Overview of reports of thromboembolic adverse drug reactions associated with cyproterone/ethinylestradiol

Introduction

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) formally started a safety review of Diane 35® (cyproterone acetate 2 mg, ethinylestradiol 35µg), associated names and its generics at its 4-7 February 2013 meeting.
The Europe-wide review has been initiated at the request of the French medicines regulatory agency (ANSM), following the announcement of its plan to suspend the marketing authorisations for Diane 35® and its generics for acne treatment in France over the next three months. This was the result of an analysis of known data, including reports of venous and arterial thromboembolism (VTE and ATE, the formation of blood clots in the veins or arteries) recorded in the French national pharmacovigilance database in association with Diane 35® and its generics over a period of more than 20 years [1].

As part of the safety review of Diane 35® and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 micrograms, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) is inviting all stakeholders, e.g., healthcare professionals, patients' organisations and the general public, to submit data relevant to the procedure so that they can be considered during the review [2].

Diane 35® was given marketing authorization in the Netherlands in 1987. In the Netherlands, Diane 35® and generic products are only authorised for the *treatment of acne, seborrhea or light hirsutism in women childbearing age if hormonal treatment is considered necessary* [3]. Although cyproterone/ethinylestradiole also works as an oral contraceptive, it should not be used as a contraceptive, but should be reserved for women who need
treatment of the above-described, androgen-dependent disorders.
It is advised to stop treatment 3 to 4 months after the condition for which cyproterone/ethinylestradiole was prescribed has disappeared.
Repeat courses of cyproterone/ethinylestradiole may be given as the androgen-dependent condition returns [3].

Although cyproterone/ethinylestradiole is not indicated for use as an oral contraceptive drug, wide-spread off-label use is expected.

With this overview Lareb wishes to inform to Medicines Evaluation Board about the current number of cases of suspected thromboembolic adverse drug reactions associated with the use of Diane 35® and generic products.

Reports

On February 20, 2013 the Netherlands Pharmacovigilance Centre Lareb had received 325 reports related to the use of cyproterone/ethinylestradiol. These reports contained a total of 579 possible adverse drug reactions (ADRs). Of these ADRs 109 were related to thromboembolism. In 8 reports a fatal outcome was reported. In seven cases with a fatal reaction, a thromboembolic ADR was

reported. In one case with a fatal outcome, the ADR considered a hepatic neoplasm.
An overview of the reported thromboembolic ADRs is presented in table 1.

Table1. Reports of suspected ADRs related to thromboembolism associated with cyproterone/ethinylestradiol

Suspected adverse drug reaction (MedDRA PT)	Number of times reported
Pulmonary embolism	42
Thrombosis	34
Deep vein thrombosis	10
Cerebral infarction	5
Cerebrovascular accident	3
Embolism venous	2
Pelvic venous thrombosis	2
Transient ischaemic attack	2
Cerebral thrombosis	1
Venous thrombosis limb	1
Venous thrombosis	1
Intracranial venous sinus thrombosis	1
Cardiac arrest	1
Cerebral haemorrhage	1
Retinal artery occlusion	1
Myocardial infarction	1
Coronary artery thrombosis	1
Total	109

It is important to note that one patient can suffer from multiple ADRs

A total of 8 cases with a fatal outcome were reported. The details of these reports are described below.

Report 149755 (date occurrence ADR December 2012)
This well documented serious spontaneous report (Death) from a consumer concerns a female aged 11-20 years, with pulmonary embolism following administration of cyproterone and ethinylestradiol for hirsutism with a latency of five months after start. She died as a result of the pulmonary embolism. She used temazepam 10 mg (when needed) as concomitant medication.
An autopsy was performed. There was saddle embolus and several smaller emboli were found. The latter ones probably must have caused necrosis of a portion of the lung in an earlier stage. The autopsy report is not available yet. The family will contact the GP first. There was no history of venous thrombosis or pulmonary embolism. She smoked cigarettes, but it is not known how much, or how many years she smoked. BMI was 29.4 kg/l2 (weight 80 kg, l 1.65 m). During a physical examination last year no hypertension or cardiac disease had been discovered. There was no known lipid disorder. The cholesterol level was known to be normal. She did not have diabetes, a liver disorder, pancreatitis or migraine. Diseases in which there could be an increased risk for thrombosis, such as chronic inflammatory bowel disease did not exist.

