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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: nomegestrol-containing products and chlormadinone-containing products

Procedure number: EMEA/H/A-31/1510

Zoely EMEA/H/A-31/1510/C/1213/60

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1. Information on the procedure

Meningioma is a rare brain tumour which forms from the meninges. Although most meningiomas are benign tumours, their intracranial location may lead to serious and potentially lethal consequences. Women are approximately twice likely to develop it as men, suggesting a role of sexual hormones in the physiopathology.

The risk of meningioma associated with nomegestrol acetate (NOMAC) use is known since 2018. Indeed, this risk was then discussed during the PSUSA assessment (PSUSA/00002181/201801) covering nomegestrol monotherapy-containing products and added to the product information (PI). In the meantime, some publications reported case reports of meningioma regression after nomegestrol discontinuation suggesting a hormonal/progestin role of the drug in the growth of these tumours. Additionally, the risk was discussed during the PSUSA assessment of nomegestrol in combination with estradiol (PSUSA/00002182/201801) leading to changes to the PI to recommend close monitoring of meningiomas when used as hormone replacement therapy (HRT). The PI of Zoely was amended to reflect this risk.

For chlormadinone acetate (CMA)-containing medicinal products, an increase of case reports of meningiomas was observed in France in 2019 and further risk minimisation measures (RMMs) were implemented at national level, including amendments of the PI of all chlormadinone 5 and 10 mg containing products to reflect the risk of meningioma.

To further clarify the relationship between both chlormadinone acetate or nomegestrol acetate and the risk of meningioma, two pharmacoepidemiological studies have been conducted by the French group, EPI-PHARE (Nguyen et al. 2021), based on data from SNDS (Système national des données de santé - French National Health Data System). Results suggested an increased risk of meningiomas depending on dose and duration of treatment with nomegestrol acetate or chlormadinone acetate.

On 22 September 2021, the French national competent authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) therefore 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 nomegestrol acetate-containing products and chlormadinone acetate-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

Nomegestrol acetate and chlormadinone acetate are both progestin derivatives with anti-gonadotropic effects. Both progestins have additional antiestrogenic but also antiandrogenic activity. Their antiandrogenic activity has been shown to be 30% (CMA) and 90% (NOMAC) compared to cyproterone acetate (CPA) that was set as the reference antiandrogenic progestin with a 100% antiandrogenic activity in castrated, androgen-treated rats (Kuhl 2005).

CMA is the acetate salt form of chlormadinone, a synthetic progestin with anti-androgenic and anti-gonadotropic effects. CMA is authorised as monotherapy and in combination therapy with estrogens.

NOMAC is the acetate salt form of nomegestrol, a 19-norprogesterone derivative with high biological activity at the progesterone receptor, a weak anti-androgenic effect, and no effects on estrogen, glucocorticoid, or mineralocorticoid receptors. Products containing NOMAC are authorised as monotherapy and in combination therapy with estradiol hemihydrate.

Chlormadinone acetate 2 mg, 5 mg and 10 mg tablets

Approved indications for CMA-containing products differ between the different strengths and between the different countries in which these products are authorised. Overall, CMA in monotherapy is approved for g*ynaecological disorders related to progesterone insufficiency and particularly those observed in the premenopausal period (menstrual irregularities, premenstrual syndrome, mastodynia, etc.), functional haemorrhages and fibroid menorrhagia, artificial cycle in combination with an oestrogen* and for CMA 2 mg only - *progestogen challenge test*.

Chlormadinone acetate 1-2 mg in combination with ethinylestradiol 0.03-0.05 mg, tablets and film-coated tablets

In combination, CMA 1-2 mg and ethinylestradiol (EE) 0.03 mg is authorised for *hormonal contraception*. In addition, in two Member states (CZ, SK), this combination is authorised for treatment of *moderate papulopustular acne* i*n women for whom hormonal contraception with CMA/EE acetate is indicated.*

CMA 1-2 mg/EE 0.05 mg combination is indicated for:

- *hormonal contraceptive product (ovulation inhibitor) for women in whom breakthrough bleeding that is not tolerated still occurs after several cycles of taking a combination preparation with 35 µg ethinylestradiol or less.*
- *It is also used in women for the treatment of*
    - *acne*
    - *rapidly greasing hair, often with increased hair loss (seborrhoea oleosa)*
    - *hair loss that is caused by male hormones (androgenic alopecia)*
    - *abnormal facial and body hair growth (hirsutism)*

Nomegestrol acetate 5 mg tablets

NOMAC 5 mg in monotherapy is approved in the following indications:

- In women before menopause, nomegestrol is indicated for menstrual disorders associated with insufficient or no secretion of progesterone, especially in cases of:

- *menstrual cycle disorders: oligomenorrhea, polymenorrhea, spaniomenorrhea, amenorrhea (after etiological assessment)*
- *functional genital haemorrhages: metrorrhagia, menorrhagia, including those following fibroids;*
- *functional symptoms preceding menstruation or occurring during menstruation: dysmenorrhea essential, premenstrual syndrome, cyclic mastodynia.*

- Endometrial hyperplasia (PT only)

- In postmenopausal women: as replacement therapy, in combination with an estrogen.

NOMAC was also available in dosage 3.75 mg in France, however marketing was discontinued in December 2021.

Nomegestrol acetate 2.5 mg/ estradiol hemihydrate 1.5 mg film-coated tablets (Zoely)

NOMAC 2.5 mg in combination with estradiol is approved via centralised procedure for o*ral contraception.*

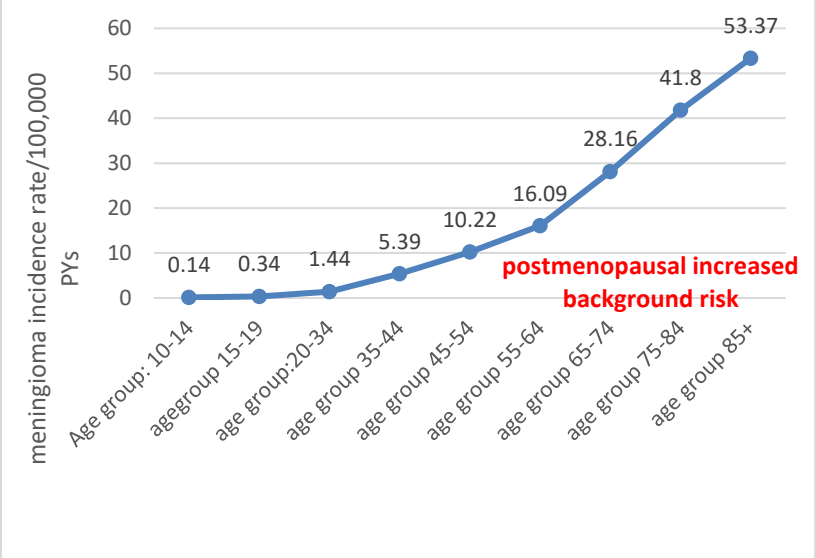
Nomegestrol acetate 3.75 mg/ estradiol hemihydrate 1.5 mg tablets (Naemis)

NOMAC 3.75 mg in combination with estradiol is approved as *Hormone Replacement Therapy* (HRT) *for oestrogen deficiency symptoms in women at least 6 months since last menses.*

2.1.1. Meningioma

Meningioma is the most common primary tumour of the central nervous system (CNS) comprising 36% of all tumours and 53% of non-malignant primary CNS tumours in the United States of America (USA). The risk of meningioma sharply increases with an average annual age-specific incidence rate of 1.44/100,000 persons between 20-34 years of age to 41.8/100,000 persons between the age of 75-84 (see figure below) and are 2.3 times more common in females compared to males. Interestingly, the incidence of meningioma is significantly higher (p-values < 0.0001) in women of African origin compared to Caucasian women, however, the underlying reason remains unknown (Ostrom et al. 2016).

