NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the PRAC made by France:

Product Name(s) in the Referring Member State, if applicable	Cyproterone -containing medicinal products
Active substance(s)	cyproterone acetate
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	Oral and injectable use
Applicant(s)/Marketing Authorisation Holder(s) in the referring Member State	BAYER HEALTHCARE Arrow EG labo Sandoz Teva Biogaran Mylan Zentiva Besins International

Background

Cyproterone is a progesterone derivative with anti-androgenic properties. In the EU, indications of cyproterone varies greatly between countries.
As an example, the 50 mg strength is indicated in France in major feminine hirsutism of non-tumoral origin (idiopathic, polycystic ovary syndrome), when they have a serious impact on psycho-emotional and social life whereas it is indicated in some other EU Member States for severe forms of androgen-induced increased facial and body hair (high-grade hirsutism) or/and severe forms of androgen-related hair loss (androgenetic alopecia).
The 2 mg strength, in fixed association with 0,035 mg of ethinylestradiol (Diane 35), is indicated in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) or hirsutism, in women of reproductive age. The 1 mg strength, in association with estradiol valerate 2 mg (Climene) is indicated in hormone replacement therapy.

Meningioma is a rare tumour (incidence 8/100 000 PY)[1]. Although most meningiomas are encapsulated and benign tumours, their intracranial location may lead to serious and potentially lethal consequences. Women are approximately twice as likely to develop it as men, suggesting a role of sexual hormones in the physiopathology. Case-reports published in the literature suggest that tumours caused by cyproterone would

[1] Ostrom QT, Gittleman H, Liao P, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2010–2014. Neuro-Oncol 2017;19:v1–88. doi:10.1093/neuonc/nox158

shrink after treatment discontinuation, and suggest that surgery (the reference treatment of meningioma) might not be required in that case[2,3].

The risk of meningioma associated with cyproterone use is known since 2008[4] and led the PhVWP in 2009 to recommend changes in the product information of cyproterone- containing products at a dosage of 10, 25, 100 mg or more (EMEA/CHMP/PhVWP/644462/2009[5]). Particularly, a contraindication has been added in case of "Meningioma or a history of meningioma". At that time, the product information of medicines containing less than 10 mg of cyproterone was not updated as no risk of meningioma had been identified with these dosages. However, the risk had not been quantified and the cumulative dose-effect relationship was not characterised.

Risk of meningiomas

Epidemiological data
To further clarify the relationship between cyproterone and the risk of meningioma, the French Health Insurance (CNAM) has conducted a pharmaco-epidemiological study on 253,777 women exposed to medicines containing 50 or 100 mg cyproterone retrieved from the French national health data system. The study especially compared those who received high doses (more than 3 g over 6 months, then continued treatment; n=139,222) to those with low exposure (less than 3 g over 6 months, then stop treatment; n=114,555). The occurrence of meningioma (defined by inpatient management of cranial meningioma by neurosurgical resection, decompression or radiotherapy) in these women was monitored for 7 years.

The final results that were made available in June 2019 show that the risk of meningioma is multiplied by 7 for women treated with high doses over a long period (more than 6 months) *vs* women treated with low doses. There is also a strong dose-effect relationship as the risk markedly increases with the cumulative dose, reaching a hazard ratio (HR) of 20 after 5 years of treatment at a dose of 50 mg/day (20 days per month). After discontinuation of exposure to cyproterone for at least one year, the risk of meningioma decreased markedly, but remained slightly higher than the background risk without exposure.
A location of the tumor at the anterior skull base appeared to be almost specifically associated with prolonged exposure to cyproterone.

The study also shows that in 19% of the cases, cyproterone was reintroduced after surgery. This could suggest a lack of awareness by healthcare professionals of the association between the risks of meningioma and exposure to cyproterone.
The results suggest a substantial off-label use as only 15% of women in the cohort were prescribed cyproterone for hirsutism (identified by co-prescription of medical care commonly used in this pathology) which is the only authorized indication in France for women. The other uses are more difficult to characterise as the indication is not mentioned in the database, but associated information strongly suggests off label use (contraception, acne); absence of co-prescription of an estrogen is also observed.

French scientific advisory committee (CSST)
Considering these preliminary results, the ANSM has created a temporary specialized scientific committee (CSST) which aimed to discuss the conditions of use and prescription of this drug in order to limit this risk.

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2 Bernat, A. L. et al. Growth stabilization and regression of meningiomas after discontinuation of cyproterone acetate: a case series of 12 patients. Acta Neurochirurgica 157, 1741–1746 (2015).

