07 February 2013
EMA/PRAC/60232/2013

PRAC List of questions

To be addressed by the marketing authorisation holder(s)
for combined hormonal contraceptives containing medicinal products

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

Procedure number: EMEA/H/A-31/1356

Zoely EMEA/H/A-31/1356/C/1213/0010
Ioa EMEA/H/A-31/1356/C/2068/0007
Evra EMEA/H/A-31/1356/C/410/0031

INN: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate

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The marketing authorisation holders (MAHs) for combined hormonal contraceptives (CHCs) containing progestogens (INNs: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate) are requested to provide the following by 11 March 2013:

Question 1

a) The MAH(s) are requested to provide information on their currently authorised CHCs medicinal products in the different Member States and their current marketing status in the different EU Member States, including information about the indication(s). Contraindications, warnings and precautions, and undesirable effects included in the summary of product characteristics (SmPC) and the package leaflet regarding the risk of venous thrombosis and arterial thrombosis, should be provided, as well as main differences between the SmPCs/PLs in the different EU Member States. These data should be tabulated as indicated in the annexed table(s).

b) Please also provide marketing information on sales figures in the different EU Member States and estimated patient exposure (in patients-years) by country in 2012 (method used for estimation should be explained and detailed). The estimated target population (women between 15 and 49 years) by country should also be provided and stratified by age group if possible (<18, 18-35, >35).

Question 2

The MAH(s) should provide a cumulative comprehensive analysis of clinical trials (including both MAH sponsored and non-sponsored studies), pharmaco-epidemiological studies and published literature, relevant to evaluate the risk of venous and arterial thromboembolic effects with their CHC medicinal product(s). The effect of age and switching/new users should be specifically examined where possible. The analysis should also critically review the risk of venous and thromboembolic effects with your product compared with levonorgestrel.

Question 3

The MAH(s) should discuss the balance of benefits and risks of their product(s), providing justification and relevant supporting data/evidence for the maintenance of its currently approved use. The epidemiology of any serious risks included in the justification should be provided for the user population and should include, for example, the background rate, morbidity, sequelae and case fatality rate in the suggested age ranges.

Question 4

a) The MAH should provide details of any specific measures that have already been taken in order to minimise the risk of venous and arterial thrombosis in users of their medicinal product(s) and comment on the impact of such measures.

b) Please provide a review of all post-marketing spontaneous reports of venous and arterial thrombo-embolism that have been reported in women with your product since 2001. Cases should be identified using the narrowed SMQ MedDRA version 15.1 “Embolic and thrombotic events venous (20000084)” and the “Embolic and thrombotic events, arterial (20000082)”.
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). These data should be tabulated as indicated in the annexed table.

Question 5

a) In addition, where appropriate, the MAH(s) should provide proposals and justification with supportive evidence for any measures to further minimise the risk of venous and arterial thrombosis including changes to the summary of product characteristics, labelling and package leaflet which could be taken in order to improve the benefit/risk of these medicinal products.

b) The MAH(s) should comment on how the risks, the risk factors and the risk minimisation measures would be communicated to healthcare professionals and women, and how any educational programme on the risks would be delivered.

TABULATION

Question 1

a)

INNs	Product name	Indication(s)	Type of marketing authorisation	Strength	Pharmaceutical form	Route of administration	Marketing status

Contra-indications (SmPC)	Warnings and precautions (SmPC)	Undesirable effects (SmPC)	Contra-indications (PIL)	Warnings and precautions (PIL)	Undesirable effects (PIL)	Main differences between the SmPC/PIL in the different EU Member States

b)

INNs	Product name	Country	Sales figures	Estimated patient exposure (in patients-years)	Estimated target population (women between 15 and 49 years)

Question 4

Nature of the TE event	Total number of cases	Number of cases with at least one risk factor identified	Number of cases with a fatal issue	Time to onset (in months) (mean, median, maximum and minimum)
Pulmonary embolism (PE)				
Venous thrombosis (VT, i.e. venous thrombosis without PE, excluding superficial thrombosis)				

Risk factor for venous TE:

- age of the user (> 35 years),
- BMI > 30 kg/m^2,
- biological abnormality: presence of antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant), activated protein C resistance, antithrombin deficiency, protein C deficiency, protein S deficiency),
- extrinsic risk factor for venous thromboembolism: immobilization > 3 days, travel > 5 hours, trauma, surgical operation, concomitant medication carrying a known risk for thrombosis, history of VTE in close relatives (children, parents, brothers and sisters).
- intrinsic risk factor for venous thromboembolism : personal history of VTE, medical condition associated with adverse circulatory events (for example: cancer, lupus, haemolytic uremic syndrome), post-partum < 3 weeks.