Figure 1 - Average annual age-adjusted incidence rates for meningioma (based on data from Ostrom et al. 2016)



According to the current World Health Organisation (WHO) classification system of tumours of the CNS (5th edition) 2021, meningioma is primarily subdivided into 3 grades (I-III) depending on histological and cytological criteria. Overall, benign meningioma grade I that are usually slow-growing and non-metastatic, represent around 80% of all meningioma, while grade II atypical meningioma occur in around 15-20% and grade III anaplastic meningioma are described in 1-3% of all meningioma cases. Meningioma derives from the meninges and can occur as spinal (12%) or intracranial tumours (around 88%).

According to the recently updated European Association of Neurooncology (EANO) Guideline (Goldbrunner et al. 2021), incidentally detected meningioma without symptoms or in older patients or both, should be managed with a "watch and scan" strategy, while in case of a necessary treatment, surgery is the first choice. In case of rapid meningioma growths, a resection according to Simpson grade I should be achieved accompanied by a follow-up interval of 6 months to 5 years and annually thereafter. For a Simpson grade IV-V resection radiotherapy should be conducted. For WHO grade II tumours, the EANO Guideline recommends a radical surgery followed by fractioned radiotherapy due to the high risk of recurrence and systemic metastasis. Pharmacological treatment is not established for these kinds of tumours. According to Hollaczek and colleagues (2019), the 5-year survival rate was

86.7% in patients ≥75 years of age and 98.5% in those aged ≤54 years strongly depending on the meningioma grade. According to Ostrom and colleagues (2016), the 10-year survival rate is 77.7% for younger patients (20-44 years) decreasing with increased age.

Genetic and other risk factors:

According to the recent WHO classification of tumours of the central nervous system 2021, several genes/molecular patterns are known to be altered in case of meningioma: NF2, AKT1, TRAF7, SMO, PIK3CA; KLF4, SMARCE1, BAP1 in subtypes; H3K27me3; TERT promoter, CDKN2A/B in CNS WHO grade 3. The most prominent one is the existence of neurofibromatosis type 2 (NF), a hereditary condition that increases the risk of meningioma. Approximately one-half of patients with NF2 show meningioma occurrence and multiple meningioma are common (Goutagny et al. 2010). External risk factors such as ionizing radiation especially those of the head and neck have been described (Buerki et al. 2018; Wiemels et al. 2010; Umansky et al. 2008). Some less well-established risk factors are still under discussion such as obesity, head trauma in the past and cell phone use among others, thus a certain level of background risk in the general population is possible.

Hormonal influence and receptor expression:

Hormonal factors are intensively discussed as risk factors for the occurrence of meningioma due to the higher prevalence in women compared to men. High levels of progesterone receptor expression and lower levels of androgen or estrogen receptors have been detected by several authors especially for WHO grade I meningioma (e.g. Korhonen et al. 2010; Hsu et al. 1997). Additionally, in-vitro studies have shown a growth-promoting effect of progestins on meningioma tissue but the progesterone-antagonist mifepristone failed in demonstrating a growth inhibition (Yongli et al. 2015). One recently published study by Peyre et al. (2018) detected more multiple meningioma in women treated for a long time (mean 15 years) with progestins compared with a meningioma control group (48% vs. 5%, $p < 10^{-12}$), and also more often located at the skull base (64% vs. 50%, p= 0.03). The authors proposed a shift in mutational landscape due to a higher frequency of PIK3CA mutations ($p < 10^{-8}$) and TRAF7 mutations ($p < 0.001$) following progestin-treatment compared with the control population of meningioma. Further on, PIK3CA-mutant and progestin-induced meningiomas were associated with younger age in the whole population (51 years versus 57 years, p= 0.015 and 48 years versus 58 years, $p < 5 \times 10^{-5}$). It is of interest that the skull base is a preferred location for meningioma growth after progestin-treatment and the expression of progesterone receptors in the skull base arachnoid tissue is higher than in other tissues. However, with regard to the limitations of the study by Peyre et al. (2018), e.g. the low patient number and retrospective design, the role of progestins in tumorigenesis of meningioma remains unknown.

2.2. Risk of meningioma in association with CMA or NOMAC use

No cases of meningioma could be identified in clinical trials performed with CMA or NOMAC-containing medicinal products. The absence of meningioma cases might be understood in light of the rarity of the event, the size and duration of the clinical trials and the fact that meningiomas are normally very slowly growing.

As part of this review, the PRAC considered all available data in relation to the risk of meningiomas with CMA or NOMAC-containing products, including pharmacoepidemiological data, data from spontaneous reporting and from the literature. A summary of the most relevant information is included below.

2.2.1. Pharmacoepidemiological studies by EPI-PHARE group (Nguyen et al. 2021)

To further clarify the relationship between both chlormadinone acetate or nomegestrol acetate and the risk of meningioma, two pharmacoepidemiological studies have been conducted by the French Health Insurance (CNAM)- EPI-PHARE group (Nguyen et al. 2021), based on data from SNDS (Système national des données de santé - French National Health Data System). The primary objective of the two retrospective cohort studies was to evaluate the real-life impact of:

(i) Prolonged use of CMA and risk of intracranial meningioma in women;

or

(ii) Prolonged use of NOMAC and risk of intracranial meningioma in women.

In addition, the studies pursued the following secondary study objectives:

- to evaluate the dose-effect relationship,
- to define the course of the risk of meningioma after discontinuation of CMA/NOMAC,
- to identify the specific characteristics of meningiomas associated with CMA/NOMAC,
- to measure the effective CMA/NOMAC discontinuation rate after meningioma treatment, and
- to estimate the number of meningiomas treated by surgery or radiotherapy attributable to the use of CMA/NOMAC in France between 2007 and 2018.

The event of interest was neurosurgical resection, decompression or radiotherapy for one or more intracranial meningiomas.

To estimate the association between prolonged intake of CMA or NOMAC and the risk of intracranial meningioma, both studies used administrative health data from the SNDS linked with hospitalisation data from the PMSI (programme de médicalisation des systèmes d'information). The identified source populations are representative for the female French population aged between 10 and 70 years who started treatment with (i) CMA or (ii) NOMAC between 2006 until 31st December 2018, as the SNDS covers around 99% of the French population – which in itself represents one of the largest population in the European Union.

Both cohort studies compared the group of "exposed" women with a group of "very slightly exposed" women (control group):

i. For CMA, women were considered to be "exposed" if they had received a cumulative dose greater than 360 mg during the first six months following initial exposure. The control group was dispensed a maximum cumulative dose of 360 mg CMA or less (i.e. equal to three or fewer standard packs of twelve 10 mg tablets during the first six months of exposure). 828,499 patients were included in the main study, including 469,976 (56.7%) in the "exposed" group and 358,523 (43.3%) in the control group.