3 Botella, C., Coll, G., Lemaire, J.-J. & Irthum, B. Méningiomes intracrâniens et utilisation prolongée d'acétate de cyprotérone à dose conventionnelle chez la femme : à propos de deux cas de régression tumorale après arrêt du traitement. Neurochirurgie 61, 339–342 (2015).

4 Froelich S, Dali-Youcef N, Boyer P, Kehrli P, et al. Does cyproterone acetate promote multiple meningiomas? Endocr Abstr10thEuropean Congress of Endocrinology. Berlin. Germany., 16;2008. p. 105.

5 HMA 2009. PhVWP Report on Cyproterone acetate and the risk of meningiomas Provided to the CMD(h) on behalf of National Competent Authorities. URL: https://www.hma.eu/222.html

In October 2018[6], the CSST issued some general clinical guidelines and specific imaging recommendations (especially MRI) on the appropriate use of cyproterone to further minimize the risk of meningioma.

Pharmacovigilance survey

A total of 298 cases reported to ANSM from 2014 to 2018 were analysed. The results[7] were presented on 18 June 2019 during a meeting in presence of patient's representatives. The results are complementary to the CNAM's study results. cyproterone appears to be widely used off-label in France for acne or contraception indications. The patients were generally exposed for a long time before the diagnosis of a meningioma (mean 14.7 years [6 months to 35 years]). Meningiomas associated with cyproterone use are mostly located on the skull base, which seems specific to meningioma associated with cyproterone. Moreover, multiple meningioma seems associated with long duration of exposure. The evolution of cases was not documented in 52% of cases; when available, treatment discontinuation with follow up by MRI led to regression of the tumour in half of the cases. This survey also points out the issue of meningioma management which occurs during a pregnancy several months/years after cyproterone discontinuation as it seems to exacerbate pre-existing cyproterone-born meningioma.

Regarding products containing a lower dose of cyproterone (1 or 2 mg), the data are more limited, but several cases have been reported. At this stage, the role of these medicines in the occurrence of meningioma cannot be excluded.

National measures and referral to the PRAC

Considering the substantial off-label use that was observed in France in the CNAM study (and therefore the unintended high exposure in France), and considering that meningiomas can lead to serious consequences, the ANSM, awaiting for further assessment at the European level, has implemented risk minimisation measures for higher dosages of cyproterone-containing medicines (i.e. 50 and 100 mg), including[8]:

- changes in the product information: requirement for an annual risk acknowledgement form conditionning the delivery of the medicine, including warnings in sections 4.2 and 4.4 of the SmPC and in the legal status (conditions of prescription and delivery) of the medicine. Additional recommendations in section 4.4 of the SmPC about the need to perform an MRI before the start of the treatment, also reminded in section 4.3, and MRI monitoring requirements during long-term treatment. Similar changes were also implemented in the patient leaflet ;
- the introduction of an annual risk acknowledgement form signed by both the prescriber and patient, conditioning the delivery of the medicine by the pharmacist;
- an information sheet by ANSM for the patient treated with Androcur and generics on the risk of meningioma;
- a letter was also sent by CNAM/ANSM to patients who had a prescription of Androcur and generics in the last two years, and to prescribers who prescribed these in the last two years;
- a DHPC to prescribers and another DHPC to pharmacists are currently being sent.

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[6] ANSM, 2018. Androcur et génériques (acétate de cyprotérone, 50 mg et 100 mg) et risque de méningiome : l'ANSM publie des recommandations pour la prise en charge des patients - Point d'information. URL: https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Androcur-et-generiques-acetate-de-cyproterone-50-mg-et-100-mg-et-risque-de-meningiome-l-ANSM-publie-des-recommandations-pour-la-prise-en-charge-des-patients-Point-d-information

[7] ANSM, 2019. Acétate de cyprotérone (Androcur et ses génériques) et risque de méningiome : Résultats de l'enquête de pharmacovigilance - Point d'Information. URL: https://www.ansm.sante.fr/S-informer/Actualite/Acetate-de-cyproterone-Androcur-et-ses-generiques-et-risque-de-meningiome-Resultats-de-l-enquete-de-pharmacovigilance-Point-d-Information

[8] ANSM 2019. Acétate de cyprotérone sous forme de comprimés dosés à 50 ou 100 mg (Androcur et ses génériques) : mesures pour renforcer l'information sur le risque de méningiome - Point d'Information. URL : https://ansm.sante.fr/S-informer/Actualite/Acetate-de-cyproterone-sous-forme-de-comprimes-doses-a-50-ou-100-mg-Androcur-et-ses-generiques-mesures-pour-renforcer-l-information-sur-le-risque-de-meningiome-Point-d-Information

In view of the above and the necessity to take an action at EU level, France considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC

Signed [redacted] Directeur général

Date 02 JUIL. 2019