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	LUTENYL, LUTERAN, ZOELY, BELARA, NAEMIS and generics
Active substance(s)	Nomegestrol containing products and Chlormadinone containing products
Pharmaceutical form(s)	Tablets
Strength(s)	All
Route(s) of Administration	All
Applicant(s)/Marketing Authorisation Holder(s) in the referring Member State	Theramex Arrow Biogaran EG labo Mylan Sandoz Zentiva Gédéon richter Teva Sanofi

Background

Nomegestrol acetate [NOMAC] and chlormadinone acetate [CMA] are both progestin derivatives with antigonadotropic effects.

In the EU, these medicines are indicated in different gynaecological disorders such as amenorrhea, breast tenderness, hormone replacement therapy, menorrhagia and uterine bleedings related to fibromas or not, menstrual cycle abnormal, menstrual disorder, metrorrhagia, oligomenorrhea, polymenorrhea, premenstrual syndrome, primary dysmenorrhea, endometriosis (chlormadinone only).

For nomegestrol acetate, only the 5 mg strength is marketed in the EU. In France, a 3.75 mg strength is authorized but is no longer marketed since 2021.

NOMAC is also authorized, through the EU, in combination with estradiol, in two medicines: Zoely containing 2.5 mg of NOMAC and 1.5 mg of estradiol which is authorized in contraception and Naemis, containing 3.75 mg of NOMAC and 1.5 mg of estradiol authorized in menopausal symptoms.

For chlomadinone acetate, several strengths are marketed within the EU: 2 mg (in DE); 5 and 10 mg (FR). CMA is also authorized in contraception associated with ethinylestradiol (in the EU): Belara containing 2 mg of CMA and 30 µg of ethinylestradiol.

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.

The risk of meningioma associated with nomegestrol use is known since 2018. Indeed, this risk has been discussed during the PSUSA assessment (PSUSA/00002181/201801), and added to the product information. (in sections 4.3, 4.4 and 4.8 of the SmPC and in the package leaflet). In the meantime, several publications reported case reports of meningioma regression after nomegestrol discontinuation (1–3) which is very suggestive of an hormonal/progestin role of the drug in the growth of these tumours.
For chlormadinone, in France, we observed, during the period 2015-2019, an increase of case reports in our national pharmacovigilance database. Chlormadinone was the only suspected drug. Moreover, in the literature, cases of regression of meningioma after drug discontinuation have been reported in male patients (prostatic cancer)(4). Pieces of evidence have led to the product information update in France, with the risk of meningioma in 2019 for chlormadinone 5 and 10 mg products. Of note, the German product information for chlormadinone 2 mg mentions that this medicine is contraindicated in case of hormone dependent tumours (e.g., meningioma).

Literature suggests that meningioma associated with chlormadinone and nomegestrol exposure tend to shrink after treatment discontinuation, meaning that surgery (the reference treatment of meningioma) might not be required in that case (1-3).

Issues to be considered

Epidemiological data
To further clarify the relationship between both chlormadinone and nomegestrol and the risk of meningioma, the French Health Insurance (CNAM) has conducted a pharmaco-epidemiological study (observational cohort study) based on SNDS (Système national des données de santé - French National Health Data System) data.

This study was performed on more than 1 million of women who used nomegestrol acetate or chlormadinone acetate between the 1st January 2007 and the 31st December 2017.

This study confirms the increased risk of meningioma in women exposed to these progestins, and shows a significant increase in the risk with the cumulative-dose received and the patient's age. Main results show that:

- the risk of meningioma leading to intracranial surgery increases sharply with age: it is, for example, 3 times higher for women aged 35 to 44 than for those aged 25 to 34;
- women treated for more than 6 months with nomegestrol acetate or chlormadinone, have a three-fold higher risk of meningioma compared to the baseline risk;
- women exposed to a cumulative dose of nomegestrol acetate of more than 6 g have a risk of meningioma increased by a factor of 12;
- women exposed to a cumulative dose of chlormadinone acetate of more than 8,6 g have a risk of meningioma increased by a factor of 7;
- after discontinuation of treatment by nomegestrol acetate or chlormadinone acetate, respectively, for at least one year the risk of meningioma returns to baseline;
- meningioma located in the anterior skull base and middle base seem to be more specific to potent progestins

[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

These results are comparable to those obtained for cyproterone acetate, although the amplitude of risk was lower. However, the population concerned is larger and older. For the most exposed populations, the risk of meningioma associated with chlormadinone acetate was high, but slightly lower than that linked with nomegestrol acetate, and markedly lower than that associated with cyproterone acetate.

Other progestins:

Despite an obvious role of the sex hormones in the occurrence of meningioma, only a small number of epidemiological studies have evaluated the role of endogenous and exogenous sex hormones in the risk of meningioma.

Some authors have investigated whether the use of exogenous sex hormones, such as oral contraceptives and/or hormone replacement therapy (HRT), is associated with an increased risk of meningioma, but these studies have globally not demonstrated any strong and consistent association (5–11). There is no evidence, at the present time, of an excess risk of meningioma in women using oral contraceptives (7,10). More consistent associations have been demonstrated with hormone replacement therapy (HRT), although the increased risk appears to remain limited (6,12–17).

A recent national pharmacovigilance survey retrieved a few case reports of meningioma reported with progestins but for which the causal relationship cannot be firmly addressed (progesterone, desogestrel, medrogestone, drospirenone, dydrogesterone, etonogestrel, levonorgestrel, promegestone, norethisterone, tibolone).

French scientific advisory committee (CST)
Considering these preliminary results, the ANSM has created a temporary specialized scientific committee (CST) which aimed to discuss the conditions of use and prescription of these drugs in order to limit this risk. Patients and HCPs were members of this committee. In December 2020, the CST issued recommendations on the indications which were still considered with a positive benefit/risk ratio. The CST recommended against the use of these medicines to treat menopausal symptoms as well as gynaecological disorders such as menstrual disorders or premenstrual syndrome. Moreover, the CST gave specific imaging recommendations (especially MRI) for women treated for long term.

National measures and referral to the PRAC
In July 2021, considering the recommendations from the CST as well as the substantial off-label use (contraception) 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 further assessment at the European level, has implemented the following risk minimisation measures:

- changes in the product information: requirement for an annual risk acknowledgement form conditioning 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. MRI monitoring requirements during long-term treatment introduced in 4.4. Similar changes were also implemented in the package 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 for the patient on the risk of meningioma;
- a DHPC to prescribers and another DHPC to pharmacists were sent.

In the light of the new safety data derived from two recent epidemiological studies, the risk of meningioma associated with chlormadinone acetate and nomegestrol acetate is now established and dependent from the cumulative dose received. Moreover, the older are the women the higher is the risk. As in some authorized indications (for both substances), women are likely to be treated for several years including menopausal period, we consider that the benefit risk ratio in several indications needs to be revised.

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 CHMP on the basis of a recommendation of the PRAC

Signed [redacted] Date 22 SEP. 2021

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