Translated French Government Reports on Cyproterone Acetate and Meningioma (2018–2019) (ASNM/CNAM)

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English Translated (2018/06/13)

Committee scientific specialized temporary (CSST) meningioma and cyproterone acetate

Session of 06/13/2018 from 4 p.m. to 6 p.m. room A011

1. Introduction

The ANSM in collaboration with the National Health Insurance Fund (CNAM)/Lariboisière neurosurgery team has been working for several months on the risk of meningiomas associated with cyproterone acetate (Androcur). If the risk was already known and mentioned in the product SPC (following a European arbitration in 2009), the strength of the link was not known until now.

Historical reminder of the measures taken around cyproterone acetate

Cyproterone acetate (CPA) is a progestin that has strong antigonadotropic and antiandrogenic activity. Its indications for the 50 mg dosage are:

- Severe female hirsutism of non-tumor origin (idiopathic, polycystic ovary syndrome), when it has a serious impact on psycho-emotional and social life.
- Palliative anti-androgenic treatment of prostate cancer.

For the hirsutism indication in women, the marketing authorization regimen is 50 mg/day for 20 days combined with estrogen.

The first European discussions on the risk of meningiomas under cyproterone acetate began in 2009, when France launched a signal on the basis of a publication by Pr Froelich highlighting an association between cyproterone acetate and the occurrence meningiomas.

This signal was evaluated and then discussed with Germany as a rapporteur country for the 2009 PhVWP and modifications to the SPC (and corresponding sections of the leaflet) were made for specialties containing more than 2 mg of cyproterone acetate, in order to implement this risk.

Thus, the SPC/manual have been modified to add:

- a contraindication in 4.3 "existence or history of meningiomas"
- a note in 4.4: "cases of meningiomas (single and multiple) have been reported in case of prolonged use (several years) of ANDROCUR at doses of 25 mg and more per day. If a meningioma is diagnosed in a patient treated with ANDROCUR 50mg, treatment should be stopped"
- a mention in 4.8 "cases of meningiomas (single and multiple) have been reported in case of prolonged use (several years) of ANDROCUR at doses of 25 mg and more per day".

Following this arbitration, the ANSM set up a survey of PV in classic monitoring extended to other synthetic progestogens without a class effect can not be clearly demonstrated on the risk of meningioma, given the few events reported.

Sales data for CPA 50 mg in France in 2017

Androcur 50 mg marketed by Bayer represents 1/4th of CPA sales, the other market shares are represented by generics (Mylan, Biogaran, Sandoz, etc.).

The estimated number of women exposed to CPA is around 57,000 in France in 2017. Note that 82% of sales of 50 mg relate only to women. Compared to other countries in Europe (UK, IT, DE, ES), France represents around 60% of CPA sales in these 5 countries in 2016. Around 80% of meningioma cases observed in the PV Europe database are French cases, this is probably related to the majority exposure in France.

Openmedic 2017 data for the distribution of Androcur 50 mg sales according to prescribers show an initial or renewal prescription made in descending order by doctors: Gynecologists (39%), general practitioners (27%), hospital prescribers (all specialties (15%), endocrinologists (10%), surgeons (3%), and dermatologists (3%). The distribution rates are a little different from those observed in the CNAM study and carried out on the initial prescriptions from the SNIIRAM/SNDS database. Gynecologists are the most numerous prescribers by both data sources.

Recent issues

Since 2009, there has been an increase in the number of meningioma cases reported under CPA. On the basis of this increase in cases, the Bayer laboratory also asked the ANSM to modify the dosage regimen in 2012 in order to align with most European treatment regimens. The rationale of the laboratory was that the occurrence of French cases was related to the dosage regimen proposed in France (3 possible regimens). However, the new dosing regimen proposed by Bayer remained identical in terms of the monthly cumulative dose compared to the existing regimens. After several rounds of discussion, the dosage regimen was finally modified in 2015 with a single regimen at 50 mg/d + estradiol (orally or percutaneously) for the first 20 days of the cycle + additional local contraception the first 2 cycles. This diagram corresponds to the practice of using CPA in France.

In the national pharmacovigilance database (BNPV), a progressive increase in the number of cases of meningiomas declared under CPA was observed since 2009 to reach 100 cases in June 2018. Cases of meningiomas are also reported with other progestogens (nomegestrol [acetate] and chlormadinone

[acetate] in particular) but the number of cases (about ten each) is much less with these specialties compared to CPA while exposure is greater. It should be noted that the risk was identified with the CPA at 50 mg but not for the association CPA (2 mg) + EE (Diane pill) and the sales of Androcur 50 mg are approximately two times lower than those of Diane.

2. Presentation of the CNAM study on the risk of meningioma associated with cyproterone acetate

The risk of meningioma is already known and mentioned in the leaflet for patients and in the summary of product characteristics (SPC) of these drugs since 2011. If the risk was known, until now the quantification of the risk between taking these drugs and the appearance of meningioma were not evaluated, in particular with regard to the dosage, the duration of exposure, and the cumulative dose.

To answer this question, a study was undertaken by Health Insurance in cooperation with the neurosurgery department of Lariboisière Hospital. This study relates to data from the health insurance databases[1] on 250,000 women exposed to cyproterone acetate (start of treatment between 2007 and 2014) of which 140,000 had had at least three boxes (i.e. 3000 mg) during of the first 6 months of treatment. The occurrence of an operated meningioma was followed in these women for 7 years. Full results will be available later.

[1] National Inter-Regime Information System for Health Insurance (SNIIRAM) and Information Systems Medicalization Program (PMSI)

However, the first available results of this study suggest that:

- The use of cyproterone acetate in women with at least three prescribed boxes (i.e. 3000 mg) during the first 6 months would expose to a risk of occurrence of meningioma multiplied by 7 compared to women with low exposure (HR of 6.8 after adjusting for age).
- A strong dose-effect relationship is observed: the risk of meningioma onset would be multiplied by more than 20 beyond a cumulative dose of 60,000 mg, which corresponds for example to treatment at a dose of 50 mg/day 20 days a month for 5 years.
- The risk of meningioma increases sharply with the age of the patient.
- The risk of meningioma decreases very strongly after stopping treatment.
- More than 500 meningiomas of women exposed to cyproterone acetate were treated in neurosurgery or neurology between 2007 and 2015.
- The primary prescribers of CPA (50 or 100 mg[2] generic or not) are gynecologists (57%), dermatologists (12%), generalists (18%), endocrinologists (10%), and other specialties much less represented (source CNAM).
- There is a high off-label use of CPA in poorly identified indications.

[2] The 50 mg dosage represents 97% of CPA sales in France in 2017.

3. Discussion

There is a much greater use of CPA in France, compared to other European countries. There is no clear rationale.

In terms of alternatives used in other European countries, it seems that for PCOS (polycystic ovary syndrome) spironolactone is mainly used as well as GnRH analogues and even flutamide. It should be noted that these uses are off-label in France and in Europe.

Gynecologists are said to use CPA in the management of endometriosis and in some forms of acne resistant to common treatments (off-label).

The CNAM study is the first study to quantify the risk of meningioma occurring in patients on CPA. This study constitutes an almost exhaustive database of women consuming high-dose CPA, the average duration of follow-up is 3 years (maximum duration 8 years) for the incident population (2007 to 2015). The number of women exposed is very large (290,000 person-years versus 6,700 person-years in a Spanish study) and the dose-effect relationship with an RH of around 20 for high cumulative doses is an important causal argument.

