients were exposed to high daily doses of cyproterone and high cumulative doses (>12g) were reached in a short

period of time (7 months – 5 years). An association between short term use of high daily doses cyproterone treatment and the development of meningioma can be considered established in these 4 well documented cases due to the plausible temporal relationship, the lack of known risk factors and as negative cerebral MRI scans were obtained before the start or during the first years of treatment with cyproterone.

Low dose cyproterone combination products

The MAH Bayer identified 50 meningioma cases with the use of Diane-35. However, 36 of these 50 cases were confounded by the use of high dose cyproterone and therefore excluded. The remaining 14 cases were generally poorly documented. The reporting rate can be calculated to be 0.015 cases per 100,000 treatment years, which compares with a reporting rate of 11.1 cases per 100,000 treatment years.

No substantial new information has been provided by other MAHs on the association between low dose CPA and meningiomas.

None of the reported cases from any of the MAHs provided evidence for a causal association of the use of low dose CPA with the occurrence of meningioma.

2.2.3.2. Pharmacovigilance survey by the ANSM

Prior to triggering this review at a European level, the ANSM performed a pharmacovigilance survey on the risk of meningioma in association with cyproterone. The ANSM analysed the meningioma cases reported in France between April 2014 and October 2018. The search identified 298 cases of meningioma. The cumulative review submitted for assessment by the MAH Bayer contained 780 cases of meningioma reported for cyproterone acetate. Almost all cases originated from France. It can therefore be assumed that the 298 cases identified in the pharmacovigilance survey performed by ANSM are also included in the cumulative review of the MAH Bayer. Furthermore, additional cases were identified in the search from Bayer as the data lock point of the search was 01 July 2019 and the majority of cases were reported after Q3 2018. The results of the review of ANSM and the cumulative review performed by Bayer were comparable.

2.2.3.3. Eudravigilance analysis

A search performed in the EudraVigilance database identified 871 meningioma cases in the period 1995-28 August 2019. Of these cases, 628 (72%) were reported in 2018-2019. Furthermore, 606 of the case reports received in 2018 and 2019 stem from a single country, France. The vast majority of these reports concern cyproterone as single ingredient, referred to female patients (92.5%) and were non-fatal. Cyproterone-containing medicinal products were mostly used for skin appendage conditions, followed by obstetric and gynaecological therapeutic procedures and ovarian and fallopian tube disorders. The mean time-to-onset of meningioma cases was 14 years, with an interquartile range between 8 and 20 years. Of the 871 cases, 14 were reported for low dose cyproterone combination products and no cyproterone-only product was used. It can be concluded that these 14 cases are the same cases described by MAH Bayer. None of these reported cases provided a clear association between the use of low dose cyproterone combination products and the occurrence of meningioma. Of the 857 remaining cases, 780 were described in the response of MAH Bayer. The remaining 77 cases can be considered originating from other cyproterone-containing products and a small proportion might be reported in the period between 01 July 2019 (data lock point used by Bayer) and 28 August 2019 (data lock point of EudraVigilance analysis). As a total of 314 cases had been identified by other MAHs

in their responses, it can be concluded that at least 75% of these cases were duplicates from the cases included in the analysis provided by MAH Bayer. The overall pattern described in the EudraVigilance analysis performed by EMA is comparable with the pattern seen in the 780 cases described by the MAH Bayer. The EudraVigilance search confirms the analyses of the data submitted by Bayer and described in literature.

2.2.4. Discussion

From the review of post marketing cases (spontaneous reporting and literature) (N=780) it can be concluded that in the majority of cases cyproterone was used longer than 5 years and in daily doses of 50 mg. This confirms what was known for this risk in line with the conclusions of the PhVWP in 2009. Although the number of post marketing cases with a relatively short exposure time is considered low (n=47), these cases provide sufficient evidence to establish an association between short term use of high daily doses cyproterone and the development of meningioma.

The study of Weill adds to this knowledge that in women, the risk of meningioma increases with higher cumulative doses of CPA-only. 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 majority of post marketing cases and cases included in observational studies originated from France and therefore not all aspects of this review can be extrapolated to other European countries.

As the three observational studies performed in Spain, UK and France showed comparable relative risks for meningioma with high dose CPA-only, it can be concluded that the relative risks measured in these studies are generalizable to Europe.

However, unlike several other EU countries, 10 mg CPA is not marketed in France and overall France accounts for 39% of the EU patient exposure to CPA. Furthermore, as 93% of the post marketing cases are reported in France, the reporting rates and prescription patterns described in these cases are only representative of France and cannot be extrapolated to other European countries.

Furthermore, the Weill et al study showed that in France, in 30% of the meningioma cases, patients continued or resumed CPA after being treated for meningioma. This raises questions on the effectiveness of the risk minimisation measures in place at the time the study was performed. In the PI of cyproterone-only products it is already clearly stated that use of CPA is contraindicated in patients with meningioma and if a patient treated with cyproterone is diagnosed with meningioma, treatment must be stopped. Health care professionals should be reminded of the currently included contraindications and warnings.

