8 February 2013
Patient Health Protection
EMA/PRAC/69149/2013

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products

Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1357

INN/active substance: cyproterone acetate/ethinylestradiol (2 mg/0.035 mg)

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The marketing authorisation holders (MAHs) for cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products are requested to provide the following:

Question 1

The MAHs should provide information on the currently authorised combination of cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products in the different Member States and their current marketing status, including information about the indication(s), treatment duration, contraindications, warnings and precautions, and undesirable effects included in the summary of product characteristics (SmPC) and the package leaflet (PL). Please tabulate the main differences between the SmPCs/PLs in the different EU Member States.
Any specific information related to the contraceptive effect or the risk of venous and arterial thrombosis mentioned in the SmPC or the PL should be specified.

Question 2

The MAHs should also provide information on sales figures and estimated patient exposure worldwide and by country for the EU market per year and cumulatively in women year (method used for estimation should be explained and detailed).

Question 3

Please provide all available information data regarding the potential off-label use with this combination. The off-label use must be analysed regarding each indication as specified in the SmPCs for each country.

Question 4

a) Please provide a cumulative comprehensive analysis from non-clinical studies, clinical trials (including both MAHs sponsored and non-sponsored studies), pharmaco-epidemiological studies, published literature, that are relevant to evaluate the risk of venous and arterial thromboembolic effects with cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products.

b) Please provide a detailed cumulative review of venous and arterial thrombo-embolic events reported since marketing authorisations using the SMQ MEdDRA version 15.1 “Embolic and Thrombotic events” SMQ 20000081.
Separate analysis should be provided for venous and arterial effects.
Results should be presented in terms of numbers of cases, reporting rates (in total and in each of the above age groups). The focus of this review should be the evaluation of compliance with SmPC recommendations, including information on the proportion of all cases of VTE or ATE reported in patients with an identified listed contraindication or precaution/risk factor (as listed in sections 4.3 and 4.4 of the SmPC).
In both analyses, the following cases should be particularly detailed and discussed:
   i. Cases in which cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal product is the only product administered or the only suspected.
   ii. Information should be provided on concomitant medication, in particular whether the patient is reported to be taking another hormonal contraceptive.
   iii. Cases in which one or more thrombo-embolic risk factors have been identified,
   iv. Cases in which no other thrombo-embolic risk factor has been identified

This review should include information on age, indication of use, duration of treatment, time-to-onset since treatment initiation, outcome, seriousness, concomitant medications, relevant medical history.
A line listing of all reported cases should be provided with the responses and CIOMS forms should be made available upon request. This review aimed to identify the cases with a non-compliance with the SmPC regarding the contraindications or the risk factors.

Question 5

Please provide a detailed cumulative review of all fatal cases reported since marketing authorisations. This review should include information on age, indication of use, duration of treatment, time to onset since treatment initiation, outcome, seriousness, concomitant medications, relevant medical history. An assessment of causality should also be provided and possible risk factors discussed.

Question 6

Please provide a detailed cumulative analysis per year and by country of pregnancy cases reported in women treated with cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products since marketing authorisation.

Question 7

Taking into account the safety profile of the product and particularly the risk of thrombo-embolic events and the risk of misuse as a contraceptive only, please provide an analysis of the balance of risks and benefits of cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products, in each currently approved indication(s) in the EU (where this is not a specific indication).

Question 8

a) Please provide details of any specific measures that have already been taken in order to minimise the risk of thrombo-embolic events in patients using cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products and comment on the impact of such measures.

b) Please provide proposals and justification with supportive evidence for any further risk minimisation measures to address the risk of thrombo-embolic events in patients using cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) combination, including changes to the summary of product characteristics, labelling and package leaflet, which could be taken in order to improve the benefit-risk of cyproterone acetate / ethinylestradiol (2 mg/0.035 mg) containing medicinal products. Please also comment on how the impact of such measures should be monitored and assessed.