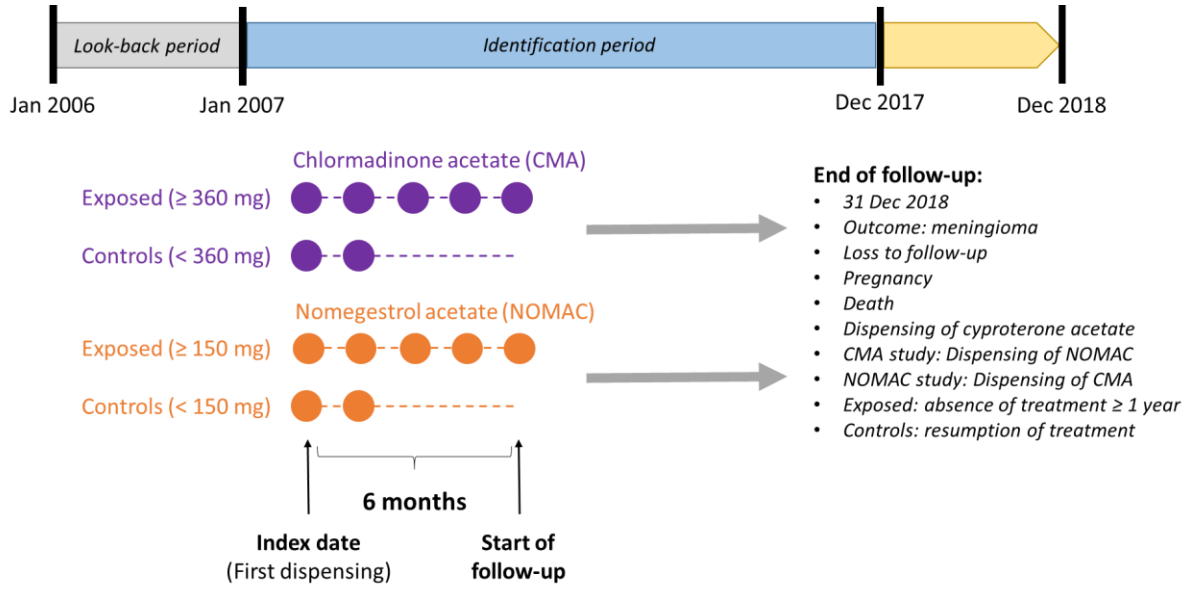
ii. For NOMAC, women were considered to be "exposed" if they had received a cumulative dose greater than 150 mg during the first six months of exposure. The comparator group consisted of "very slightly exposed" women in whom the cumulative exposure reached a maximum of 150 milligrams NOMAC or less (i.e. equal to a maximum of three standard packs of ten 5 mg tablets during the first six months of exposure). 1,060,779 patients were included in the main cohort including 535,115 (50.4%) in the "exposed" group and 525,664 (49.6%) in the control group.

Consequently, the control groups consisted of women who discontinued treatment fairly soon or, in the case of CMA, received low-dose therapies. Women in the control group taking low doses of CMA were excluded from the study if they continued the treatment after the first six months. Therefore, the control group only retained women who had actually discontinued treatment.

Women with previous hospital diagnoses of neurofibromatosis type 2 and/or known history of meningioma with any hospital diagnosis prior start of follow-up (starting 6 months after the first dispensing) were excluded in both studies. Previous exposure to certain progestins was considered as an additional exclusion criterion. In the SNDS study on CMA, further exclusion criteria were any dispensing of cyproterone acetate or nomegestrol acetate prior start of follow-up, whereas the SNDS study on NOMAC additionally excluded women exposed to cyproterone acetate or chlormadinone acetate.

The study design of both studies is shortly outlined in the figure below (see Figure 2).

Figure 2: Schematic representation of the study design (modified from the cyproterone acetate referral, procedure EMEA/H/A-31/1488)



Analysis and Results

The primary analysis features a Cox proportional hazard model to compare the incidence of (surgically or radiologically treated) meningioma in the "exposed" cohort with the "slightly exposed" control group. Results were adjusted for age, which was treated as a time-dependent variable. Age was closely linked with the risk of meningioma, whereas other potential confounders - such as co-prescription of estrogens – showed no association and were therefore not included in the model. Besides age, cumulative dose was also considered as a time-dependent variable and stratified analyses were conducted to check the impact of dose-dependent effects.

With regard to CMA-treatment, Nguyen and colleagues found that prolonged exposure to chlormadinone acetate was associated with a risk increase for intracranial meningioma (aHR 4.4, 95% CI: 3.4-5.8). Reporting by strata of cumulative dose point to a positive dose-effect relationship, as the risk for intracranial meningioma increased with higher cumulative CMA dose, see Table 1 below.

Table 2: Incidence, relative risk and adjusted hazard ratio of meningioma according to exposure to chlormadinone acetate

	PY	Cases	Incidence per 100,000 PY	RR [95%CI]	HRa [95%CI] (a)
Slightly exp. (≤0.36 g)	1,535,775	104	6.8	Ref.	Ref.
Exposed (> 0.36 g)	888,305	164	18.5	2.7 [2.1-3.5]	4.4 [3.4-5.8]
Cumulative dose					
]0.36 g; 1.44 g [	259,034	13	5.0	0.7 [0.4-1.3]	1.1 [0.6-2.2]
[1.44 g; 2.88 g [	168,109	19	11.3	1.7 [1-2.7]	2.6 [1.4-4.7]
[2.88 g; 5.76 g [	177,799	22	12.4	1.8 [1.2-2.9]	2.5 [1.5-4.2]
[5.76 g; 8.64 g [	100,432	24	23.9	3.5 [2.3-5.5]	3.8 [2.3-6.2]
8.64 g and higher	182,931	86	47.0	6.9 [5.2-9.2]	6.6 [4.8-9.2]

[a] Adjustment for age; cumulative dose and age considered as time-dependent variables

With regard to NOMAC-treatment, Nguyen and colleagues observed that prolonged exposure to nomegestrol acetate was also associated with a risk increase for intracranial meningioma (aHR 4.5, 95% CI: 3.5-5.7) – a strong dose-dependent association was observed in addition. Stratified analyses showed that the risk for intracranial meningioma increased with higher cumulative NOMAC dose; the increased risk was over 12-fold beyond cumulative exposure of 6 grams (see Table 2 below).

Table 3: Incidence, relative risk and adjusted hazard ratio of meningioma according to exposure to nomegestrol acetate

	PY	Cases	Incidence per 100,000 PY	RR [95%CI]	HRa [95%CI] (a)
Control group. (≤0.15 g)	2,418,616	169	7.0	reference	reference
Exposed (> 0.15 g)	884,716	171	19.3	2.8 [2.2-3.4]	4.5 [3.5-5.7]
Cumulative dose					
]0.15 g; 0.6 g [	330,660	21	6.4	0.9 [0.6-1.4]	1.1 [0.6-1.8]
[0.6 g; 1.2 g [	158,642	17	10.7	1.5 [0.9-2.5]	1.7 [0.9-2.9]
[1.2 g; 3.6 g [	234,002	41	17.5	2.5 [1.8-3.5]	2.6 [1.8-3.8]
[3.6 g; 6 g [	87,064	24	27.6	3.9 [2.6-6.1]	4.2 [2.7-6.6]
6 g and higher	74,349	68	91.5	13.1 [9.9-17.4]	12.0 [8.8-16.5]

a Adjustment for age; cumulative dose and age considered as time-dependent variables

Conducted complementary analyses of prevalent users, already exposed in 2006, showed even higher risk estimates. For the CMA prevalent cohort, the authors attributed 44.9 cases/100,000 person-years, which corresponds to an age-adjusted HR of 9.9 (95% CI: 6.8-14.4). In comparison, for the NOMAC prevalent cohort, the authors attributed 73.7 cases/100,000 person-years, which corresponds to a HR of 13.0 (95% CI: 10.1-16.7). Consistent with the results of the primary analysis, a strong dose-dependent association was also observed among prevalent users.