In France, the current PI includes a recommendation to perform MRI brain imaging at the start of CPA treatment, after 5 years of CPA treatment and every 2 years thereafter. The incidence of meningioma in the general population is very rare in both women (3.71 to 6.85 per 100,000 women) and men (1.8 to 3.01 per 100.000 men), and based on a background prevalence of meningiomas of 6.85 per 100,000 women, performing an MRI at the start of CPA treatment would translate into 15,000 MRIs be

performed to detect 1 case of meningioma. Furthermore, the study by Weill et al showed that the aHR after 5 years of use is increased by a factor 21. Taking into account the prevalence of 6.85 per 100.000 women as used in the previous calculation, this would correspond to performing an MRI on 730 women exposed to 5 years of cyproterone treatment to detect 1 case of meningioma.

Based on the cumulative review on the literature and post-marketing cases, no new safety issue concerning the occurrence of meningioma with low-dose CPA could be identified. In the context of large post-marketing patient exposure, only a small number of cases were identified resulting in a low reporting rate, also compared to the high dose CPA products and the background incidence of meningioma. It is further noted that many of the cases reported with low dose combination products are confounded by use of high-dose CPA containing products. The majority of post-marketing reports were received in France and are possibly due to a previous temporary suspension of the low dose CPA products in this country. None of the reported cases from any of the MAHs provided a clear association with the use of low dose CPA with the occurrence of meningioma.

Extrapolation of the risk seen in women who used 50 mg and 100mg 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.

3. Benefit-risk balance

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 previous 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 et al. confirms the current scientific knowledge. This study is the first study with enough statistical power to stratify the exposure by cumulative dose. These stratified results showed a strong cumulative dose-effect relation, indicating that the risk of meningioma increases with higher cumulative doses of cyproterone.

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.

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.

The PRAC considered the need for a recommendation for MRI monitoring of patients before and regularly during treatment. However, in view of the burden on individual patients and the very large number of MRIs to be performed to diagnose a single case of meningioma in a patient without any symptoms due to the low incidence of meningioma with use of CPA, PRAC considered that this measure would not be proportionate. The PRAC considered that a controlled access programme for cyproterone products would also not be proportionate to the small absolute risk of meningioma, and that in view of the fact that approximately three-quarters of meningiomas are asymptomatic, additional risk minimisation measures such as an educational tool for patients or a prescriber checklist are unlikely to have an impact in terms of risk minimisation.

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 (see section 4.1.1).

4. Risk management

4.1. Pharmacovigilance activities

4.1.1. Non-interventional studies

The MAHs of high dose cyproterone-containing products are to submit a joint study protocol for an observational (non-interventional) cross-sectional survey within 6 months of the CMDh position/EC Decision (as applicable) for this referral procedure. Collaboration among MAHs is strongly encouraged. At a minimum this study protocol should include the following key elements:

- The primary objective should be to assess the physicians' awareness and level of knowledge of the information included in the SmPC and DHPC regarding risk of meningioma.

- At a minimum, this study should obtain information on the physicians' knowledge on the following existing and new risk minimisation measures:
- Restriction of the indication to second line treatment.
- Treatment should be used for the shortest possible time and with the lowest effective dose
- The contraindication: Meningioma or a history of meningioma
- Cyproterone treatment should be stopped if a patient is diagnosed with meningioma

This study should be performed in at least 5 European countries including France.

In the study protocol a thorough discussion should be provided on the following elements (see GVP XVI. Appendix I):

- Sampling procedures and recruitment strategy; including a discussion on a representative sample of prescribers in different indications
- Design and administration of the data collection instrument
- Analytical approaches
- Ethic, privacy and overall feasibility of the study.

4.2. Risk minimisation measures

4.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to minimise the risk of meningioma associated with the use of cyproterone-containing medicinal products. These changes include amendments to sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC of medicinal products containing only cyproterone, and sections 4.3, 4.4 and 5.1 of the SmPC of medicinal products containing cyproterone either in combination with ethinylestradiol or estradiol valerate.

The package leaflet was amended accordingly.

4.2.2. Direct healthcare professional communication/Communication plan

The PRAC agreed on the wording of a direct healthcare professional communication including information on:

- occurrence of meningiomas (single and multiple) in association with the use of cyproterone acetate, primarily at doses of 25 mg/day and above.
- risk of meningioma increases with increasing cumulative doses.
- use of cyproterone acetate is contraindicated in patients with a meningioma or a history of meningioma.
- if a patient treated with cyproterone acetate is diagnosed with meningioma, treatment must be permanently stopped.
- new restrictions on use of cyproterone in all indications except prostate carcinoma.

5. Grounds for 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 or interventions 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 on 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.