The basic characteristics of the patients (age, socioeconomic status, history, initial prescriber) are close between the exposed and unexposed group, which makes it possible to exclude a significant selection bias. The exposed/unexposed women in this study, by definition, have no associated chronic disease (diabetes, hypertension) because these conditions were exclusion criteria.

This study has certain limitations:

The therapeutic indication is poorly defined, follow-up is limited to 8 years while the majority of meningiomas occur after 10 to 30 years of exposure to CPA. There is also a detection bias, since this study does not identify unoperated meningiomas, which would suggest that the absolute risk is probably underestimated compared to the actual incidence.

Meningioma is the most common benign tumor of the CNS, benign in 90% of cases, its incidence is around 8 per 100,000 person-years. It increases with age (from 0.14/10,000 below 20 years of age, to 49/100,000 beyond 85 years of age). Meningiomas are very vascularized tumors, therefore with a significant risk of operative and postoperative hemorrhage.

The standard treatment is surgical, in the event of neurological or HTIC symptoms or tumor progression.

Meningiomas on CPA have the particularity of regressing completely after stopping treatment (in almost all the cases described by the neurosurgery team at Lariboisière Hospital).

Knowledge about the risk of meningioma under CPA and the regression of these tumors without necessarily resorting to surgical treatment will have a strong impact on the therapeutic management of patients.

As these meningiomas are no longer operated in most cases at the CHU de Lariboisière, there is no longer phenotyping of tumors in order to characterize receptors or other molecular aspects.

In the 2014 pharmacovigilance survey (which included cumulative data up to 2013 from the national pharmacovigilance database), it was shown that the development was not always favorable despite a regression in the size of the tumor in 6 out of 40 cases for which information was available. Some patients have had surgery with neurological (visual) sequelae and one death has been reported. At the time, the

diagnosis was probably later than the current diagnosis, which may explain the proportion of sequelae observed.

4. Actions to be taken

1) In view of the misidentified uses, probably off-label and the old indication (approved in 1994), and taking into account the new safety data provided by the CNAM on the risk of meningioma associated with CPA, it appears it is necessary to redefine more precisely the indications for Androcur 50 mg in women to better define the situations where the benefit/risk ratio remains favorable. Certain terms of the indication such as "severe" or "idiopathic" hirsutism must be clarified by positioning, for example, the product after failure of the alternatives (that is to say, hormonal contraceptives). The rational of post-menopause treatments should also be discussed.

The last recommendations of the SFE (2008) on the treatment of hyperandrogenism recommended an estrogen–progestogen alone in 1st intention, then CPA and spironolactone as therapeutic alternative. The position of the CPA in this decision tree is to be redefined as well as the maximum duration of use since it appears that the risk is greatly increased to 5 years at normal dose of use.

2) The issue of use in transgender patients was also raised, specific information should be provided via patient associations.

3) The learned societies concerned (SFE, SFEDP, CNGOF, SFD, FNDGM) and neurosurgeons will be officially contacted by the ANSM in order to draw up recommendations concerning the use of CPA in order to regulate the risks linked to its prescription and determine what to do in the event of a meningioma. A common position will then be determined with the ANSM on the use of the product during a future CSST.

4) Pending the publication of the CNAM report, the CSST recommended, on the basis of the new information available, the development of an information point by the ANSM on the risk of occurrence of meningioma linked to taking CPA.

As the SFE and CNGOF congresses take place in September and December respectively, communication within these congresses could be envisaged.

English Translated (2018/10/01)

Committee scientific specialized temporary (CSST) meningioma and cyproterone acetate

Session of 10/01/2018 from 4:30 p.m. to 8 p.m. room A012

1. Introduction

This CSST follows that of 13.06.18 where the first results of the epidemiological study carried out by the Health Insurance and the neurosurgery department of the Lariboisière hospital were returned. This study highlighted an increased risk of meningioma occurring in women treated with cyproterone acetate (CPA) for long periods at high doses (risk multiplied by 7 for all patients beyond 6 months of treatment with use of an average dose greater than or equal to 25 mg/day and risk multiplied by 20 beyond a cumulative

exposure of 60 g of CPA (i.e. for example 5 years of treatment at 50 mg/day 20 days per month or 25 mg/day 20 days per month for 10 years)).

Also, the ANSM wished to bring together for the second time the CSST composed of endocrinologists, endocrinologist-pediatricians, gynecologists, neurosurgeons, and dermatologists with the aim of developing recommendations for health professionals relating to the use of Androcur and its generics in order to manage the risk of meningioma linked to taking these drugs.

Pr Sébastien Froelich is appointed president of the CSST and will respond to requests from the Press if necessary for questions relating to the problems of the CSST.

A toll-free number has been set up to answer questions from patients and healthcare professionals.

In the absence of consensus on recommendations for monitoring and use, the ANSM may have to choose a final position.

2- General recommendations for patients treated with cyproterone acetate

- Should we ban the use of CPA?

The committee is unanimous on the importance of this treatment due to the absence of an authorized drug alternative for the management of patients with severe hirsutism with repercussions on their psycho-emotional and social lives. It is an effective treatment that requires proper prescription. This treatment is also used in transgender women who have not had an orchiectomy.

- Indications:

The group recalls that the current indication corresponds essentially to polycystic ovary syndrome (PCOS) with severe hirsutism and that the first-line treatment of PCOS is estrogen-progestogen contraception.

Although the CNAM study was not designed to demonstrate use outside of marketing authorization, it did identify uses that do not fall under the current marketing authorization. This is further confirmed by European sales figures which show a higher prescription in France compared to other European countries with a comparable population.

In particular, the following uses were considered unjustified:

- acne,
- seborrhea,
- moderate idiopathic hirsutism,
- contraception.

CPA is sometimes used in endometriosis. Although the recommendations of learned societies do not recommend the specific use of this molecule in the absence of clinical trials, this specialty could constitute an alternative in certain forms of severe endometriosis (expert opinion).

It is not recommended to prescribe Androcur in postmenopausal women. Indeed, the incidence of meningiomas increases with age in women, these patients then become particularly at risk and should not be treated with Androcur or its generics.

Treatment is also not recommended in children where their risk-benefit balance is not established.

- Dosage and duration of treatment

The risk of developing a meningioma is dose dependent. The longer the duration of treatment, the greater the cumulative dose and the greater the risk. In the CNAM study, the risk of operated meningioma is around 4/1000 patient-years for prolonged use beyond 5 years of use at 50 mg/day.

Therefore, the lowest possible dose should be used to control the symptoms. It is not legitimate, given the risk, to treat patients for years without regularly reassessing the value of continuing to prescribe.

3- Brain imaging follow-up recommendations for patients treated with cyproterone acetate

These recommendations apply to transgender women, men, and women who have not had an orchiectomy treated with CPA. The procedure to be followed is identical because it depends on the dose and the duration of use of the CPA.

The objectives of this brain imaging follow-up are:

1) Identify patients who have a pre-existing meningioma before initiating CPA treatment
2) Identify patients who will develop a meningioma during treatment with CPA.

- Initiation of treatment:

An MRI should be performed for all patients at the start of treatment (within the first 6 months). Since a history of meningioma or the existence of a current meningioma being a contraindication already established in the SPC for Androcur and its generics, performing an MRI makes it possible to exclude an asymptomatic meningioma preexisting in the treatment. The initiation of CPA treatment on a preexisting meningioma is likely to modify the evolutionary profile of the meningioma and in particular to accelerate its growth. In addition, while meningiomas that appear de novo under CPA regress or stabilize in most cases when treatment is stopped, meningiomas pre-existing in treatment may not regress when CPA is stopped. The ongoing pharmacovigilance survey on CPA and meningiomas should provide information on this point.