Treatment discontinuation of CMA or NOMAC was associated with a risk reduction for intracranial meningioma in both, incident and prevalent users. For incident users, the risk of meningioma in the group who discontinued use of CMA for at least one year, without resuming treatment, decreased to an adjusted hazard ratio of 1.4 (95% CI: 1.1-1.7), whereas the risk of meningioma after discontinuing exposure to NOMAC was no longer greater than the risk of the control group (aHR: 1.0, 95% CI: 0.8-1.3). Data from stratified analyses showed that the magnitude of the risk reduction was dependent on the dose taken before discontinuation - the higher the cumulative dose, the lower the risk reduction. This observation was in line with the results from the prevalent users – expected to be exposed on average with a higher dose than incident users. In prevalent users, adjusted hazard ratios of 1.8 (95% CI: 1.3-2.7) and 1.5 (95% CI: 1.1-1.9) were observed for former users of CMA or NOMAC, respectively.

To identify a possible pattern of common sites for meningiomas, the authors focused on different anatomical sites in the skull. The absolute and relative risks of meningioma in the various anatomical regions of the brain differed considerably according to the type and level of exposure. No clear similar risk pattern could be observed when comparing risk estimates of CMA or NOMAC. However, the internal third of the middle skull base affecting the spheno-orbital region seemed to be particularly affected by both compounds – CMA and NOMAC – with a 7.5- and 12.5-fold excess risk, respectively. Further analyses conducted by the study authors have shown that the use of antiepileptic drugs, known to be associated with further risks such as teratogenicity, in the second year following the initial hospitalisation was significantly higher in the CMA exposed group compared with the control group (43.5% vs 26.4%). Comparable results have been detected for NOMAC: antiepileptic drug treatment continued for more than one year after surgery for more than 38.3% of patients exposed to NOMAC compared with 24.3 % in the control group.

While the estimated background incidence of symptomatic meningioma is only 7/100,000 person-years, the observed meningioma risk is rather high. Consequently, the number of symptomatic meningiomas attributable to CMA exposure has been estimated to average 34 cases per year and 60 cases for NOMAC in France. A major concern was the observation that 39.6 and 45.9% resumed CMA and NOMAC intake during the year following neurosurgery or radiotherapy, respectively.

Some study limitations such as lack of stratified analyses by indication and treatment duration; observed study time; potential influence of detection bias by more extensive monitoring; potential risk factors acting as potential confounding variables; and missing information on non-reimbursed medicinal products were raised in the context of this referral procedure. While the limitations were acknowledged and assessed, these were considered not to have an impact on the level and magnitude of the risk observed as described above.

2.2.2. Literature review

A literature review of the risk of meningioma in relation to progestins use, conducted by the MAHs, identified several recent publications, the most relevant of which are summarised below:

Graillon et al. 2021: this publication describes meningiomas in 53 patients who used progestins, mostly CPA, NOMAC or CMA at high doses with a mean duration of 17.5 years. Dechallenge was mostly positive, with differences between these three progestins. For low dose progestins no meningioma was reported. Overall, higher progestin dosage, longer duration of therapy and additional pharmacodynamics effects of different progestins (anti-androgenic effects) are considered risk factors.

Malaize et al. 2021: the study retrospectively included 71 adult women who had at least one meningioma in the context of progestin intake. Data was collected from 1995 to 2018 and 125

progestin-associated meningiomas were found. CPA was administered in 47 cases (66.2%), CMA in 14 cases (19.7%), NOMAC in 7 cases (9.9%), and a combination of progestin treatments in 3 cases (4.2%). In this study, progestin treatment was an approved indication only in 27.0%. After meningioma was diagnosed in patients, the management of progestin treatment was known for 68 patients (95.8%). Progestin was withdrawn in 80.9%. Furthermore, progestin treatment discontinuation has grown over time with promising results in terms of efficacy and safety. Magnetic Resonance Imaging (MRI) follow-up demonstrated a regression in 29.6%, a stability in 68.5% and an ongoing growth in 1.9% of cases.

Apra et al. 2020: this publication concerns Spheno-Orbital Osteomeningiomas (SOOM). The patients were treated with different progestins with a median duration of 10 years. An association with progestin receptor expression is suggested. It should be noted that in this study, the dose of CMA was 5-10 mg and the dose of NOMAC was 5 mg as mono-components. An association with meningioma with lower dosage of these progestins cannot be derived from this study.

A retrospective study by **Devalckeneer et al. (2021)** included 69 patients treated with CPA and NOMAC (mean exposure 16 years) and CMA (ca. 10 years). Progestins were used at high dosages in all cases (CPA >50 mg, NOMAC 5 mg, CMA 5-10 mg daily). CPA at high dose was associated with meningioma. The authors conclude that a relationship between meningiomas and CMA or NOMAC remains unclear. Nevertheless, the authors recommend the following steps for the prescription of CMA and NOMAC (presumably in relation to dosages used in this study):

- Obtain reference MRI before starting the treatment then 5 years after its start if patient remains asymptomatic. Obtain MRI if any symptoms appear; after this cut-off of 5 years and in absence of meningioma diagnosis, systematic MRI every 2 years.
- If medical achievable, choose non continuous and counterbalanced regimens over continuous progestin alone treatment.

Two other publications (**Wiemels et al. 2010 and Ogasawara et al. 2021**) describe the epidemiology of meningiomas, but do not concern progestins as associated drugs.

AbiJaoude et al. 2021: this publication reports sustained growth of intraosseous hormone-associated meningiomas after cessation of progestin therapy. In one report a 51-year-old woman developed plaques meningiomas during treatment with nomegestrol for metrorrhagia. TTO was 30 years, and after discontinuation and surgical removal there was a recurrence of the tumour. In the second report a 57-year-old woman developed plaques meningiomas during treatment with NOMAC. The woman, who had endometriosis, had been receiving NOMAC for 15 years. The second case remains inconclusive. After discontinuation of NOMAC only a small tumour regression was observed after many years.

Salle L, Salle H. 2020: this publication describes a 48-year-old woman, who developed meningioma of the skull base while receiving contraception with NOMAC. The information is limited for a causality assessment, although a causal relationship remains possible.

Passeri et al. 2019: this publication describes spontaneous regression of meningiomas after interruption of NOMAC. Patients were diagnosed with meningioma at different time intervals or prolonged use of NOMAC or having switched from another prolonged use drug to NOMAC which aggravate the disease. The event was resolved/resolving after interruption of NOMAC. The three cases described by the authors have limited information on patient's anamnesis, concomitant disease and medication, however, a causal association due to long-term treatment with NOMAC cannot be excluded in these cases.

Champagne et al. 2019: this publication describes the progression (but not the emergence) of the tumour related to NOMAC, with positive dechallenge. According to WHO criteria, the causality with the progression of the tumour is probable.

Shimizu et al. 2008: this publication describes spontaneous regression of an asymptomatic meningioma associated with discontinuation of progesterone agonist administration. The article describes a 80-year-old male who was diagnosed with meningioma after long-term treatment with CMA for benign prostatic hypertrophy. The therapy was continued further 9 months with no symptoms or progression. Thereafter, CMA was withdrawn and after 2 years, the tumour revealed remarkable regression (positive dechallange). The causality is probable.

Peyre et al. 2018: the authors describe the vulnerability of certain meningeal cells and mutations to hormone-induced tumorigenesis. However, a specific causality assessment for CMA or NOMAC is not possible since only one (of 40) woman with previous CMA-treatment was retrospectively involved.

Telugu et al. 2020: this publication describes estrogen and progesterone receptor in meningiomas (immunohistochemical analysis). The authors found no statistically significant relationship between the positivity of progesterone receptor in gender, location, tumour grade, and various histological subtypes.

