<Date>

Direct Healthcare Professional Communication (DHPC)

Chlormadinone acetate and nomegestrol acetate: Measures to minimise the risk of meningioma

Dear Healthcare Professional,

<Names of marketing authorisation holder> in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

Summary

- **Medicinal products containing chlormadinone acetate (5-10 mg/tablet) or nomegestrol acetate (3.75 -5 mg/tablet) are only indicated when other interventions are considered inappropriate. Treatment should be restricted to the lowest effective dose and shortest duration.**
- **There is an increased risk for developing meningioma (single or multiple) after use of chlormadinone acetate or nomegestrol acetate, primarily at high doses over prolonged time. The risk increases with cumulative doses.**
- **Products containing chlormadinone acetate or nomegestrol acetate are contraindicated in patients with a meningioma or a history of meningioma.**
- **Patients should be monitored for meningiomas in accordance with clinical practice.**
- **If a patient treated with chlormadinone acetate or nomegestrol acetate is diagnosed with meningioma, treatment must be permanently stopped.**

Background on the safety concern

The nationally approved medicinal products and the wording of the indications varies between EU countries. *[Indication details to be amended on national level as needed]*:

Therapeutic indications for high-dose chlormadinone acetate or nomegestrol acetate monotherapy in a dose of <5-10 mg> <and> <3.75-5 mg, respectively>, in women include [*to be amended by NCAs due to different marketing authorisations*]. <In combination with estradiol, nomegestrol acetate in the strength 3.75 mg is also indicated for the treatment of hormone replacement therapy (HRT) for oestrogen deficiency symptoms in women at least 6 months since last menses.> Therapeutic indications for low dose (2 mg) chlormadinone acetate monotherapy include [*to be amended*]. <Low dose containing chlormadinone acetate or nomegestrol acetate in combination with an oestrogen are indicated as hormonal contraceptives.>

Meningioma is a rare, most frequently benign tumour that forms from the meninges. Clinical signs and symptoms of meningioma may be unspecific and may include changes in vision, hearing loss or ringing

in the ears, loss of smell, headaches that worsen with time, memory loss, seizures or weakness in extremities.

Recently, results from two French epidemiological cohort studies observed a cumulative dose-dependent association between chlormadinone acetate or nomegestrol acetate and meningioma.[1;2] These studies were based on data from the French health insurance (CNAM) and included a population of 828,499 patients for chlormadinone acetate and 1,060,779 for nomegestrol acetate. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose chlormadinone acetate (cumulative dose > 360 mg) or high dose nomegestrol acetate (cumulative dose > 150 mg) and women who were slightly exposed to chlormadinone acetate (cumulative dose ≤ 360 mg) or nomegestrol acetate (cumulative dose ≤ 150 mg).

Results for chlormadinone acetate:

Cumulative dose of chlormadinone acetate	**Incidence rate (in patient-years)**	**HRadj (95% CI)[a]**
Slightly exposed (≤0.36 g)	**6.8/100,000**	**Ref.**
Exposed to > 0.36	**18.5/100,000**	**4.4 [3.4-5.8]**
1.44 to 2.88 g	**11.3/100,000**	**2.6 [1.4-4.7]**
2.88 to 5.76 g	**12.4/100,000**	**2.5 [1.5-4.2]**
5.76 to 8.64 g	**23.9/100,000**	**3.8 [2.3-6.2]**
More than 8.64 g	**47.0/100,000**	**6.6 [4.8-9.2]**

[a] Adjusted hazard ratio (HR) based on age; cumulative dose and age considered as time-dependent variables.

A cumulative dose of 1.44 g for example can correspond with around 5 months of treatment with 10 mg/day.

Results for nomegestrol acetate:

Cumulative dose of nomegestrol acetate	**Incidence rate (in patient-years)**	**HRadj (95% CI)[a]**
Slightly exposed (≤0.15 g)	**7.0/100,000**	**Ref.**
Exposed to > 0.15	**19.3/100,000**	**4.5 [3.5-5.7]**
1.2 to 3.6 g	**17.5/100,000**	**2.6 [1.8-3.8]**
3.6 to 6 g	**27.6/100,000**	**4.2 [2.7-6.6]**
More than 6 g	**91.5/100,000**	**12.0 [8.8-16.5]**

[a] Adjusted hazard ratio (HR) based on age; cumulative dose and age considered as time-dependent variables.

A cumulative dose of 1.2 g for example can correspond with 18 months of treatment with 5 mg/day for 14 days each month.

In view of these data, treatment with high-dose chlormadinone acetate or high-dose nomegestrol acetate should be limited to situations where other interventions are considered inappropriate. Treatment should be restricted to the lowest effective dose and shortest duration.

No new safety concern regarding a risk of meningioma associated with the use of low dose (2 mg) chlormadinone acetate containing medicinal products or low dose (2.5 mg) nomegestrol acetate containing contraceptives could be identified. However, as the risk of meningioma increases with increasing cumulative doses of products containing chlormadinone acetate or nomegestrol acetate, low dose products are contraindicated in patients with meningioma or history of meningioma and treatment should be permanently stopped in case of signs and symptoms of meningioma.

Call for reporting

Healthcare professionals should report adverse events in patients taking CMA- or NOMAC-containing products to [NCA] to < insert local details: names, postal address, fax number, website number> <in accordance with the national spontaneous reporting system>.

Company contact point

Should you have any questions regarding the use of chlormadinone- or nomegestrol-containing products, please contact:

<A table of Marketing authorisation holders and contact points>

List of literature references:

1) Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de chlormadinone et risque de méningiome intracrânien: une étude de cohorte à partir des données du SND". Available at: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_chlormadinone_avril-2021-1.pdf

2) Nguyen P et al. (2021) - EPI-PHARE - Groupement d'intérêt scientifique (GIS) ANSM-CNAM "Utilisation prolongée de l'acétate de nomégestrol et risque de méningiome intracrânien: une étude de cohorte à partir des données du SNDS". Available at: https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_nomegetrol_avril-2021.pdf

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	All products containing chlormadinone acetate or nomegestrol acetate
Marketing authorisation holder(s)	All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The single letter circulated in each Member State should cover all active substance-containing products authorised in that Member State. It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.
Safety concern and purpose of the communication	Measures to minimise the risk of meningioma including restriction in use for high dose chlormadinone acetate (5-10 mg) or high dose nomegestrol acetate (3.75-5 mg) and contraindications and warnings for all products containing chlormadinone acetate or nomegestrol acetate.
DHPC recipients	Endocrinologists, gynaecologists, general practitioners, learned societies and any other relevant target groups as agreed at national level.
Member States where the DHPC will be distributed	All EU Member states where the products are marketed. The DHPC might need to be adapted depending on which products are authorised in the individual Member State.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	07/07/2022
DHPC and communication plan (in English) agreed by CHMP	21/07/2022
Submission of translated DHPCs to the national competent authorities for review	CHMP Opinion + 5 calendar days
Agreement of translations by national competent authorities	CHMP opinion + 14 calendar days
Dissemination of DHPC	EC decision + 5 calendar days