EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PRAC List of questions

To be addressed by the marketing authorisation holder(s) for cyproterone-containing medicinal products

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

Procedure number: EMEA/H/A-31/1488

INN/active substance: cyproterone

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Questions

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

A. For CYPROTERONE ONLY-containing medicinal products (higher strength)

Question 1

Concerning the cyproterone-containing medicinal products, the MAHs are requested to provide in tabulated format (see Annex I):

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

b) Patient exposure in patient years by product, member state and indication in the EU for the period 2009-2019. Data on the use in clinical practice including information on indication, dose and duration of treatment are expected.

c) Information included in the summary of product characteristics (SmPC) and package leaflet (PL) on posology, and regarding the risks of meningioma on contraindications, warnings and precautions, and undesirable effects. Please highlight the main differences between the product 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 cyproterone: molecular aspects, histology, incidence/prevalence observed in population, and localisations. 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 meningioma taking into account information from all sources (e.g. clinical studies, published literature including the French study by Weill and colleagues (2019)[1] "*Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme*" and post-marketing cases). The MAHs should discuss the risk factors (including age, gender, previous radiation, genetic disorder, ethnicity, etc.) for meningiomas with cyproterone 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.

[1] Weill A et al. (2019) - https://ansm.sante.fr/S-informer/Actualite/Acetate-de-cyproterone-Androcur-et-ses-generiques-et-risque-de-meningiome-publication-du-rapport-complet-de-l-etude-de-pharmaco-epidemiologie-Point-d-information

Question 4

The MAHs should discuss whether additional pharmacovigilance activities are needed which could include preclinical and clinical studies, to further characterise the risk of meningioma.

Question 5

The MAHs should discuss whether risk minimisation measures (e.g. advice for screening and monitoring in the product information) are warranted. The feasibility in the different EU Member States of any further measures should be discussed and proposals should be submitted.

Question 6

The MAHs should discuss the impact of the risk of meningioma on the benefit-risk balance of cyproterone-containing products for each authorised indication.

B. For CYPROTERONE in combination with OESTROGENS-containing medicinal products (low strength)

Question 1

The MAHs should provide cumulative patient exposure in patient-years (PY), since the marketing authorisation of their medicinal products.

Question 2

The MAHs should provide a cumulative review of meningioma for their product(s) taking into account information from all sources (e.g. clinical studies, published literature including French study by Weill and colleagues (2019)[2] "*Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme*", and post-marketing cases).

Question 3

Taking into account the response to Question 1 and considering new data suggesting that the risk of meningioma is dose/duration-dependant, the MAHs should discuss the impact of the risk of meningioma on the benefit-risk balance of their product(s) in each authorised indication.

Question 4

The MAHs should discuss the need for risk minimisation measures and whether additional pharmacovigilance activities are needed to better characterise the risk of meningioma.

[2] Weill A et al. (2019) - https://ansm.sante.fr/S-informer/Actualite/Acetate-de-cyproterone-Androcur-et-ses-generiques-et-risque-de-meningiome-publication-du-rapport-complet-de-l-etude-de-pharmaco-epidemiologie-Point-d-information

Annex I

Question 1

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

[1]. MAH should clearly indicate for which country a specifically dedicated presentation/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.

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			