

27 March 2023

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

Dear Healthcare Professional,

Theramex Australia Pty Ltd in agreement with the Therapeutic Goods Administration (TGA) 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.**
- **In Australia high dose products mentioned in first paragraph are not available, only ZOELY (containing 2.5 mg nomegestrol acetate and 1.5 mg estradiol) is marketed.**
- **There is an increased risk for developing meningioma (single or multiple) after use of chlormadinone acetate or nomegestrol acetate, primarily at high doses over a 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. This is already included in the current ZOELY Product Information in Australia.**
- **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 countries outside of Australia.

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

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

In line with the Product Information, healthcare professionals should report any suspected adverse reactions in patients taking ZOELY to the TGA at <https://www.tga.gov.au/reporting-problems>.

Company contact point

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

Theramex Australia Pty Ltd

Email address: medinfo.au@theramex.com

Phone number: 1800 THERAMEX (or 1800 843 726)

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 noméggestrol 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

Signature

Local Safety Officer and QPPVA