- Treatment monitoring:

- In previously treated patients who had an initial MRI, taking into account the time to onset of the meningioma, it is recommended to perform a new MRI 5 years later, then every 2 years if the MRI at 5 years is normal and if the treatment is continued.
- In patients already treated for several months or years and who have never performed an MRI, it is recommended to perform a brain MRI as soon as possible, then no later than 5 years of treatment, and then every 2 years if the treatment is pursued.

- In patients who have stopped treatment, there is no need to perform routine brain imaging in the absence of clinical signs. The risk of meningioma after stopping exposure to CPA for at least one year decreases markedly: it is approximately twice the basic risk without exposure.

- In case of discovery of meningioma:

Treatment should be stopped. A neurosurgical opinion is recommended as well as a multidisciplinary discussion concerning the hormonal therapeutic strategy to adopt if necessary. Indeed, meningiomas which appear under CPA regress or stabilize after stopping treatment in most cases, a conservative (non-surgical) approach is often possible. This should be discussed on a case-by-case basis with the neurosurgeon.

Notes:

- *In order to highlight small meningiomas, brain MRI must be performed in 3D sequence, axial section, after injection of gadolinium.*
- *These general recommendations and imaging surveillance could be redefined depending on the progress of knowledge on the subject (results of new clinical studies, data from the literature, pharmacovigilance survey, etc.)*

4. Discussion/next steps

- Communication with patients and health professionals on the general recommendations for the use of CPA and those concerning the performance of brain imaging.
- Discussion on a CNAM/ANSM letter that could be sent to patients and health professionals in order to contact patients treated with CPA.
- Discussion on the value of a national meningioma registry and MRI monitoring.
- Discussion on the extension of the CNAM study to anti-gonadotropic progestins: Lutenyl (nomegestrol acetate) and Luteran (chlormadinone acetate) first. Meningiomas have also been reported with these progestins.
- Discussion on the upcoming pharmacovigilance survey on CPA and meningiomas, in order to better characterize the risk (CRPV Fernand Widal and Strasbourg).

5. Conclusion

Unanimously, the group decides on the following general recommendations for use and radiological monitoring for the use of CPA:

General recommendations:

- Non-MA indications such as acne, seborrhea, and moderate hirsutism should be avoided;
- The use of CPA in children and postmenopausal women is not recommended;
- The prescription (indication and dosage) must be reassessed annually taking into account the individual benefit/risk ratio and the development of symptoms;
- The minimum effective dosage to control symptoms should be used;
- Prolonged use and high doses are to be avoided (cumulative dose effect with risk multiplied by 7 for all patients treated for a duration of more than 6 months and risk multiplied by 20 beyond 5 years of treatment at the dosage 50 mg/day over one cycle).

Radiological monitoring as part of the treatment:

- MRI brain imaging (magnetic resonance imaging) should be performed at the start of treatment for all patients;
- In the event of continuation of treatment, the MRI will be renewed at the latest at 5 years then every 2 years if the MRI at 5 years is normal;
- Physicians are asked to contact their patients currently being treated with the medicinal product Androcur or its generics in order to reassess the need to continue their treatment and consider an MRI check if the continuation of treatment is decided;
- In patients who have stopped treatment, there is no need to perform brain imaging in the absence of clinical signs;
- If meningioma is found, treatment should be stopped permanently. A neurosurgical opinion is recommended;
- CPA meningiomas regressing or stabilizing after stopping treatment in most cases, a conservative (non-surgical) approach is often possible. This should be discussed with the neurosurgeon.

Next steps

- ANSM communications will be established at the end of the CSST.
- Consultation with patient associations.
- Results of the pharmacovigilance survey on CPA and meningiomas (second quarter 2019).
- Discussion with the CNAM on letters to send to healthcare professionals and patients.
- Implementation of an epidemiological study coordinated by GIS-EPIPHARE to measure the risk of meningiomas associated with the use of nomegestrol acetate (Lutenyl)/chlormadinone acetate (Luteran) +/- other progestins (according to a method similar to that carried out for the study with the CPA).
- Monitoring of sales figures for CPA consumption, the expected objective being a significant reduction in prescriptions in justified indications.

Reference:

Prolonged exposure to high doses of CPA and risk of meningioma in women (cohort study using SNDS data) - Long summary, March 2019. Alain Weill and Joël Coste (Department of Public Health Studies - Caisse Nationale de health insurance).

English Translated (2019/10/23)

Temporary Scientific Committee
“Meningioma and cyproterone acetate - Continuation of work”

"Progestins and risk of meningioma"
October 23, 2019

Course of the session

Meningiomas and progestins: continuation of the work

Presentation of the dossier

Reminder of previous actions carried out on cyproterone acetate

Following the presentation of the results of the study of the National Health Insurance Fund (CNAM) on the risk of meningioma associated with exposure to high doses of Cyproterone Acetate (CPA) during the first Temporary Specialized Scientific Committee (CSST) of June 2018[1], the following actions were carried out:

- CSST of October 2018: Recommendations for the use of CPA and monitoring by brain imaging[2];
- Launch of two pharmacovigilance surveys in October 2018 (one on meningiomas on CPA and the other on meningiomas on progestins, respectively carried out by the CRPVs of Paris-Fernand Widal and Strasbourg);
- Two consultation meetings with representatives of users of cyproterone acetate (Androcur and generics) and health professionals in November and December 2018[3]: Proposal to create a certificate of information on the risk of meningioma and sending CNAM-ANSM letters to users and physicians prescribing CPA;
- Amendments to the CPA Marketing Authorizations in July 2019 to include the performance of brain imaging under surveillance and to clarify that the issuance of CPA will now be subject to an annual certificate of information on the risk of meningiomas. This annual certificate must be signed by the prescribing doctor and the patient before any delivery of the product by the pharmacist[4];
- CNAM-ANSM information letters addressed to prescribing physicians and patients who have had at least one issue of the specialty in the previous two years (sent in June 2019) [4];
- Implementation of the certificate of information intended for patients and doctors conditioning the delivery of CPA in pharmacies: effective in July 2019 for treatment initiations and in January 2020 for treatment renewals [3];
- Triggering of the reassessment of the European CPA risk benefit in July 2019 in order to modify the safety information on the Summary of Product Characteristics (RCP) / CPA notices based on the results of the CNAM study.
- Monthly monitoring of CPA sales and reports on other specialties (based on nomegestrol [acetate], chlormadinone [acetate], and spironolactone).

