Overview of the analysis 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 the French national pharmacovigilance database where reports of venous and arterial thromboembolism (VTE and ATE) in association with Diane 35® and its generics over a period of more than 20 years are recorded [1].

As part of the safety review of Diane 35® and other medicines containing cyproterone acetate 2 mg and ethinylestradiol 35 µg, the PRAC has invited all stakeholders, e.g., healthcare professionals, patients' organisations and the general public, to submit data relevant to the review [2].

Diane 35® was given marketing authorisation 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 of childbearing age if hormonal treatment is considered necessary* [3]. Although cyproterone/ethinylestradiol also works as an oral contraceptive, it is not indicated for the use 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/ethinylestradiol was prescribed has disappeared.
Repeat courses of cyproterone/ethinylestradiol may be given as the androgen-dependent condition returns [3]. The SmPC extensively mentions an increased risk of venous and arterial thromboembolic events under section 4.4. (warnings and precautions for use) and 4.8 (adverse drug reactions) [3].

Although cyproterone/ethinylestradiol is not indicated for use as an oral contraceptive drug, wide-spread off-label use is expected. The number of users of cyproterone/ethinylestradiol in 2011 was 161,630 [4].

After media attention on the association between thromboembolic adverse drug reactions (ADRs) and the use of cyproterone/ethinylestradiol, Lareb received a high number of reports about this association. The ADRs were mainly reported by consumers. The Medicines Evaluation Board (MEB) and the Ministry of Health were informed regularly about reports that Lareb received and especially about the cases with a fatal outcome.

The large number of reports that Lareb received called for a more detailed analyses. Aim of this review is to provide an overview of the characteristics of all reports submitted to the Netherlands Pharmacovigilance Centre until April 3rd 2013. A distinction will be made between the use of cyproterone/ethinylestradiol for the labelled indication and the use as an oral contraceptive.

Method

For the analyses the total number of reports received where cyproterone/ethinylestradiol was the suspect drug was specified.
Further analyses of the reports was focused on reports with thromboembolic ADRs.
A specified list of follow-up questions for patients and healthcare professionals was sent to all reporters who reported a thromboembolism or fatal ADR associated with cyproterone/ethinylestradiol submitted to our centre after February 1st 2013. Consumers

were asked for permission to contact their healthcare professional in order to obtain more information when the initial report was not clear enough. This specified list of follow-up questions had not been sent to reporters who reported before February 1st 2013, however all reports of thromboembolic ADRS related to cyproterone/ethinylestradiol were taken into account in the analysis.

Reports of thromboembolic ADRs where cyproterone/ethinylestradiol was the suspect drug were selected from the Lareb database based on ATC-code G03HB01 using an MS Access® query.
The following information in the reports was taken into account:

- ID of the report
- The reporter type (General Practitioner, Specialist Doctor (Hospital)Pharmacist, Consumer, Medical Doctor non-specified, other Healthcare professional and Marketing Authorisation Holder)
- Seriousness of the reaction according to the CIOMS criteria (Hospitalisation, Lifethreatening, Disabling, Death, Congenital Anomalies, Other)
- Receive date of the report
- Patient's birthdate or patient's age at the occurrence of the ADR
- Patient's BMI (kg/m^2)
- The indication classified as acne, oral contraceptive, hirsutism, seborrhoea or other indication
- The reported adverse drug reaction(s) classified as arterial thrombosis (including MedDRA® Preferred Terms like myocardial infarction, transient ischemic attack), venous thrombosis, pulmonary embolism or unspecified thrombosis. The final classification was made by trained pharmacovigilance assessors.
- The action taken with the suspect drug
- Startdate of the suspect drug
- Date of occurrence of the adverse drug reaction
- Latency period
- Outcome of the reported reaction
- Whether the patient was treated with anticoagulant drugs
- Delay between the first symptoms and diagnosis of the ADR
- Presence of risk factors including smoking, prior thrombosis, history of thrombosis in the direct family, immobilisation (for instance due to surgery or long flights), malignancies, phlebitis or varices in the patient's medical history, hypertension, migraine, hypercholesterolemia, cardiac disorders, Factor-V-Leiden deficiency or Activated Protein C (APC) resistance, decreased Protein S or C levels, increased homocysteine level and 'other' risk factors.

Cut-off values for hypercholesterolaemia were specified as Total cholesterol >5 mmol/L , LDL >2.5 mmol/l, Tricycerides >1.7 mmol/l or HDL ≤ 1 mmol/l for men and or HDL ≤ 1.2 mmol/l for women [5].
Cut-off values for increased homocysteine levels were specified as 16.4 micromol per liter (µmol/liter) for men and 13.4 µmol/l for women [6].

