Divergent positions to CHMP opinion

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

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

Procedure number: EMEA/H/A-31/1510/C/1213/60

Nomegestrol or chlormadinone containing medicinal products

Divergent statement

The following CHMP Members consider that the benefit-risk ratio of nomegestrol and chlormadinone containing products is uncertain in the following indications in view of the identified risk of meningioma: HRT (Hormone Replacement Therapy), dysmenorrhea, gynaecological disorders related to progesterone insufficiency (menstrual irregularities, premenstrual syndrome, mastodynia), based on the following grounds:

These compounds may lead to meningioma formation mostly in the spheno-orbital region which might be a difficult area to reach by surgery, as there is not known pharmacotherapy of meningioma so far.

In the aforementioned therapeutic indications, women are older (mean 40 years old) compared to other gynaecological uses (e.g., contraception). Data from the two French pharmacoepidemiological studies, on which the referral was triggered, have highlighted that meningioma risk is highly related to the age of women. Women treated either for perimenopausal disorders or HRT have a higher risk of meningioma compared to other exposed women due to their higher age.

Medicinal products containing nomegestrol acetate or chlormadinone acetate mono-substances are used in various gynaecological indications, potentially in long-term treatment as some disorders could last from menarche to menopause (e.g., menstrual irregularities).

The data of efficacy of these substances in these indications are old and should have been reassessed in the light of the magnitude of the risk meningioma, which is a rare but a serious risk exposing women to potential severe sequels.

Moreover and according to clinical guidelines, alternative therapies, not known to increase meningioma risk, are available in each of the above mentioned indications.

The restriction of the use of nomegestrol containing products and chlormadinone containing products to those situations where other interventions are considered inappropriate, as per the PRAC recommendation, appears therefore not risk-proportionate and exposes women to an unnecessary risk as alternative options exist.

Therefore, unless the benefits are clearly re-assessed, indication by indication, and considering the new data about the risk of meningioma, the benefit-risk is uncertain in these aforementioned indications and as a precautionary measure, these products should not be used in these indications.

The divergent statement concerns also the absence of recommendation for requesting a post-authorisation safety study to assess the effectiveness of the risk minimization measures which will be implemented in the EU countries as an outcome of this referral. Irrespective of the nature of the study (HCP survey, drug utilization study), a dedicated study performed by the concerned MAHs is essential to know whether the healthcare professionals will adhere to the risk minimization measures agreed by PRAC.

CHMP Members expressing a divergent opinion:

- Jean-Michel Race (France)
- Alexandra Branchu (Luxembourg)