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**IMPORTANT MEDICINE  
SAFETY INFORMATION**

APPROVED  
BY THE



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

Dear Healthcare Professional,

Theramex Ireland in agreement with the European Medicines Agency and the Health Products Regulatory 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.**
- **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.**

***Background on the safety concern***

The nationally approved medicinal products and the wording of the indications varies between EU countries.

Approved indications for high dose nomegestrol acetate (3.75mg-5mg) and chlormadinone acetate (5-10mg) as monotherapy or in combination with estradiol or ethinylestradiol vary between countries and are generally indicated as hormonal replacement therapy (HRT) and for gynaecological and menstrual disorders.

Low dose containing chlormadinone acetate (1-2mg) or nomegestrol (2.5mg) acetate in combination with an oestrogen are indicated as hormonal contraceptives.

In Ireland the only combination of these actives marketed is Zoely, which is a combination of low-dose nomegestrol acetate (2.5mg) and estradiol (1.5mg) and is indicated for oral contraception.

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.<sup>1;2</sup> 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) <sup>a</sup>
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]

<sup>a</sup> 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) <sup>a</sup>
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]

<sup>a</sup> 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 norgestrel 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) norgestrel acetate containing contraceptives could be identified. However, as the risk of meningioma increases with increasing cumulative doses of products containing chlormadinone acetate or norgestrel 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 via HPRA Pharmacovigilance, website: [www.hpra.ie](http://www.hpra.ie).

### ***Company contact point***

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

Theramex Ireland Limited

Email address: [medinfo.ie@theramex.com](mailto:medinfo.ie@theramex.com)

Phone number: +35319036075

### ***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](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 norgestrel 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\\_norgestrel\\_avril-2021.pdf](https://www.epi-phare.fr/app/uploads/2021/04/epi-phare_rapport_acetate_norgestrel_avril-2021.pdf)



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