Another French population-based case control study was recently published to assess the risk of intracranial meningioma with three potent progestogens (CPA ≥25 mg/day, NOMAC 3.75-5 mg/day and CMA 2-10 mg/day) using health insurance data from the SNDS **(Hoisnard et al. 2022)**. In this study, the authors analysed cases that underwent surgery for intracranial meningioma in France from 2009 to 2018. Cases were matched to five control subjects for sex, year of birth and area of residence. Progestogen exposure was defined as progestogen use within the year before surgery for cases or the same date for their controls. In total, 25,216 cases were included (75% women, median age 58 years). Progestogen exposure was noted for 9.9% of cases (2497/25,216) and 1.9% (2382/126,080) of controls, with an odds ratio (OR) of 6.7 (95% CI 6.3–7.1). The risk increased from CMA (OR 3.3, 95% CI 3.3-3.6) to NOMAC (OR 4.7, 95% CI 4.3-5.1) to CPA (OR 18.3, 95% CI 16.0-21.1).

2.2.3. Other post-marketing safety data

2.2.3.1. Data submitted by the marketing authorisation holders of CMA and NOMAC

Chlormadinone acetate:

The MAHs with MAs containing CMA identified case reports from post-marketing sources (literature articles and spontaneous reports from HCPs (healthcare professionals) and consumers) and presented evaluations of their causal association.

For low dose CMA (2 mg) monotherapy only a few case reports have been retrieved by the respective MAH and most of them are confounded by CPA treatment in the patient's history. However, a medically confirmed case from DE describes the occurrence of meningioma during hormone replacement therapy (HRT) with the addition of chlormadinone acetate in a 52-year old female patient who received CMA (2 mg) for HRT (dose, frequency and treatment duration not reported). Patient's medical history included long time HRT. Further information is lacking but a causal association cannot be excluded.

For combination products with low-dose CMA/EE in the contraception indication, the MAHs did not identify any case report.

The majority of post marketing cases were provided for the originator product. In total, 5 970 cases reporting 10 680 adverse drug reactions were retrieved with the originator product for CMA in

combination with EE, however no case reported occurrence of meningioma. Furthermore, all MAHs with the combination product CMA/EE agreed that no safety information on the risk of meningioma was found for the combination product.

For high-dose CMA therapy (5 mg and 10 mg) Sanofi identified 316 cases in the global MAH's database as shown in Table 3.

Table 3 Number of meningioma cases with chlormadinone per age group, indication and dosing (modified from the figures provided by the MAH Sanofi)

Age group (years)	**Number of cases**
18-30	2
30-40	38
40-50	**162**
50-60	79
60-65	8
>65	13
Missing	13
Indication	**Number of cases**
Contraception (off-label)	**82**
Endometriosis	59
Menopause/HRT	13
Uterine fibroid/leiomyoma	10
Heavy menstrual bleeding	10
Intermenstrual bleeding	9
Dysmenorrhoea	8
Other (including ovarian cyst, breast pain etc.)	82
Missing	52
Daily Dose	**Number of cases**
5 mg	8
10 mg	**100**
25 mg	1
5-10 mg	4
5-25 mg	1
Missing	201

As outlined in the table 3 above, most cases describe CMA-use for contraception (off-label) and the treatment of endometriosis. Most cases belong to women between 40-50 years of age. 273 case reports have a compatible chronology with a time to onset between 10-15 years and a treatment duration of (in most cases 10 mg CMA) between 5-10 years followed by 10-15 years. All the cases were unsolicited with the majority (>92%) reported by health authority. The MAH retrieved 23 cases with a positive dechallenge and 91 cases with a negative dechallenge, while in other case reports, dechallenge is unknown. The outcome was flagged as "recovering/recovered" in 47 cases, recovered with sequelae in 37 cases and not recovered in 207 cases. None of the cases reported fatal outcome. The fact that most case reports are highlighted as "not recovered" at the time of the report, is in line with the data identified within the EVDAS-search on CMA-containing medicinal products. In the majority of cases (52%), information on risk factors was not provided. When provided, reported risk factors included history of radiation therapy and meningioma, drugs like nomegestrol, progesterone and desogestrel, BMI of >25, and breast cancer.

The MAH Viatris further identified 20 case reports mentioning meningioma with CMA-containing medicinal products. Out of them, 1 case shows a positive dechallenge and 4 cases describe a negative dechallenge. The outcomes of the cases were reported as recovered/recovered with sequelae/recovering in 4 cases and not recovered/unknown in 16 cases. Of the reported 20 cases, chlormadinone was suspect in 10 cases mainly based on the long-term use of the drug for several years. In the remaining 10 cases chlormadinone was reported as suspect along with other co-suspect drugs or confounded by patients' medical history. Unfortunately, the cases have very limited information and are confounded precluding a thorough assessment.

Nomegestrol acetate:

For Lutenyl (in the strengths 3.75 mg and 5 mg NOMAC-monotherapy), the MAH retrieved 441 cases of meningioma from Eudravigilance. Of them, 205 were classified by the MAH as possibly related, 85 as unlikely related and 151 as unassessable according to WHO-UMC causality assessment scale. Almost all case reports (around 98%) were reported from France with a sharp increase starting in 2018 following a PI update and ANSM communication as a consequence of the observed increase of case reports of meningiomas. The mean duration of Lutenyl use before meningioma diagnosis was 12.2 years (minimum 1 year and maximum 35 years) but was only available in around 12% of the cases retrieved by the MAH. This is in accordance with the EVDAS-search discussed in section 2.2.3.2 below.

Table 4: Number of meningioma cases with Lutenyl per age group, indication and dosing (modified from the figure provided by MAH Theramex Ireland)

Age group (years)	**Number of cases**
20-29	1
30-39	34
40-49	**153**
50-59	**152**
60-69	30
70-79	15
80-89	1
Missing	55
Indication	**Number of cases**
Contraception (off-label)	**88**
Endometriosis (off-label)	70
Uterine fibroid/myoma	24
Menopause/HRT	20
Menorrhagia	18
Fibroadenoma (off-label)	15
Metrorrhagia	15
Other (including ovarian cyst, mastodynia,	90
Missing	110
Dose	**Number of cases**
2.5 mg	2
3.75 mg	20
5 mg	**93**
7.5-11.25 mg	5
78.75 mg-100 mg	4
1 DF (dosage form)	50
Other (including 13 DF, 20 DF, 21 DF and	84

Missing	183

As shown in table 4 above, most cases belong to women between 40-59 years of age for the indication contraception (in-label only for the lower dose combination with estradiol) and endometriosis (not approved indication for NOMAC). However, there could be a bias towards an older age due to delayed or stimulated reporting. This theory is supported by the fact that over half of the case reports (57%) have a timeline of more than 6 months between the adverse event onset date versus the case receipt date of the initial report. Only in approximately one third (28%) of cases, less than 6 months have passed between the adverse event onset date and the case receipt date. In the remaining cases (15%), the adverse event onset date is unknown. Most cases lack further helpful information on the cumulative dose, patient's anamnesis and concomitant exposures with other progestins. 6 case reports have been identified mentioning a positive dechallenge. In addition, three cases describing a negative dechallenge have also been retrieved. In all other cases the de- and rechallenge was unknown. In those cases that reported the patient's outcome, it was highlighted as "not recovered or recovered with sequelae" at the time of the reporting but there are also reports mentioning "recovering". No fatal outcome was reported.

One case, presented by MAH Sandoz, refers to a 37-year-old female patient with medical history of memory loss, headache and asthenia, who received nomegestrol acetate for birth control at a dose of 5 mg, once daily, for the duration of 20 years. The patient experienced amnesia, meningioma (meningioma of left greater sphenoid wing and right sphenoid ridge) associated with long-term use of nomegestrol acetate (serious) headache, asthenia, partial seizures and peri-tumoral edema. On an unknown date, one month after the cessation of nomegestrol acetate, MRI showed a significant volume decrease of the left sphenoidal meningioma (40.7 cm3) as well as peri-tumoral edema, a left sided large (54.5 cm3) paraclinoidal meningioma spanning the left greater sphenoid wing surrounded by edema. A smaller meningioma (1.8 cm3) located on the contralateral sphenoid wing was also detected. One year after the cessation of nomegestrol acetate, an additional tumour volume reduction was observed for both meningiomas with a volume reduction of 76% (13.1 cm3) of the largest meningioma. On an unknown date, action taken with nomegestrol acetate was temporarily withdrawn and the patient fully recovered from meningioma.

