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Chlormadinone acetate and norgestrel 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 norgestrel 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 norgestrel acetate, primarily at high doses over prolonged time. The risk increases with cumulative doses.**
- **Products containing chlormadinone acetate or norgestrel 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 norgestrel 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 norgestrel 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, norgestrel 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 norgestrel 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>.

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 nomegestrol 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