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[1]-https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Androcur-acetate-de-cyproterone-et-generiques-risque-de-meningiome-lors-d-une-utilisation-prolongee-Point-d-information

[2]-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-despatients-Point-d-information

[3]-https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Acetate-de-cyproterone-Androcur-et-risque-demeningiome-l-ANSM-poursuit-ses-actions-pour-renforcer-l-information-des-utilisateurs-Point-d-Information

[4]-https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Acetate-de-cyproterone-sous-forme-decomprimes-doses-a-50-ou-100-mg-Androcur-et-ses-generiques-mesures-pour-renforcer-l-information-sur-le-risque-demeningiome-Point-d-Information

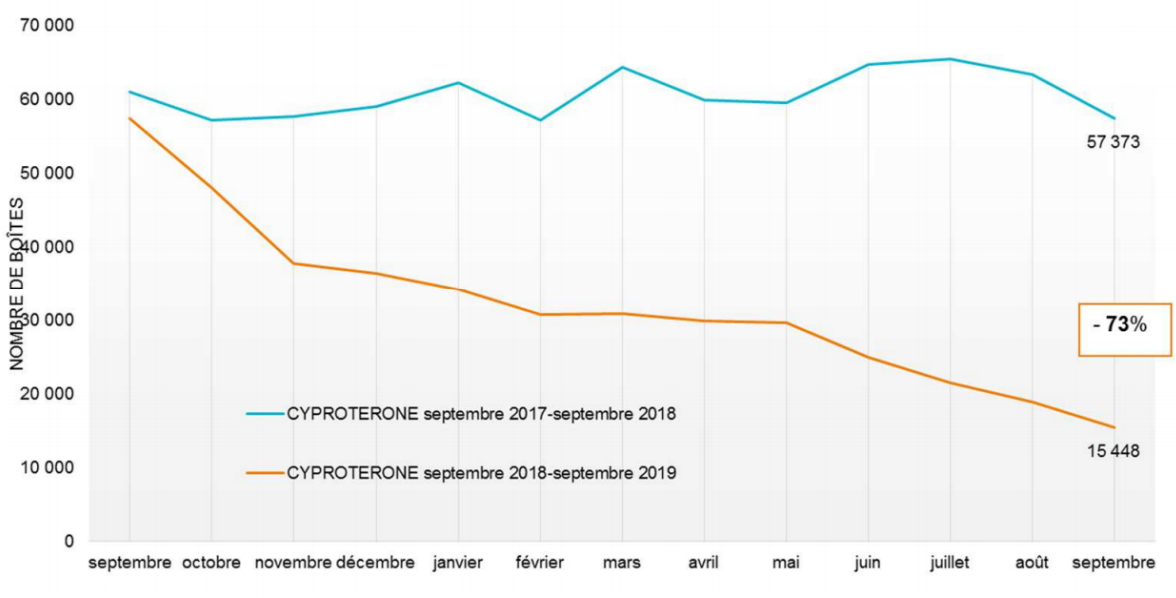
I. Evaluation of the result of the actions implemented to control the risk of meningioma under CPA

1. Sales data

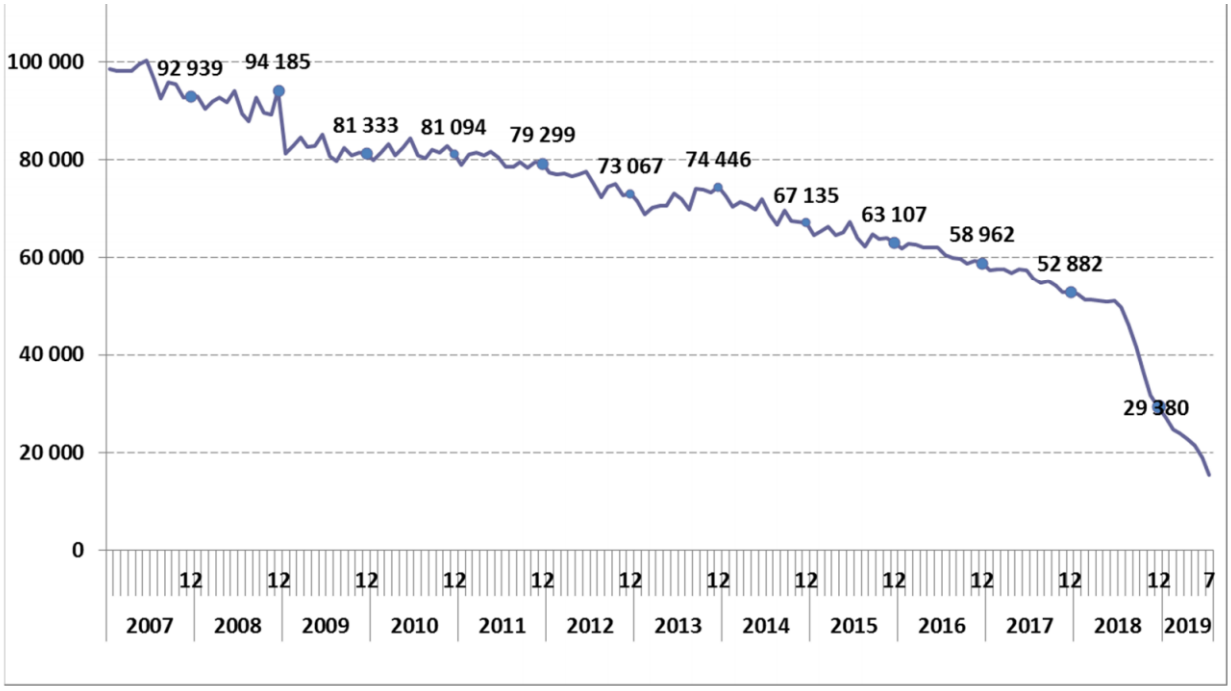
All of the actions carried out enabled the reduction in CPA consumption by more than 70% between September 2018 and September 2019.

The decline in sales figures started with the first communication in September 2018 to reach around 50% at the start of 2019 and continued until June/July 2019 when the sending of CNAM/ANSM letters and the setting in place of the certificate accentuated the fall in sales (-70%). In terms of women exposed, this corresponds to approximately 60,000 women exposed to CPA per month in 2017, then 30,000 women/month at the end of 2018 and finally 15,300/month in July 2019.

Evolution of CPA sales in pharmacies from September 2017 to September 2019
(Source: Sell Out - OPEN HEALTH)

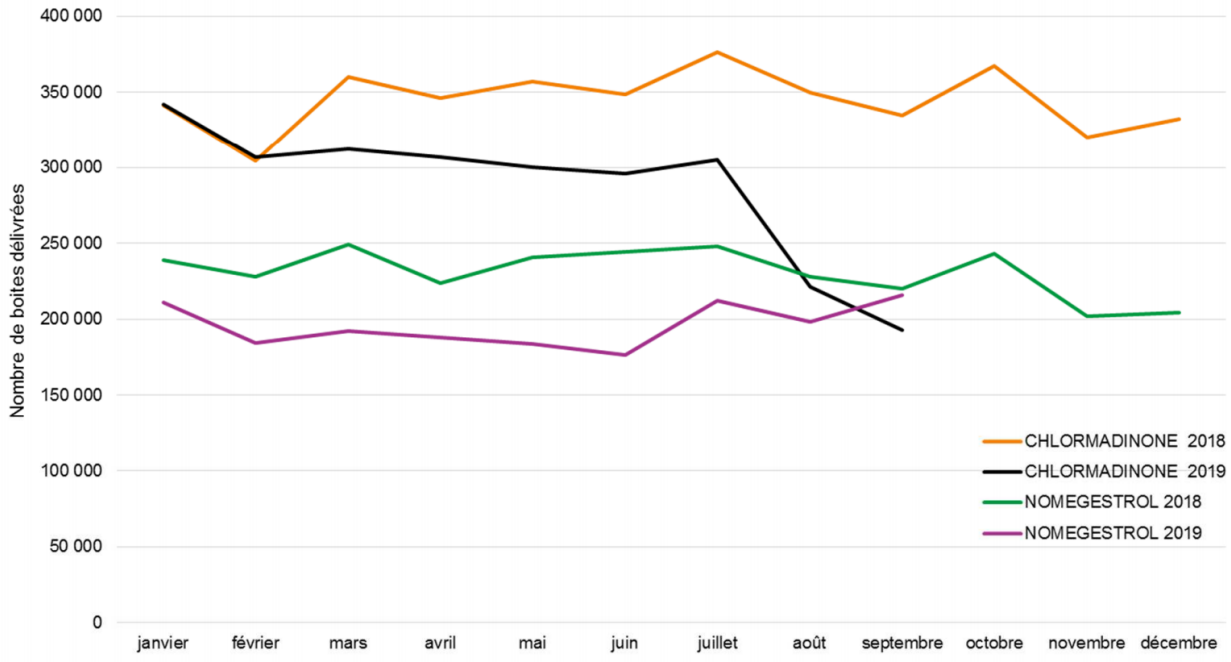


Number of women treated with cyproterone acetate per month (source CNAM)