There was also very little information on the type of meningioma detected, not allowing for a more specific characterisation of the cases. Furthermore, there is a high chance that risk factors are under-reported or not reported at all since information on additional meningioma risk factors such as radiation exposure, ethnicity or genetic disorders was lacking from the identified meningioma cases.

Several cases reported the use of NOMAC and CPA- or CMA-containing products in varying chronological sequences and durations. The use of NOMAC alongside CPA was reported in 6.4% of cases, the use of NOMAC alongside CMA in 13.4% of cases and the use of NOMAC alongside CPA or CMA or both in 17.7% of cases. Such use of several different progestins/hormonal preparations, which is highly likely during a woman's life makes the establishment of an exposure-response relationship difficult.

For combination products with lower-dose NOMAC/E2 in the indication HRT and hormonal contraception, three case reports were retrieved by the MAH, however in one of these cases a higher dose of NOMAC had been used (i.e. 5 mg/day) for contraception:

1) 50-year-old female patient who received Zoely for contraception for ca. 10 years. Three months after cessation, patient was diagnosed with meningioma. The outcome of the event was reported as recovered with sequelae.

2) 45-year old women who received Zoely for "non-contraceptive" reasons since 09/2016. Concomitant therapies included lorazepam, escitalopram, ketazolam, omeprazole, imidapril hydrochloride, probucol, dipyrone and vitamins (B12 B6 B1). In 11/2017 the patient was diagnosed with meningioma grade 1. Treatment with Zoely was discontinued and the patient hospitalised for radiotherapy in 02/2018. The subject received 33 sessions of radiotherapy, no surgery was performed and no chemotherapy done. The subject reported that tumour has maintained its size with radiotherapy treatment. She was also treated with dexamethasone.

3) Case showing a tumour progression after NOMAC-use. The patient remained symptom-free over a 10 months observation period. However, no combination is mentioned and the case is confounded by CPA-treatment in the past.

2.2.3.2. EudraVigilance analysis

EMA performed an analysis of EudraVigilance (EV) data on cases of meningioma reported with chlormadinone- or nomegestrol-containing medicinal products with the data lock point 15/11/2021. Altogether, 359 case reports with CMA (8.8% out of 4098 cases) and 461 case reports for NOMAC (13.6% out of 3388 case reports) have been retrieved, almost all in females and most of them aged between 40 to 60 years. The case reports describing meningioma mainly derived from France with a sharp increase in 2019 potentially due to the high media coverage in this country. This is in contrast to non-meningioma cases showing a more diverse geographical distribution.

Most cases contained single components and only a few case reports for combination products such as Zoely have been reported. The main indication was, however, (oral) contraception and endometriosis. This is of interest since neither CMA nor NOMAC are approved for hormonal contraception as a single component (in contrast to other progestin-only pills).

Further on, it is noted that about 60 case reports contain treatment information on both progestins under discussion (i.e. CMA or NOMAC); thus HCPs may switch to the other progestin in case of unsatisfaction with the first one. The same is noted for cyproterone acetate, which is the second-most frequently co-reported progestin in the case reports retrieved and known to be associated with an increased risk of meningioma. This needs to be considered for any changes of the product information and treatment warnings further discussed in this AR.

The mean time-to-onset was 12-15 years explicitly for the detection of meningioma, which underlines that most of them are asymptomatic over a long time-period or the unspecific and individual symptoms of a meningioma cannot in all cases be associated with a meningioma by HCPs and patients. However, the outcome in most of these cases is highlighted as not recovered or recovered with sequelae, which is of concern and needs to be further elucidated with regard to the data from spontaneous reporting and literature articles. None of the cases reported a fatal outcome.

2.2.4. Discussion

From the review of post marketing cases provided by the MAHs (spontaneous reporting and literature) it was noted that:

- In the majority of cases, meningioma was described after high daily doses of CMA 5 mg-10 mg (316 cases) and NOMAC 3.75-5 mg (441 cases, of which 205 classified as possibly related) with long time-intervals of 5 years and longer. This is in line with the EVDAS-search conducted by EMA. Most cases belong to women between 40-59 years of age for the indications contraception (off-label use except for the combination with estradiol) and endometriosis (not approved indication for NOMAC). A long-term therapy is therefore considered a risk factor for meningioma and high cumulative doses will be

reached. Meningioma in the past and radiation therapy were also mentioned as risk factors in the case retrieved by the innovator MAH.

- No case reports showed a causal association between CMA and a shorter treatment duration or low dose CMA-monotherapy.

- For CMA in combination with ethinylestradiol, no case reports clearly showing a possible causal association with meningioma was identified.

- For NOMAC-combination therapy, only three cases have been detected (one without explicitly mentioning a combination) including two showing an at least possible causal association with meningioma have been detected. The role of estrogen receptors on meningioma tissue is currently unknown.

The results obtained from both studies by Nguyen at al. reliably showed an increased risk for intracranial meningioma after exposure to either CMA or NOMAC – especially in case of high cumulative doses or longer exposure duration. Overall, the extent of risk increase was similar between incident users of CMA and incident users of NOMAC (CMA aHR: 4.4, 95% CI: 3.4-5.8 vs. NOMAC aHR: 4.5, 95% CI: 3.5-5.7). The strength of association, the strong dose-dependent effects and the risk reduction observed after treatment discontinuation of at least one year support the association between CMA/NOMAC exposure and increased risk of meningiomas.

Low-dose CMA (1-2 mg)- or low-dose NOMAC (2.5 mg)-containing products were not covered by the SNDS-database and were therefore not included in the analysis provided by the study authors. Nevertheless, Nguyen et al. detected a statistically increased relative risk of 1.7 (95% CI: 1-2.7) starting from a cumulative CMA dose of 1.44 g, and 2.5 (95% CI: 1.8-3.5) with a cumulative NOMAC dose of 1.2 g, further increasing with higher doses. By taking the posology for the different indications into account, the cumulative CMA or NOMAC-dose can be referred to a specific time-interval after that the cumulative dose will be reached approximately. Examples of indications with a slightly different dosing regimen were chosen to calculate time-intervals to reach the cumulative dosing "thresholds" from Nguyen et al. 2021, demonstrating that a cumulative dose of 1.44 g or 1.2 g will be reached after plausible timeframes for the underlying indications. Depending on the indication, a statistically increased risk of meningioma is reached after only 5 menstrual cycles or months (in the indication endometriosis) to 11 months (in the indication HRT) with high-dose CMA-monotherapy. A statistically significant increase was detected after several (18) months in the treatment of HRT (with 5 mg/d) and after 24 months in the premenopausal setting e.g. for menstrual disorders with NOMAC-containing products. A potential risk of meningioma was maybe apparent with low-dose CMA or NOMAC-containing products. For example, for low-dose CMA-monotherapy, a cumulative dose of 1.44 g will be reached after around 60 cycles (i.e. 5 years) in the treatment of HRT and after around 36 cycles (3 years) if used for mastodynia. For low dose NOMAC-combination products, a cumulative dose of 1.2 g is reached after 20 menstrual cycles in the indication contraception. Nevertheless there is clearly a lower risk of meningioma associated with lower dose products and a causal association with low-dose products has not been established, yet, which warrants a differentiated wording in the PI.