Results

On April 3, 2013 the Netherlands Pharmacovigilance Centre Lareb had received a total of 621 reports about cyproterone/ethinylestradiol. In Figure 1, the cumulative number of reports is shown.

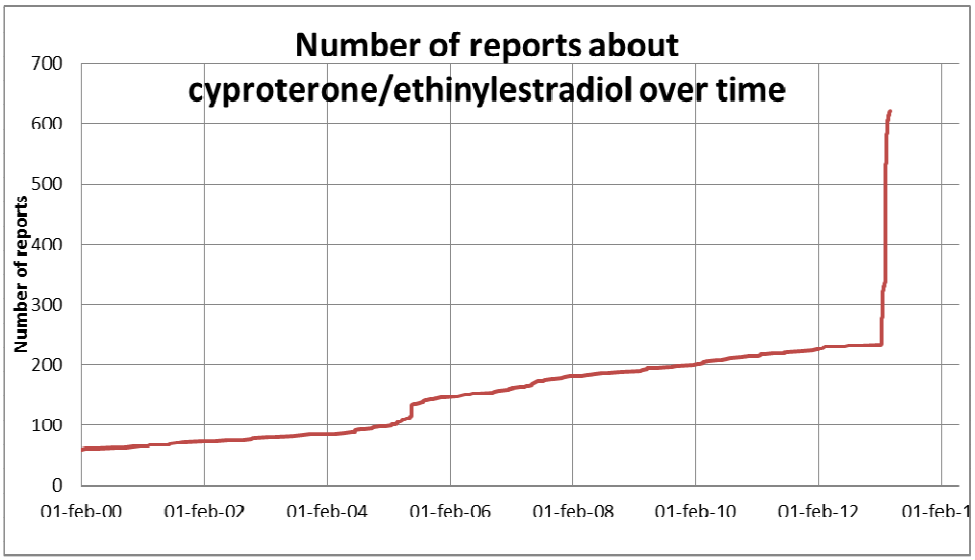


Figure 1: Cumulative number of reports Lareb received about cyproterone/ethinylestradiol in the period 2000-2013

As a result of the extensive media-attention in the Netherlands, a total number of 388 reports were received after February 1st 2013. Many of these reports concerned ADRs that occurred in the past. Figure 2 gives an overview of the number of reports of thromboembolic events grouped by year of onset, both by the total number of reports and the number of reports per 100,000 prescriptions. The increase of both curves over time is a strong indication for a recall bias. Events that occurred a long time ago are less likely to be reported.

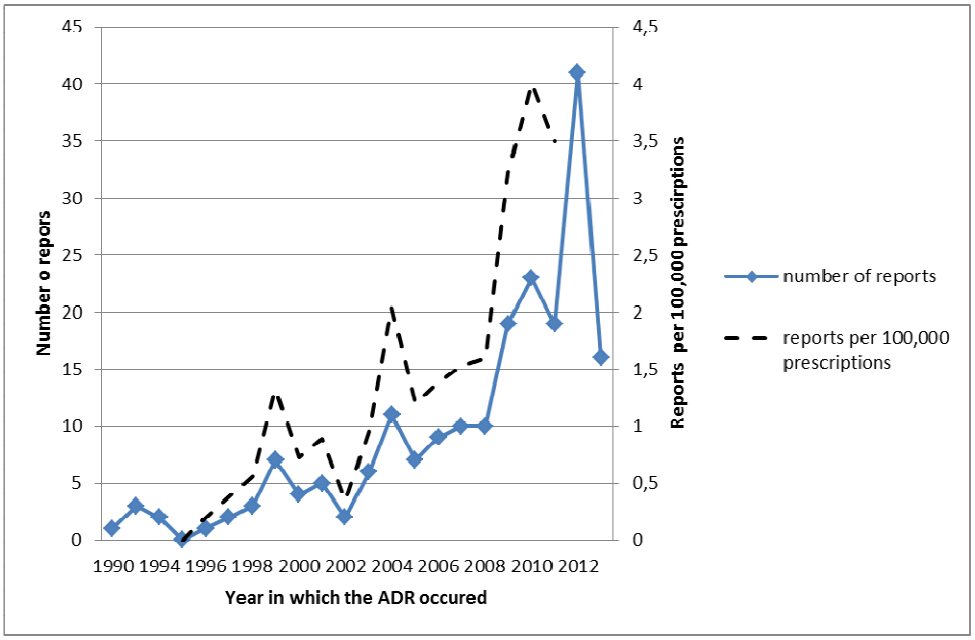


Figure 2. Number of reports grouped by date of onset per year (1990-2013) and the annual number of reports per 100,000 prescriptions (1996-2011)

Characteristics of reports of thromboembolic events

The 621 reports included 309 reports of *thromboembolic adverse drug reactions* related to the use of cyproterone/ethinylestradiol. One report could consist of multiple adverse drug reactions.