Evolution of sales of Chlormadinone [Acetate] and Nomegestrol [Acetate] in pharmacies from January 2017 to September 2019

(Source: Sell Out - OPEN HEALTH)

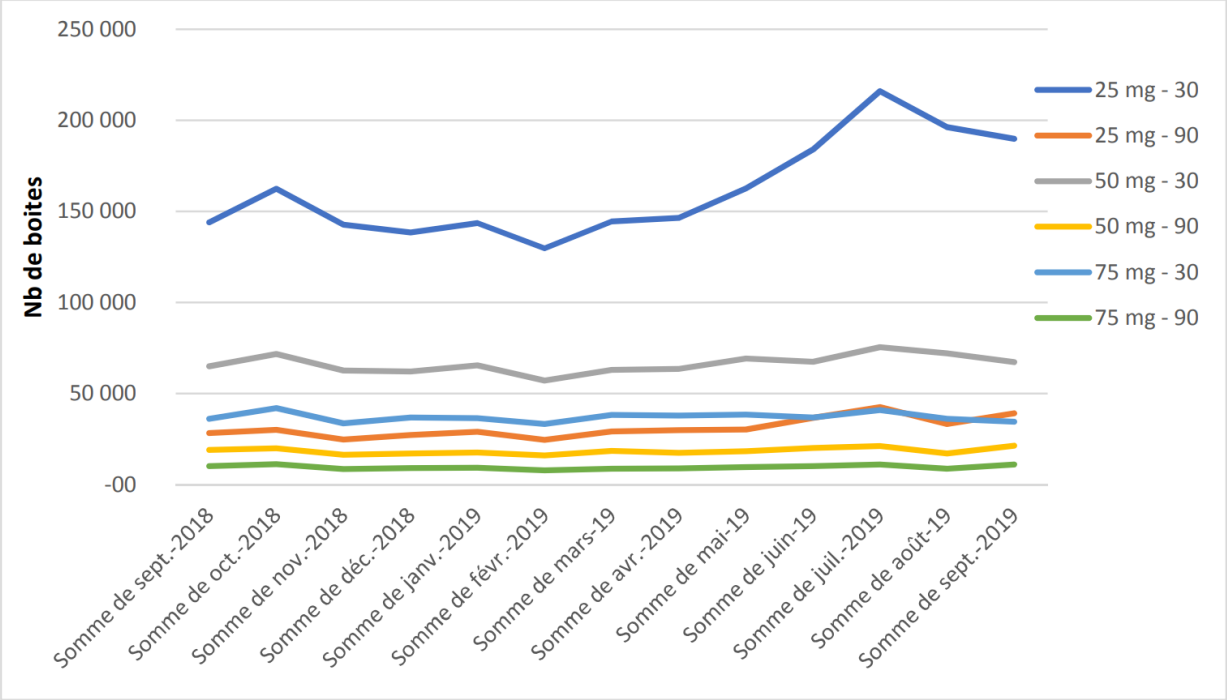


This drop in CPA sales figures is not correlated with a report on other high-dosed progestogens such as nomegestrol acetate [NMG] (Lutenyl and generics) and chlormadinone acetate [CMA] (Luteran and generics).

We also observe a clear decrease in sales of Lutenyl and Luteran after the communication from the ANSM in February 2019 on the potential risk of meningioma linked to these two substances[5], then in August 2019 for Luteran probably also linked to stock-outs successive of these progestins in 2018 and 2019.

[5]-https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Luteran-acetate-de-chlormadinone-et-Lutenylacetate-de-nomegestrol-et-leurs-generiques-des-cas-de-meningiome-rapportes-Point-d-information

Evolution of sales (in number of boxes) of spironolactone (Openhealth sell-out source)



An increase in sales of spironolactone 25 mg has been observed since June 2019. However, spironolactone is used for its anti-androgenic properties in hirsutism in certain countries, especially in the United States (non-AMM). A partial postponement of the use of cyproterone [acetate] to spironolactone is therefore probable and is the subject of specific monitoring by the ANSM for this specialty also used outside of marketing authorization.

Note that the French Society of Endocrinology (SFE) is currently working on updating the recommendations for the use of treatments in hirsutism.

2. European reassessment procedure for CPA and meningiomas

The European procedure under re-evaluation of the CPA risk/benefit balance and its possible consequences on French marketing authorizations were discussed. Monitoring by Magnetic Resonance Imaging (MRI), as recommended in France, is considered essential by CST experts but will not necessarily be adopted by other European countries given the cost and access to care which differ from country to country, as do reimbursements for imaging procedures.

European sales data prior to July 2019 confirms that France was leading CPA sales in the European Union, with 40% of CPA sales across all strengths. Compared to the 5 European countries comparable in terms of population (Germany, Spain, UK and Italy), 60% of sales of the 50 mg dosage concerned France in 2018.

To date, the risk reduction measures concerning the CPA implemented by the ANSM remain national, no recommendation or modification of the SPC/Notices has been made by the other countries pending the finalization of the arbitration.

3. Follow-up of reported meningioma cases for cyproterone acetate, nomegestrol [acetate], and chlormadinone [acetate]

Number of cases cumulatively reported in the national pharmacovigilance database until October 21, 2019 (generics included):

	Total number of cases	Total number of Product ONLY cases (not currently or in the past associated with Androcur or generics)
Cyproterone acetate 50, 100 mg (Androcur) and generics	637	NA
Cyproterone acetate 2 mg + ethinylestradiol 35 µg (Diane) and generics	43	13
Nomegestrol acetate 5 mg (Lutenyl) and generics	119	108
Chlormadinone acetate 5, 10 mg (Luteran) and generics	86	75

A pharmacovigilance survey concerning the risk of meningioma on progestins (including NMG and CMA) is underway.

II. Risk of meningiomas with chlormadinone [acetate] and nomegestrol [acetate]

1. Background

Chlormadinone acetate and nomegestrol acetate are progesterone derivatives used in particular in the management of menopause, menstrual disorders, and endometriosis.

Meningiomas associated with the use of chlormadinone acetate or nomegestrol acetate have been observed when using these drugs in therapeutic doses. Cases of regression of meningiomas have been reported after discontinuation of NMG and CMA in the literature, which would tend to demonstrate a role of the drug in the development of meningioma (Champagne et al, Passeri et al, Shimizu et al, Fushimi et

al). The pharmacological plausibility associated with rare cases of meningiomas declared with these two substances, led the ANSM to modify the SPC and notices of NMG and CMA respectively in 2017 and 2018 to include the risk of meningioma (sections contraindication, setting warning, and side effects) although at this stage, in the absence of an epidemiological study such as that carried out with CPA, it is not possible to formally conclude, that women who use these drugs present a risk meningioma higher than that observed in the general population, nor to quantify it in general (dose or duration of use). This is why an epidemiological study is in progress, by expert epidemiologists of the Epi-Phare scientific interest group, in order to determine if the use of these two progestogens is actually associated with an over-risk of developing a meningioma. The results should be available at the end of the first half of 2020.