Further on, a decrease risk after discontinuation has been recognised by the study authors; thus further information for HCPs and patients need to be included in the product information (PI) to help mitigating this risk.

Some of the articles provided by the MAHs show new case reports with an at least possible or probable causal association showing meningioma occurrence after long-term use and higher daily dosages with CMA or NOMAC-treatment (e.g. Graillon et al. 2021; Apra et al. 2020; Passeri et al. 2019; Champagne et al. 2019).

Additionally, the observed results on the recently published case control study by Hoisnard and colleagues (2022) using data from the SNDS are consistent with the findings from Nguyen and colleagues (2021) and previous findings from cohort studies assessed in the context of the Article 31 referral procedure on cyproterone acetate (procedure EMEA/H/A-31/1488). Compared to the overall risk of current users, only low risk estimates were observed by Hoisnard et al. for short-term use (< 1 year of exposure in the year prior index date). However, due to the short time interval between drug intake and the event, it cannot be concluded that short-term use (< 1 year) is in general without risk. In contrast to short-term use, a significant association is shown in particular for prolonged use (>1 year). These findings are in line with post-hoc analyses of the EPI-PHARE studies by Nguyen et al. showing an increase in risk with longer treatment duration of CMA or NOMAC.

3. Benefit-risk balance

The efficacy of chlormadinone acetate or nomegestrol acetate, also in combination with ethinylestradiol or estradiol, in their authorised indications, has been assessed at the time of authorisation in central and national MAA procedures, and is considered to be established.

The two recent cohort studies by Nguyen et al. (2021), aimed to evaluate the real-life impact of prolonged use of CMA or NOMAC on the risk of meningioma in women, add to the current knowledge well-defined, structured, long-term data based on administrative health data from the SNDS (Système National des Données de Santé), which covers around 99% of the French population. The results showed an increased risk for intracranial meningioma after exposure to CMA or NOMAC with high cumulative dose and longer exposure duration, with potential decrease after discontinuation of CMA or NOMAC.

The analysis of post-marketing cases points as well towards an increased risk of meningioma during long-term use with high dose products (CMA 5-10 mg and NOMAC 3.75-5 mg) for different indications. For CMA, most cases reported refer to use of the product in the endometriosis indication. For NOMAC, the highest number of cases have been reported in the context of off-label use (contraception and endometriosis) followed by reports in the authorised treatment of uterine leiomyoma and heavy menstrual bleeding.

In addition, a EudraVigilance (EV) analysis of cases of meningioma reported with CMA or NOMAC-containing medicinal products retrieved 359 case reports with CMA-containing products and 461 case reports with NOMAC-containing products, almost all in females, most of them aged between 40 to 60 years. The case reports mainly derived from France with a sharp increase in 2019. Only a few case reports with the low dose NOMAC combination products such as Zoely were retrieved.

Low-dose CMA (1-2 mg)- and low dose NOMAC (2.5 mg)-containing products

The risk of meningioma with the use of CMA or NOMAC has been previously recognised and is currently reflected in the PI as follows:

- Low dose CMA monotherapy-containing products: contraindication in patients with meningioma or history of meningioma.
- Low dose NOMAC combination products: contraindication in patients with meningioma or history of meningioma and a warning on the risk of meningioma.

While, as part of the review, no increased risk specifically in association to the use of low dose products could be identified, it is noted that there are situations where patients may be exposed to low dose products for a long period of time and therefore, the risk of meningioma associated to low dose products is considered a potential important risk. As the risk increases with increasing cumulative

dose, PRAC considered that a warning on this risk should be reflected in the PI of low dose CMA (1- 2 mg)- or NOMAC (2.5 mg)-containing products, and that the use of these products should be contraindicated in patients with meningioma or history of meningioma. It is to be noted that for some products, e.g. Zoely, a contraindication and a warning on the risk of meningioma were already reflected in the PI, however, PRAC recommended further amendments to the previously agreed wording to reflect the current knowledge and be in alignment with the class. Additionally, for low dose CMA- or NOMAC containing products, a targeted follow-up questionnaire should be implemented (if not yet established) for cases of meningiomas, to ensure high-quality reports and facilitate causality assessment in future. Key elements for this targeted follow-up questionnaire were agreed by PRAC.

High-dose CMA (5-10 mg)- or high-dose NOMAC (3.75-5 mg)- containing products

Although meningioma has only been reported as a rare event with CMA-containing products, the causal relationship between meningioma and high dose CMA- or high dose NOMAC-containing products is considered established. Based on this, it is considered that the benefit-risk balance for treatment options with high dose-containing products should be restricted to situations where other interventions are considered inappropriate, and the treatment should be restricted to the lowest effective dose and shortest duration. Additionally, a contraindication in patients with meningioma or history of meningioma should be added to the PI, as well as a warning that symptoms of meningioma should be monitored and that treatment should be stopped if a patient is diagnosed with meningioma. In addition, PRAC recommended that information on results of the two epidemiological studies by Nguyen et al. should be reflected in the product information.

During the present review, PRAC considered the need to recommend MRI monitoring of patients before and regularly during the course of treatment with CMA or NOMAC. 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 CMA/NOMAC, PRAC considered that this measure would not be proportionate.

In view of the findings of the studies by Nguyen et al., healthcare professionals should be reminded via a direct healthcare professional communication (DHPC) of the warning and contraindication on the risk of meningioma for all products and be informed of the new restrictions for the use of high dose CMA- or NOMAC-containing products. The DHPC is to be jointly disseminated by marketing authorisation holders in each Member State. This communication should be distributed to endocrinologists, gynaecologists, general practitioners, learned societies and any other relevant target groups to be further defined at national level.

Finally, the PRAC considered the need for additional pharmacovigilance activities to evaluate the effectiveness of the proposed risk minimisation measures and was of the view that all marketing authorisation holders should analyse the prescribing behaviour and awareness of prescribers and evaluate the effectiveness of the newly introduced RMMs in the upcoming PSURs for the respective active substances.

4. Summary of new activities and measures

4.1. Risk management

The Committee, having considered all information and data submitted in the procedure, recommends a series of risk minimisation measures and pharmacovigilance activities to further minimise and

characterise the risk of meningioma associated with CMA-containing products and NOMAC-containing products.

Each MAH of CMA- or NOMAC-containing products for which a risk management plan is in place should update their RMP within 6 months following the finalisation of this procedure to reflect the pharmacovigilance activities and risk minimisation measures listed below, as applicable, and submit it to the relevant NCA through an appropriate variation procedure.

4.1.1. Safety concerns

High dose CMA (5-10 mg)- or NOMAC (3.75–5 mg)-containing products: the Committee considered that meningioma should be added as an important identified risk in the risk management plan.

Low dose CMA (1 mg and 2 mg)-containing products or NOMAC (2.5 mg)-containing products: the Committee considered that meningioma should be added as an important potential risk in the risk management plan.

4.1.2. Risk minimisation measures

4.1.2.1. Routine risk minimisation measures

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 nomegestrol acetate- or chlormadinone acetate-containing medicinal products. These changes include amendments to the following sections of the SmPC:

- High dose CMA (5-10 mg)-containing products and high dose NOMAC (3.75–5 mg)-containing products: updates of SmPC section 4.1 to restrict the use of the products to situations where other interventions are considered inappropriate, section 4.2 to limit the treatment to the lowest effective dose and shortest duration, section 4.3 to include a contraindication in patients with meningioma or history of meningioma, section 4.4 to add a warning to monitor for symptoms of meningioma and stop treatment with these medicines if a patient is diagnosed with meningioma, section 4.8 to add meningioma as an ADR with frequency rare, and section 5.1 to include the results of the two epidemiological study results by Nguyen et al..
- Low dose CMA (1 mg and 2 mg)-containing products and NOMAC (2.5 mg)-containing products: updates of SmPC section 4.3 to include a contraindication in patients with meningioma or history of meningioma, and SmPC section 4.4 to add a warning to monitor for symptoms of meningioma and stop treatment permanently with these medicines if a patient is diagnosed with meningioma.

