Annex II

Scientific conclusions

Scientific conclusions

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

Approved indications for nomegestrol acetate and chlormadinone acetate in monotherapy or in combination with estradiol or ethinylestradiol differ between the different strengths and between the different countries. Overall, they are indicated for gynaecological and menstrual disorders, hormone replacement therapy and, at lower doses, as hormonal contraception.

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 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-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 10mg 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.

The PRAC adopted a recommendation on 07 July 2022 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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 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.

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)- or 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.

Grounds for PRAC 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.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

The CHMP, as a consequence, considers that the benefit-risk balance of nomegestrol-containing medicinal products and chlormadinone-containing medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore, the CHMP recommends the variation to the terms of the marketing authorisations for nomegestrol-containing medicinal products and chlormadinone-containing medicinal products.