EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 September 2021
EMA/PRAC/522593/2021

PRAC List of questions

To be addressed by the marketing authorisation holders for medicinal products containing nomegestrol or medicinal products containing chlormadinone

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1510

Zoely EMEA/H/A-31/1510/C/1213/60

INN/active substance: nomegestrol or chlormadinone

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. Questions

The marketing authorisation holders (MAHs) are requested to address the following questions:

Question 1:

Concerning your nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s), please provide in the annexed table:

a) Information on type of marketing authorisation (legal basis), marketing and legal status and approved indication(s). Please clearly indicate for which country a specifically dedicated strength has been granted in a particular indication.

b) Patient exposure by product, Member State, indication and age for the period since January 2011. Data on the use in clinical practice including information on dose, duration of treatment and concomitant treatment (characterisation of users, prescriptions…) for the period since January 2011.

c) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) on posology, and, regarding the risks of meningiomas, on contraindications, warnings and precautions, and undesirable effects. Please highlight the main differences between the product(s) information (PI) in the different EU Member States.

Question 2:

The MAHs should provide an in-depth description of meningiomas in general, and the specificities of the meningiomas associated with chlormadinone and nomegestrol: molecular aspects, histology, incidence/prevalence observed in population, localisations, and a discussion on a potential mechanism of meningiomas with nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s). Based on this description, the MAHs should discuss identified and potential risk factors, and gold standard management (monitoring and management) of these meningiomas.

Question 3:

The MAHs should provide a cumulative review of all available safety data relevant to evaluate the risk of meningiomas with nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s) taking into account information from all sources (including non-clinical, clinical and pharmacoepidemiological studies, published literature and post-marketing cases). As applicable, causality assessment should be performed and provided in a tabular format (annexed table). All Individual Case Safety Reports (ICSRs) should be provided separately. The MAHs should discuss the risk factors (including age, previous radiation, genetic disorder, ethnicity, etc.) for meningiomas with chlormadinone or nomegestrol use and discuss differences in the magnitude of risk for the different indications and different (cumulative) doses. If possible, the magnitude of the risk of meningiomas should be stratified by strength and duration of treatment.

Question 4:

The MAHs should thoroughly discuss the new studies conducted by the French Health Insurance (CNAM) that triggered the referral procedure. This should include a discussion on a possible dosage and duration dependence, data on meningioma recovery/improvement following the end of therapy, bias and the overall hazard ratio.

Question 5:

Taking into account the most up to date data about the risk of meningiomas, the MAHs should provide a full benefit-risk balance assessment of nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s) in each of the currently approved indication(s) in the EU. Specifically, the MAHs are requested to discuss how the benefit-risk balance may differ according to age of patients, the cumulative dose (dose and duration) and potential concomitant treatments.

Question 6:

The MAHs should provide details of any specific measures that have already been taken in order to address the risk(s) of meningiomas in users of nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s) and comment on the effectiveness of such measures.

Question 7:

The MAHs should provide proposals and justifications with supportive evidence for any risk minimisation measures (including changes to the SmPC/PL) which may improve the benefit-risk balance of nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s) for the EU, discuss their feasibility and how their effectiveness should be monitored.

Question 8:

The MAHs should discuss the need for additional pharmacovigilance activities to further characterise the risk(s) of meningiomas in users of nomegestrol-containing medicinal product(s) or chlormadinone-containing product(s) and comment on their feasibility.

2. Additional Data Review

As part of this review, the PRAC considers it necessary to perform an EudraVigilance analysis of meningiomas with nomegestrol-containing medicinal product(s) and chlormadinone-containing medicinal product(s). The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs.

Annex

Question 1

a) & b)

INN	Product name	Type of marketing authorisation (legal basis)	Marketing and legal status	Indications[1]	Pharmaceutical forms and strengths	Estimated patient exposure[2]	Doses (in clinical practice)	Treatment duration (in clinical practice)

[1]. MAH should clearly indicate for which country a specifically dedicated strength has been granted for a particular indication
[2]. Expressed in patient years and stratified by Member State, by indication and by age (<12 and 12-18). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

c)

PI	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Posology (incl. max. daily dose)			
Contraindications			
Warnings and precautions			
Undesirable effects			

Question 3

Worldwide Unique Case Identification Number; Sender's (case) safety report unique identifier	**Narrative/summary (incl. reporter type, patient's characteristics: (co)medication, concomitant disease, anamnesis, age, BMI/weight/height, TTO, dosage, duration, de/rechallenge information, surgery/therapy, recovery/improvement, seriousness, suspected drug)**	**MAH assessment**	**MAH's conclusion according to official criteria (e.g. WHO UMC criteria: unassessable, unlikely, possible, probable, certain)**