The package leaflets are amended accordingly.

4.1.3. Pharmacovigilance activities

4.1.3.1. Routine pharmacovigilance activities

Targeted follow-up questionnaires

The MAHs for low dose CMA (1 mg and 2 mg) and NOMAC (2.5mg)- containing-products are requested to implement targeted follow-up questionnaires to further characterise the important potential risk of meningioma.

These targeted follow-up questionnaires should include the following key elements:

- Patients height/weight/BMI/age
- Gestational history
- Previous/ concomitant hormonal therapy
- Personal and family history of meningioma/ neurofibromatosis type 2/ cerebrospinal irradiation/ cancer
- clinical symptoms of meningioma
- Imaging before diagnosis of meningioma/ imaging to identify meningioma/ follow-up imaging
- Management of meningioma
- Pathology report
- Monitoring/evolution.

PSUR frequency

The frequency of PSUR submission for "chlormadinone" and "chlormadinone acetate / ethinylestradiol" should be aligned with the data lock points (DLP) for the PSURs for "nomegestrol" and "nomegestrol acetate / estradiol". Consequently, the next PSURs for "chlormadinone" and "chlormadinone acetate / ethinylestradiol" should have a DLP of 31/01/2024 and be submitted within 90 days of the DLP published in the updated list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

Presentation of data in PSURs

Within the respective sections of each PSUR, MAHs should provide detailed data on the implementation of the now proposed measures and a thorough evaluation and causality assessment of all upcoming cases reporting meningioma and off-label use. It should be analysed whether case reports are received that may be indicative of contraindicated use.

Exposure data should be provided over time (starting with a timeframe before the referral procedure) and annually stratified by underlying indication (if data are available) and strength so in order to assess changes before and after implementation of the measures agreed as part of this the current referral procedure could be assessed. All MAHs should ensure that the data provided in their PSURs are adequate to enable the assessment to assess the effectiveness of the recommended risk minimisation measures.

4.2. Direct healthcare professional communication and communication plan

The Committee considered that a direct healthcare professional communication (DHPC) was needed to raise awareness of the revised/new recommendations and other risk minimisation measures agreed as outcome of this review. This communication should be distributed to endocrinologists, gynaecologists, general practitioners, learned societies and any other relevant target groups to be further defined at national level.

All concerned MAHs in each Member State are encouraged to liaise with national competent authorities to collaborate in order to prepare and circulate a single DHPC in each Member State.

5. Grounds for Recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for all chlormadinone acetate-containing products and nomegestrol acetate-containing products.
- The PRAC reviewed the available data on risk of meningioma during or following the use of medicinal products containing chlormadinone acetate or nomegestrol acetate, either alone or in combination, in particular the epidemiological studies including the French Health Insurance (CNAM) studies, as well as post-marketing case reports and data submitted by the marketing authorisation holders.
- The PRAC concluded from the data that the absolute risk of meningioma caused by treatment with products containing chlormadinone acetate or nomegestrol acetate use remains low. However, the risk increases with increasing cumulative doses and treatment duration of chlormadinone or nomegestrol acetate. PRAC also noted that risk of meningioma may decrease after treatment discontinuation.
- The PRAC therefore recommended that treatment with products containing high doses of chlormadinone acetate (5-10 mg) or nomegestrol acetate (3.75-5 mg) is restricted to situations where alternative treatments or interventions are considered inappropriate. Treatment should be limited to the lowest effective dose and shortest duration. Moreover the Committee recommended that these high dose products, are contraindicated in patients with meningioma or history of meningioma.
- The PRAC also concluded that while no increased risk of meningioma was specifically identified following use of low dose chlormadinone acetate- or nomegestrol acetate-containing medicinal products, either alone or in combination, it is noted that there are situations where patients may be exposed to low dose products for a long period of time. Given that the risk increases with increasing cumulative doses of chlormadinone acetate or nomegestrol acetate, the Committee recommended that low dose chlormadinone acetate (1-2 mg)- or nomegestrol acetate (2.5 mg)-containing products should also be contraindicated in patients with meningioma or history of meningioma.
- The Committee recommended further updates to the product information of chlormadinone acetate-containing products and nomegestrol acetate-containing products to reflect current knowledge on the risk of meningioma.

- The Committee recommended that all marketing authorisation holders should evaluate the effectiveness of the newly introduced RMMs in the upcoming PSURs for the respective active substances.

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

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

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for chlormadinone acetate-containing products and nomegestrol acetate-containing products.

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Appendix 1

Divergent positions to PRAC recommendation

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

Procedure number: EMEA/H/A-31/1510

Procedure number: EMEA/H/A-31/1510/C/1213/60

Nomegestrol or chlormadinone containing medicinal products

Divergent statement

The following PRAC Members consider that the benefit-risk ratio of nomegestrol and chlormadinone containing products is uncertain in the following indications in view of the identified risk of meningioma: HRT (Hormone Replacement Therapy), dysmenorrhea, gynaecological disorders related to progesterone insufficiency (menstrual irregularities, premenstrual syndrome, mastodynia), based on the following grounds:

In the aforementioned therapeutic indications, women are older (mean 40 years old) compared to other gynaecological uses (e.g., contraception). Data from the two French pharmacoepidemiological studies, on which the referral was triggered, have highlighted that meningioma risk is highly related to the age of women. Women treated either for perimenopausal disorders or HRT have a higher risk of meningioma compared to other exposed women due to their higher age.

Medicinal products containing nomegestrol acetate or chlormadinone acetate monosubstances are used in various gynaecological indications. The treatment duration is often long as some disorders could last from menarche to menopause (e.g., menstrual irregularities).

Moreover and according to clinical guidelines, alternative therapies, not known to increase meningioma risk, are available in each of the above mentioned indications. The data of efficacy of these substances in the current indications are old and should have been reassessed in the light of the magnitude of the risk meningioma, which is a rare but a serious risk exposing women to potential severe sequels. The restriction of the use of nomegestrol containing products and chlormadinone containing products to those situations where other interventions are considered inappropriate, as per the PRAC recommendation, appears therefore not risk-proportionate and expose women to an unnecessary risk as alternative options exist.

Therefore, unless the benefits are clearly re-assessed, indication by indication, and considering the new data about the risk of meningioma, the benefit-risk is uncertain in these aforementioned indications and as a precautionary measure, these products should not be used in these indications.

These concerns were already clearly raised by France when triggering a referral under Article 31 of Directive 2001/83/EC since women are likely to be treated for several years including menopausal period in the aforementioned indications which were expected to be further assessed.

The divergent statement concerns also the absence of recommendation for requesting a post-authorisation safety study to assess the effectiveness of the risk minimization measures which will be implemented in the EU countries as an outcome of this referral. Irrespective of the nature of the study (HCP survey, drug utilization study), a dedicated study performed by the concerned MAHs is essential to know whether the healthcare professionals will adhere to the risk minimization measures agreed by PRAC e.g., contraindication in case of (history of) meningioma for combinations, discontinuation of the drug in case of a meningioma is diagnosed, and the use of these products in last resort.

PRAC Members expressing a divergent opinion:

- Tiphaine Vaillant (France)
- Julia Pallos (Hungary)
- Nadine Petitpain (Luxembourg)
- Patricia McGettigan (Independent scientific expert nominated by the European Commission)