Pending the results of this study, faced with the potential risk of meningioma associated with two treatments widely used in the management of HRT or endometriosis, the ANSM sent a letter to healthcare professionals in February 2019 in order to inform them on the one hand, of the risk of meningiomas associated with these treatments and their generics, and, on the other hand, the addition of this risk in the information documents (SPC and leaflet) of these drugs.

2. Preliminary results of the pharmacovigilance survey

The national pharmacovigilance survey concerning meningiomas reported on progestins and carried out by the CRPV in Strasbourg will be presented to the Permanent Pharmacovigilance Scientific Committee (CSP) on November 19, 2019. The preliminary results of this survey on the NMG and the CMA were presented to CST members to discuss possible recommendations for the use of these two specialties.

Initial results show that women have been exposed to progestins for an average of 12 years when meningioma is diagnosed. As with CPA, there is a high level of off-label use (around 50% of cases) mainly in contraception. The meningiomas observed under CMA or NMG are mainly grade I when it is known. They are most often single (70%) vs. multiple (30%) and mainly located on the base of the skull (40%) or on the convexity (30%).

As a reminder, the pharmacovigilance survey on CPA found the following rates: multiple meningiomas (41%) versus single (55%) and basal (67%) versus convexity (25%).

These results seem to correspond to clinical practice in neurosurgery. The meningiomas observed in women exposed to chlormadinone [acetate] or nomegestrol [acetate] are not all similar to those observed under CPA, as regards size, multiplicity, location, structure, and evolution. The majority of meningiomas on CPA regress when treatment is stopped, except in rare cases where they continue to progress after treatment has been stopped (often atypical localization: posterior, para-sagittal, or posterior convexity). Meningiomas under NMG or CMA regress less often and/or partially, especially when they are unique. Multiple meningiomas of the anterior stage of the base of the skull under NMG or CMA would respond better to cessation of treatment, and their course would be similar to those observed under CPA.

The pathophysiological mechanism of meningiomas under progestins is based on a sensitivity of these tumors to progesterone with an effect of the cumulative dose received. However, the mechanism would probably be different between CPA and NMG/CMA, the latter substances would amplify the growth of tumors whereas CPA would rather promote tumors.

These three progestogens do not seem to have a similar pathophysiological role in the onset of meningiomas.

In addition, an identified risk factor for meningioma being age, and knowing that the average age of women exposed to NMG or CMA is around 47 years, it is not yet possible to determine the bias not induce this risk factor in the assessment of causality and only the data in epidemiology would allow to do so. The results of the pharmacoepidemiology study on progestins and meningiomas carried out by GIS-EPIPHARE, the results of which will be available at the end of the first half of 2020, will help to better characterize this risk.

In total, at this stage, although the link between taking NMG and/or CMA and meningiomas is not formally demonstrated in the absence of the results of the epidemiological study, the pharmacological plausibility, the reported cases and the possible regression meningiomas after cessation of treatment as observed in neurosurgical practice, are arguments in favor of a risk of meningiomas associated with the use of these two molecules. The precise quantification of this risk may be provided by future epidemiological data.

3. Conclusion

Pending the results of the ongoing epidemiological study on progestins and the risk of meningioma, the biological plausibility of the occurrence of meningioma under these progestins (CMA and NMG) should encourage caution, both in terms of surveillance during treatment and proper use of these drugs.

Monitoring of brain MRI during treatment with CMA or NMG has been discussed. Insofar as the current level of evidence does not yet make it possible to formally establish whether the use of these two progestogens is associated with an increased risk of developing a meningioma, the group recommends the following recommendations pending the results of the epidemiological study:

- Brain MRI at initiation and regularly during treatment does not appear necessary;
- MRI will be performed in case of clinical signs suggestive of a meningioma;
- MRI will be offered to patients treated for more than 10 years.

Regarding the non-MA observed with CMA or NMG and the indications for treatment, the CNGOF is currently developing recommendations in order to re-specify the indications and adequate durations of treatment for these high-dose progestins. It was notably recalled that they were used when an antigonadotropic therapy (without associated estrogen) was necessary (endometriosis for example) or when estrogen-progestogen contraception is contraindicated (severe metabolic disorders, old diabetes, cardiovascular risk).

These first-line recommendations, in particular for surveillance by cerebral imagery, will be reassessed on the basis of the forthcoming conclusions of the ongoing epidemiological study.

III. Drug Alternatives to CPA in Hirsutism

In France, there is no medicinal specialty with a marketing authorization in major female hirsutism besides CPA.

CPA sales figures have dropped considerably over the past year as a result of various actions to raise awareness of the risk of meningioma. This decrease was accompanied by a partial postponement of prescription for spironolactone 25 mg. Spironolactone is indeed an aldosterone antagonist, having diuretic and anti-androgenic properties. It is used in some countries as part of a marketing authorization for the

treatment of hirsutism (South America in particular) and also outside of marketing authorization for the same indication (United States for example).

The doses commonly used in the treatment of hirsutism are approximately 100 mg. French sales figures show an increase [in sales] only for the 25 mg dosage. This increase in the lowest dosage available on the market is probably linked to a recent initiation of this treatment in patients where a dose increase is expected in the long term.

The SFE is currently working on updating the treatment recommendations for hyperandrogenism. Depending on the treatments recommended, if spironolactone is deemed to be an alternative treatment in severe hirsutism with a favorable risk benefit, the ANSM will assess the regulatory framework allowing the use of spironolactone in France in this indication.

IV. What to do after the diagnosis of a meningioma under CPA/NMG or CMA regarding the continuation of hormone therapy

As a reminder, the RCP and notices of CPA, NMG, and CMA contain a contraindication in case of meningioma or a history of meningiomas since 2017 and 2018 respectively. It is contraindicated to re-administer one of these 3 progestins in a patient with a meningioma diagnosed with one of these progestogens, alone or in combination (no substitution between CPA, NMG, or CMA).

For the other progestogens (alone, in combination with a contraceptive or hormone replacement therapy for menopause), no link with meningiomas has been noted at this stage. Thus, after a diagnosis of meningioma under CPA, NMG, or CMA and stopping of these drugs, the relay by another hormonal treatment could be envisaged according to the individual benefit/risk of each patient and the presence or not of alternatives after discussion multidisciplinary between the gynecologist and/or endocrinologist and the neurosurgeon.

V. Steps to take after the diagnosis of a meningioma under CPA, NMG, or CMA regarding a pregnancy

Pregnancy is a factor favoring the occurrence or growth of meningiomas. Indeed, the combined action of progesterone and growth factors contribute to the growth of meningiomas. These are usually very vascular during pregnancy and are therefore at higher risk of bleeding.

The effect of pregnancy on pre-existing meningiomas following prolonged treatment with CPA, NMG, or CMA, whether operated or not, is not known.

A patient with a meningioma known by one of these progestogens (operated or not) and wishing to be pregnant, should be subject to multidisciplinary monitoring of her pregnancy: by a gynecologist (preferably in a hospital setting) and by a neurosurgeon and/or a neuroradiologist.