There was no thrombosis in a first degree relative. It is not known if attention has been paid to the possibility of a hereditary predisposition for venous or arterial thrombosis at the post mortem examination. There was no superficial phlebitis or varicose veins. There was no drug hypersensitivity (so far as is known neither to the active substances or to any of the excipients of Diane-35®).

Report 149853 (date occurrence ADR January 2000)
This moderately documented serious (Death) spontaneous report from a consumer concerns a female aged 21-30 years (BMI 25.2 kg/m2), with pain in calf and confusion following administration of cyproterone and ethinylestradiol with a latency of weeks after start. The dose for cyproterone and ethinylestradiol had not been changed. The patient died 4 months later, cause of death: thrombosis. Concomitant medication was not reported.
The patient has no known medical history. The patient has no known past drug therapy.

Report 149900 (date occurrence ADR October 2011)
This well documented serious (Death) spontaneous report from a consumer concerns a female aged 31-40 years, with massive pulmonary embolism following administration of cyproterone and ethinylestradiol for acne and contraception with a latency of 24 years after start. The action taken for cyproterone and ethinylestradiol is not applicable. The patient died. Autopsy was performed but the results are not (yet) available. Concomitant medication was not reported.
The patient has no known medical history. The patient has no known past drug therapy.

Report 149919 (date occurrence ADR January 2010)
This moderately documented serious (Death) spontaneous report from a consumer concerns a female aged 21-30 years (BMI 25,4 kg/m2), with headache, weight increased with unknown latency and pulmonary embolism following administration of cyproterone and ethinylestradiol for acne with a latency of years after start. The action taken for cyproterone and ethinylestradiol is not applicable. The patient was treated with anti clotting agents. A few days later, the patient died. Concomitant medication was not reported. The patient hadn't a lot physical exercise.

Report 149947 (date occurrence ADR August 2000)
This moderately documented serious (Hospitalisation, Death) spontaneous report from a consumer concerns a female aged 11-20 years. She used cyproterone and ethinylestradiol for acne. Three months after start, she had a venous pelvic thrombosis . Three weeks later, she died because of a pulmonary embolism. At an unspecified moment in time, she was hospitalized for observation (13 hours) because she was paralysed and had decreased vision. Concomitant medication was diclofenac.
The patient has no known medical history. The patient has no known past drug therapy.

Report 150080 (date occurrence ADR September 2011)
This moderately documented serious (Death) spontaneous report from a specialist doctor concerns a female aged 31-40 years, with coronary artery thrombosis following administration of cyproterone and estrogen for acne with a latency of 1,6 years after start. The action taken for cyproterone and estrogen is not applicable. The patient died. Concomitant medication was tramadol. An autopsy of the left

main branch of the coronary artery was performed showing severe stenosis and the remaining lumen being cut off by a fresh thrombus.
The medical history indicates that the patient had arthralgia. The patient has no known past drug therapy.

Report 150083 (date occurrence ADR July 2004)
This well documented serious (Lifethreatening, Death) spontaneous report from a consumer concerns a female aged 21-30 years, with pulmonary embolism following administration of cyproterone and ethinylestradiole for contraception with unknown latency. Concomitant medication was paracetamol.
In June 2004 the patient underwent surgery for scoliosis. The patient was treated with epoetin alfa 4 times before the surgery in order to donate her own blood for use after the surgery. Her Hb level after the surgery was 6.2. Cyproterone and ethinylestradiole was not withdrawn before the surgery and the patient didn't schedule a pill 'stop'-week when she was in hospital. After the surgery, the patient was partially immobilized for a while. When the patient was hospitalized in July 1 2004, she had been suffering from dyspnea for 2-3 days. She arrived in hospital by ambulance and cardiopulmonary resuscitation (CPR) was started, In the ambulance the patient had been treated with adrenaline 5 times due to asystole, which ultimately resulted in supra ventricular tachycardia. When the ambulance arrived at the hospital, the patient suffered from bradycardia without output. An echography showed a wide right ventricle and right atrial and ventricular spontaneous contrast. There was a good functioning left ventricle. The probability diagnosis was set to a massive pulmonary embolism. Surgical pulmonary embolectomy was tried. During the procedure, the patient suffered from circulatory arrests. Adrenaline was given intracardialy and the patient was reanimated. The patient died on July 1 2004.
The past drug therapy indicates that the patient used tramadol on an unspecified moment/periode, but this was already withdrawn at the time of death. The patient had also been suffering from diarrhea and vomiting at an unknown time before her death.