A total of 299 reports of thromboembolic ADRs were listed as serious according to the CIOMS criteria. One report can be serious according to multiple CIOMS criteria. See Table 1.

Table 1: Seriousness according to CIOMS criteria

CIOMS Criteria	Number of reports
Death	18
Life-threatening	181
Hospitalisation	207
Disabling	12
Congenital anomalies	0
Serious Other	54

In Table 2 the type of reporter of the ADRs is specified.

Table 2: Reporter of the reactions*

Primary reporter	Number of reports
General practitioner	4
Pharmacist	4
Specialist Doctor	7
Hospital pharmacist	1
Marketing Authorisation Holder	1
Consumer	291

* One report may have been submitted by multiple reporters, in which case duplicate cases were merged. The best documented report was selected as the master report.

The patient's age was known in 306 reports of thromboembolic ADRs, mean age was 30.5 years (standard deviation 10.5 years, range 14-57 years). Patient's mean BMI was 24,3 kg/m^2 (standard deviation 4.3 kg/m^2, range 17-43 kg/m^2).
The primary indications for use of cyproterone/ethinylestradiol are listed in Table 3. The use of this drug as an oral contraceptive and 'other' indications represents off-label use.
In Table 4 the reported thromboembolic adverse drug reactions are listed according to four specified groups. Table 5 and 6 show the action taken with the drug and the outcome of the reaction.
In Table 7 more details are given about the reports of thromboembolic ADRs with a fatal outcome.

Table 3: Primary indications for use of cyproterone/ethinylestradiol

Indication	Number of reports
Acne	147
Oral contraceptive	122
Hirsutism	10
Other	15
Unknown	15

Table 4: Reported thromboembolic adverse drug reactions*

ADR	Number of reports
Arterial thrombosis	52
Venous thrombosis	40
Pulmonary embolism	155
Thrombosis (unspecified location)	128

* One report may refer to multiple ADRs

Table 5: Action taken with the drug

Action	Number of reports
Drug withdrawn	261
Dose not changed	15
Unknown	8
Not applicable*	25

* For instance in case of death of the patient

Table 6: Outcome of the reaction*

Outcome	Number of reports
Recovered	83
Recovering	47
Not recovered	23
Recovered with sequel	130
Fatal	18
Unknown	8

* If multiple outcomes were reported for separate ADRs than the worst outcome for the patient was taken into account in the analyses

Table 7: Reports where the outcome of the thromboembolic ADR was fatal

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 149755 F, 11-20	cyproteron/etinylestradiol hirsutism		pulmonary embolism	5 months not applicable fatal
B 149853 F, 21-30	cyproteron/etinylestradiol acne		confusion, thrombosis, pain in calf	weeks no change unknown
C 149900 F, 31-40	cyproteron/etinylestradiol acne		pulmonary embolism	23 years not applicable fatal
D 149919 F, 21-30	cyproteron/ethinylestradiol acne		headache, weight increased, pulmonary embolism	years not applicable fatal
E 149947 F, 11-20	cyproteron/etinylestradiol acne		vision decreased, pelvic venous thrombosis, pulmonary embolism, paraparesis	3 months not applicable unknown
F 150080 F, 31-40 General Practitioner Duplicate =150569	cyproteron/etinylestradiol acne		coronary artery thrombosis	months not applicable fatal
G 150083 F, 21-30	cyproteron/etinylestradiol contraception		pulmonary embolism	not reported not applicable fatal
H 150167 F, 21-30	cyproteron/etinylestradiol contraception		pulmonary embolism	months not applicable fatal