The performance of an MRI before the start and during pregnancy will be discussed depending on her history, the location and size of the pre-existing meningioma, and the clinical condition of the patient.

CSP conclusions:

Pending the results of the EPIPHARE epidemiological study on NMG and CMA, the group considers that at this stage:

- **There is a plausible link between taking NMG and/or CMA and the risk of meningiomas. Although this link is not formally demonstrated in the absence of the results of the epidemiological study, the pharmacological plausibility, the reported cases, and the possible regression of meningiomas after discontinuation of treatment as observed in neurosurgical practice, are arguments in favor of a risk of meningiomas associated with the use of these two molecules. The precise quantification of this risk may be provided by future epidemiological data.**

- **The plausibility of the occurrence of these meningiomas under NMG or CMA should encourage caution, both in terms of monitoring during treatment and in terms of the proper use of these drugs. As a reminder, the modifications to the SPC/notices for the specialties based on nomegestrol [acetate] and chlormadinone [acetate] have already been carried out at the national level. Mention is made of the possibility of a meningioma risk, a contraindication in the case of a history of meningioma, and the need to stop treatment if a meningioma is discovered.**

- **At this stage, in the absence of the results of the epidemiological study whose objective is to demonstrate and quantify the risk of meningioma linked to the use of NMG and/or CMA, the group considered that the recommendations of brain imaging surveillance recommended for CPA did not apply as is for these two specialties. The following recommendations for performing brain MRI are proposed until the results of the current study are available:**
    - **MRI at initiation and regularly during treatment does not appear necessary,**
    - **MRI will be performed in case of clinical signs suggestive of a meningioma,**
    - **MRI will be offered to patients treated for more than 10 years.**

Depending on the results of the epidemiological study, scheduled for the second half of 2020, new recommendations for brain imaging surveillance and the actions to be taken may be established.

The results of the pharmacovigilance survey will make it possible to clarify some of the characteristics of meningiomas under progestins (November 2019).

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English Translated (March 2019)

Prolonged exposure to high doses of cyproterone acetate and risk of meningioma in women

Cohort study using SNDS data

Long summary

March 2019

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Declarations of interest

The declarations of interest of the authors, employees of health insurance, and/or the APHP, can be consulted online on the website of the Ministry of Solidarity and Health – Consultation of public declarations of interest

https://dpi.sante.gouv.fr/dpi-public-webapp/app/recherche/declarant

At the time of the study, none of the authors had any personal ties of interest to a company that sells the drug marketed as cyproterone acetate.

Synthesis

Context

Cyproterone acetate[1] is a synthetic progestin that has potent antigonadotropic and antiandrogenic action. Since 2007, several series of cases of meningiomas have been reported in the scientific literature during exposure for several years to high doses of cyproterone acetate (25 to 100 mg per day), however robust epidemiological data does not exist to date and, above all, estimates of the risk incurred. However, there is a biological plausibility with the known presence of hormone receptors on meningiomas.

[1] Cyproterone acetate 50 or 100 mg is marketed in France under the brand name Androcur® (Bayer laboratory) or various generics called cyproterone acetate or cyproterone.

The summary of product characteristics (SPC) and the product leaflet were modified in France in 2011, in particular to clarify that meningioma is a contraindication to taking cyproterone acetate and that its occurrence must lead to interruption of treatment. While the marketing authorization (marketing authorization) for the 50 mg dosage is limited, for women, to cases of major hirsutism when they have a serious impact on psycho-emotional and social life, wide use of the cyproterone acetate off-label is reported by the French National Authority for Health in indications such as contraception, the treatment of acne, ovarian dysfunctions, hyperpilosity, hyperandrogenism, and androgenic alopecia.

Meningioma accounts for 37% of primary brain tumors in the general population and is the most common type of brain tumor from the age of 35. Gender, age, exposure to ionizing radiation and endogenous sex hormones are the classically identified risk factors for meningioma.

Objectives

The main objective of this study was to assess in real life the impact of prolonged exposure to high-dose cyproterone acetate on the risk of meningioma in women. This study had several secondary objectives: 1) To evaluate the dose–effect relationship of the risk of meningioma in patients exposed to cyproterone acetate; 2) Specify the evolution of the risk of meningioma after stopping cyproterone acetate; 3) Describe the characteristics of meningiomas under cyproterone acetate (affected patients, location, management, etc.); 4) Measure the rate of effective discontinuation of cyproterone acetate after the diagnosis and treatment of a meningioma; 5) Estimate the number of meningioma cases attributable to prolonged exposure to cyproterone acetate.

Methods

This is an "exposed/unexposed" type cohort study based on the National Health Data System (SNDS – formerly known as SNIIRAM). It compares the frequency of occurrence of treated meningioma (event of interest) **in women aged 7 to 70 years exposed to high-dose cyproterone acetate** (defined as at least 3 boxes, or 3 grams, during the first 6 months) **and in those who were very weakly exposed** (one or two boxes during the first six months). The main study (“incidental” exposure cohort) concerned women who started cyproterone acetate (50 mg or 100 mg tablets) between 2007 and 2014 with follow-up until the end of the year 2015. An additional analysis (“prevalent” cohort) concerned women already exposed to cyproterone acetate in 2006 (the oldest year available in the SNDS) with follow-up until the end of 2015.

The event of interest was defined by the management in hospital of a cerebral meningioma by neurosurgery of excision, decompression, or radiotherapy. The comparisons were made using proportional risk Cox models comparing the incidence of events between the different groups (exposed, very weakly exposed for the main analysis) and (exposed, very weakly exposed, and stopped for the analysis sensitivity). An adjustment on the covariates at inclusion (age, specialty of the initial prescriber, context of indication, associated estrogen), was carried out while keeping only the significant ones. The cumulative dose of cyproterone acetate and age were treated as time-dependent variables.

Results

Study population

The introduction of cyproterone acetate between January 1, 2007 and December 31, 2014 affected 279,678 women. After excluding 1,760 patients under the age of 7 or over 70, 24,057 patients with long-term conditions (ALD), 76 patients with a history of meningioma or benign brain tumor at the time of the first dose and of 22 patients who died before the start of follow-up at 6 months, **253,777 women were included in the main study, of which 139,222 (54.9%) in the "exposed" group and 114,555 (45.1%) in the control group "very slightly exposed".** At inclusion women had a median age of 27 years (Q1–Q3: 21–37). The initial prescriber was a liberal doctor in 97% of the cases: gynecologist in more than half of the cases (56.7%), more rarely dermatologist (11.5%), endocrinologist (10.1%), or general practitioner (18.3%). The share of women treated for hirsutism – less than 14% – was low even if this characterization was uncertain. Overall, the "exposed" population was very similar to the "very low exposed" population. Women in the "exposed" group were slightly less socially disadvantaged (CMUc 6.5% vs. 8.2%), slightly younger – under 25 years old 42.0% vs. 37.7%, more often followed by an endocrinologist (13.1% vs. 6.4%) and less often by a dermatologist (9.3% vs. 14.3%). In contrast, in both groups the initiation of treatment was primarily the responsibility of gynecologists (55.9% vs. 57.8%).