Report 149888 (date occurrence ADR 1986)
This well documented serious (Death) spontaneous report from a consumer concerns a female aged 11-20 years, with a hepatic neoplasm following administration of cyproterone with ethinylestradiol with a latency of 3 years after start. The drug cyproterone with ethinylestradiol was withdrawn. The patient died at age 20 in 1987. Concomitant medication was not reported.
The patient has no known medical history. The patient has no known past drug therapy.

Other sources of information

SmPC

The SmPC mentions the following under section 4.4. (warnings and precautions for use): “The use of any combined oral contraceptive or cyproterone/ethinylestradiole carries an increased risk of venous thromboembolic disease (VTE) with it, including deep vein thrombosis and pulmonary embolism, as compared with no use. This increased risk is highest during the first year a woman ever uses a combined oral

contraceptive. This increased risk is less than the risk of VTE during pregnancy, which is estimated as 60 cases per 100,000 pregnancies.
There is not always complete recovery of the aforementioned disorders, in 1-2% of the cases, VTE is fatal.
Epidemiological studies have shown that the incidence of VTE in users of oral contraceptives with low estrogen content (<50 micrograms ethinyl estradiol) is up to 40 cases per 100,000 woman-years. For non-users it is 5-10 per 100,000 woman-years…"
"…There is some epidemiological evidence that the incidence of VTE is higher in users of cyproterone/ethinylestradiole comparison with users of combined oral contraceptives with low estrogen content (<50 micrograms)."
Specific risk factors for the development of venous thromboembolic events in combined oral contraceptive users are also mentioned in section 4.4. of the SmPC [3].
Section 4.4. also mentions the following: Epidemiological studies have investigated the use of combined oral contraceptive associated with an increased risk of arterial thromboembolic events (myocardial infarction, transient
ischemic attack (TIA)). Certain factors / diseases, mentioned in the SmPC, increase the risk of arterial thromboembolic disorders. If in these cases also a combined oral contraceptive or cyproterone/ethinylestradiole is used, this risk increases even more [3].
Section 4.8 (adverse drug reactions) of the SmPC refers to section 4.4. for more information on serious adverse drug reactions.

Prescription data

The number of patients using cyproterone/ethinylestradiol containing oral contraceptives in the Netherlands is shown in table 2.

Table 2. Number of patients in the Netherlands between 2007 and 2011.

Drug	2007	2008	2009	2010	2011
Cyproterone with ethinylestradiol (*Diane-35®*)	197,660	187,950	175,530	169,670	161,310

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has received a total of 314 reports on cyproterone/ethinylestradiole. Of these reports 93 considered thromboembolic ADRs. A total of 6 cases had a fatal outcome. One of the cases with a fatal outcome was not related to thromboembolism.
There are specific risk factors for the development of venous and arterial thromboembolic adverse drug reactions, namely increasing age, a positive family history, immobilization and surgery (especially the legs), or major trauma, obesity (body mass index over 30 kg/m^2), dyslipoproteinemia, smoking and hypertension among other [3]. Through follow-up questions, Lareb tries to obtain a complete picture for the reported cases. However the risk factors, like hereditary predisposition, are not always completely documented for each case.
Currently there is a lot of media attention for the association between cyproterone/ethinylestradiolemedia and thromboembolism, which has an effect on the rate of adverse drug reaction reporting, leading to a so called 'Notoriety-bias' [4]. Following the extensive media attention concerning case 149755, the additional five fatal cases were received in the week following this media attention. Recall bias could therefore be present.

Lareb will stay vigilant of any new reports of adverse reactions in association the use of cyproterone/ethinylestradiole.

- Overview of reports of thromboembolic ADRs associated with the use of cyproterone/ethinylestradiole

References

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This signal has been raised on February 2013. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).