Risk of meningioma associated with taking cyproterone acetate, measurement of the dose–effect relationship and impact of stopping CPA

As expected, the age at the start of treatment was strongly linked to the risk of meningioma. With the 25–34 age group as a reference, the Hazard Ratio was 0.2 (95% CI 0.0–1.2) for those under 25; 10.4 (4.8–2.5) for those aged 45 to 54, and 42.3 (15.9–112.3) for those aged 65 and over. Given the major effect of age on the risk of meningioma, the other variables were tested after an adjustment for age. The CMUc, the context of the medical indication, and the specialty of the prescriber, were not associated with the risk of meningioma. On the other hand, a simultaneous prescription of estrogen was significantly associated with the risk of meningioma with an age-adjusted HR = 1.6 (1.1–2.4).

In the "exposed" group and in the "very weakly exposed" group, the numbers of women hospitalized for a meningioma treated invasively (neurosurgery at more than 98%) were 69 and 20 respectively. The incidence rates (absolute risk) in the two groups were respectively 23.8 and 4.5 per 100,000 person–years, i.e. a gross relative risk of 5.2 [3.2–8.6] and an HR adjusted for age and estrogen 6.6 [4.0–11.1] for exposure to cyproterone acetate.

Analysis by cumulative dose of cyproterone acetate showed a strong dose–effect relationship; the higher the cumulative dose, the higher the risk of meningioma. The incidence rate thus reached nearly 130 cases per 100,000 person–years in the group with a cumulative exposure of more than 60 g, i.e. a gross relative risk of 28.4 [14.5–55.5]. **The age- and estrogen-adjusted HRs were not significantly**

different from 1 below 12 grams of cumulative exposure to cyproterone acetate (i.e. for example a maximum of one year of treatment with 50 mg/day 20 days per month). Beyond that, the risk greatly increased with the cumulative dose: HR = 6.4 [3.6–11.5] for 12 to 36 grams, 11.3 [5.8–22.2] for 36 to 60 grams, and 21.7 [10.8–43.5] for more than 60 grams of cumulative dose of cyproterone acetate (for example 5 years of treatment with 50 mg/day 20 days per month).

After stopping exposure to cyproterone acetate for at least one year, the risk of meningioma decreased sharply but remained slightly higher than the basic risk without exposure with an age- and estrogen-adjusted HR of 1.8 [1.0–3.2].

In women already exposed in 2006 to cyproterone acetate ("prevalent" cohort including 131,485 women), we observed, in those exposed to at least 3 grams after 2006, 485 cases of meningiomas treated in hospital for invasive therapy (neurosurgery, radiotherapy). In this cohort the incidence rate (absolute risk) was 133 per 100,000 woman–years. As for the "incident cohort", there was a strong dose–effect relationship. Thus for a dose of 12 to 36 grams of cyproterone acetate since 2006 the incidence rate was 97 per 100,000, from 36 to 60 grams was 206 per 100,000, and beyond 60 grams of cyproterone acetate the incidence rate was 387 per 100,000 (or about 4 per 1,000 woman–years). This corresponded for this exposure to an HR adjusted for age and estrogen of more than 30. It is in this last group women who were exposed for a very long time to high doses, 15 to 30 years for example, without it being possible to determine individually the start of the exposure because we do not have information in the SNDS prior to 2006.

As in the "incident" cohort, in the event of exposure stopped for at least one year, the risk fell sharply corresponding to an HR adjusted for age and estrogens of 1.8 [1.0–3.0].

Description of elements related to meningioma (patient characteristics, localization management, seriousness, etc.)

Among the 516 women (69 from the "incident" cohort – and 447 from the "prevalent" cohort – main analysis) exposed to CPA and hospitalized for a meningioma, 96.0% underwent neurosurgical intervention for tumor removal and 4.0% were treated with radiotherapy. The average age at treatment was 48.1 years (vs. 52 years for "very low exposure" women).

There was also a significant difference in the location of operated meningiomas between exposed women and those with very low exposure.

The five most frequent anatomical locations of meningiomas in women exposed to CPA concerned 1) the anterior stage of the base of the skull (n = 120), 2) the convexity of the brain without involvement of the dural venous sinus (n = 107), 3) the inner third of the middle stage of the base of the skull involving the spheno-orbital angle (n = 81), 4) the optochiasmatic and/or hypothalamic region (n = 70), and 5) the middle level of the base of the skull (n = 47). **One location seemed particularly associated – almost specific – with prolonged exposure to cyproterone acetate: it was the anterior stage of the base of the skull.** Conversely, tumors in the posterior stage of the base of the skull and in the scythe or tentacle of the brain were less often associated with prolonged exposure to CPA.

For these 516 women exposed to cyproterone acetate who had neurosurgical surgery or radiation therapy, the initial hospital stay lasted an average of 10 days. In the year following initial treatment, rehospitalization for neurosurgical intervention was observed in 2% of cases, hospitalization for epileptic

seizures or epilepticus also in 2% of cases. Anti-epileptic treatment was continued between 1 year and 2 years after discharge from hospital for nearly 28% of the patients. The death rates from all causes at 30 days from the initial stay and at 1 year were 1.2% and 1.6% respectively.

Resumption and/or continuation of cyproterone acetate after excision of a meningioma

After the diagnosis and the hospital treatment of the meningioma 29.5% of the women continued the use of cyproterone acetate including 19.3% who had more than 4 deliveries in the year, that is to say at least 4 grams of cyproterone acetate in one year.

Estimated number of meningioma cases attributable to cyproterone acetate

From the data of this study which included only women affiliated to the General Scheme including the mutual local sections (87% of the population resident in France), we can estimate at least 500 over the decade 2006–2015 the number of cases meningiomas operated or treated with radiation therapy due to prolonged exposure to high dose CPA. This estimate excludes meningiomas followed and monitored medically without invasive action.

Conclusions

This study confirms and specifies the magnitude of the risk of meningioma: increased on the order of 7 times for exposures to high doses of cyproterone acetate not exceeding 8 years. On the one hand, there was a marked dose effect and, on the other hand, a marked reduction in the risk after stopping treatment for one year, two arguments in favor of a causal relationship, moreover biologically plausible. Women already exposed in 2006 and who continued treatment with more than 60 grams of cyproterone acetate from 2006 had an absolute risk of meningioma of the order of 4 per 1000 person–years which corresponded to a multiplied risk by 30. Most of the women who were exposed for 10 to 30 years were in this population. We have estimated that more than 500 women in a decade with meningioma treated by neurosurgery or more rarely by radiation therapy are attributable to prolonged exposure to cyproterone acetate.

This study also provides precise information on the location of the meningiomas (mainly anterior stage of the base of the skull and middle stage of the base of the skull in general and the internal third of the middle stage concerning the spheno-orbital angle) and on their potential severity in terms of length of hospital stay, neurosurgical reoperation, secondary antiepileptic treatment, or even death.

Almost 30% of women continued to use cyproterone acetate after surgical removal of a meningioma, despite the absolute contraindication since 2011.

Finally, the number of women treated with cyproterone acetate between 2006 and 2014 – more than 400,000 – confirms, with the absence in 85% of cases of biological investigations compatible with hirsutism, a very wide use outside of marketing authorization.

The measures announced by the ANSM at the end of the results of this study and of the two meetings of the temporary specialized scientific committee "Meningioma and cyproterone acetate" in June and October 2018 should, on the one hand, make it possible to greatly limit the uses excluding MA in high doses of cyproterone acetate in women, and on the other hand to detect by MRI the possible existence of

meningioma before treatment or its occurrence at a stage where stopping progestogen treatment makes it possible to avoid appearance of neurological disorders.

Further studies from the SNDS are necessary to measure the impact of the actions carried out, but also the risk with other progestins that may be used as a relay for cyproterone acetate.