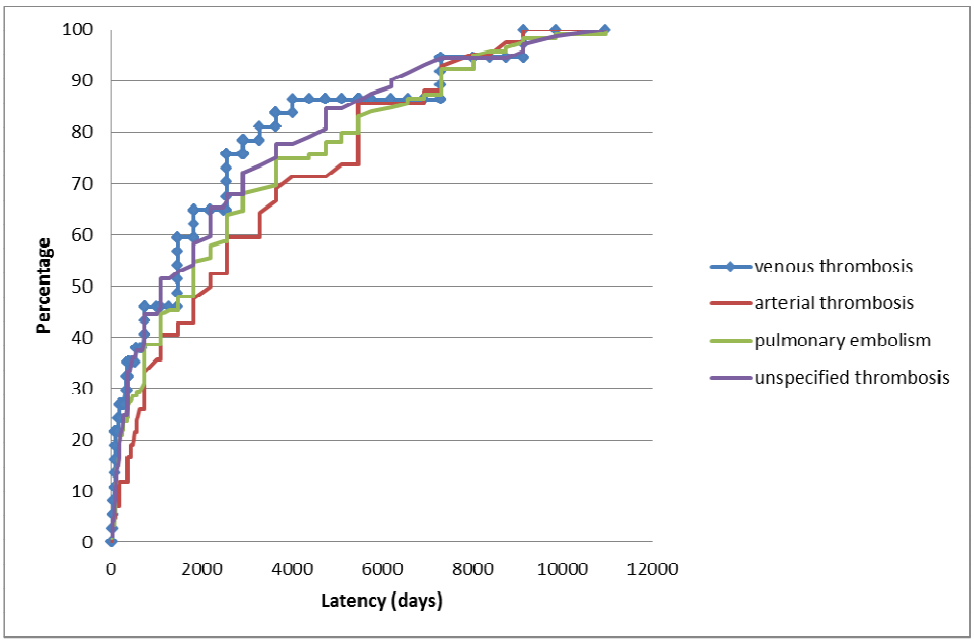
I 150194 F, 21-30	cyproteron/etinylestradiol acne	intracranial venous sinus thrombosis nos	5 years not applicable fatal
J 150446 F, 41-50	cyproteron/etinylestradiol contraception	cerebral thrombosis	20 years not applicable fatal
K 150482 F, 31-40	cyproteron/etinylestradiol acne	pain in leg, cardiac arrest, chest pressure, dyspnea	9 years not applicable fatal
L 150506 F, 21-30	cyproteron/etinylestradiol	pulmonary embolism	5 years not applicable fatal
M 150522 F, 41-50	cyproteron/etinylestradiol	thrombosis, pulmonary embolism	27 years not applicable fatal
N 150909 F, 11-20	cyproteron/etinylestradiol contraception	pulmonary embolism	year not applicable fatal
O 150966 F, 31-40	cyproteron/etinylestradiol	cerebral haemorrhage	19 years not applicable fatal
P 151134 F, 11-20	cyproteron/etinylestradiol acne	thrombosis, unconsciousness, vomiting blood	8 months not applicable fatal
Q 151145 F, 41-50	cyproteron/etinylestradiol	cerebral haemorrhage, thrombosis leg	not reported unknown fatal
R, 151697 F,	cyproteron/etinylestradiol hair thinning	thrombosis, pulmonary embolism	1.5 months not applicable fatal

* The term not applicable entails that the patient died before the suspect drug could be discontinued

Of the 309 patients with a thromboembolic ADR, 261 were known to have been treated with anticoagulant drugs and 11 patients were not treated with anticoagulant drugs. In 37 patients information about treatment with anticoagulant drugs is missing. In some of the cases other treatment options like surgery or wearing support stockings is also mentioned.

In 31 cases there was a delay between the onset of the first symptoms of the reaction and the diagnosis of the thromboembolic adverse drug reaction. This could entail that the thromboembolic ADR was initially not recognized as such by either the patient or their healthcare professional. The number of days between the onset of the first symptoms and diagnosis and treatment was not always specified however.

Time to onset



Time to onset in days for the reaction to occur after the start of cyproterone/ethinylestradiol (the time to onset has been mentioned in 241 reports).

Although pharmacoepidemiolgical studies have shown that the chance for any of the reported events to occur is higher in the first months of the use of cyproterone/ethinylestradiol, many patients experience an ADR later on. It cannot be ruled out that intermittent use has occurred in some patients. The median time to onset is approximately 2 to 3 years. There is no distinction between the time of onset in respect to the reported ADR.

Riskfactors

For the reports with a known indication (n=294), the risk factors are represented below. In respect to reports submitted to the Netherlands Pharmacovigilance Centre, no differences in risk factors seem to exist between labelled and off-label indications.

		Acne	%	OAC	%	Hirsu-tism	%	Other	%	Total	%
Smoking	Yes	28	19	16	13,1	3	30	1	6,7	48	16,3
	No	34	23,1	27	22,1	2	20	5	33,3	68	23,1
	Unk.	85	57,8	79	64,8	5	50	9	60	178	60,5
Previous thrombosis	Yes	2	1,4	1	0,8	0	0	0	0	3	1
	No	18	12,2	12	9,8	0	0	1	6,7	31	10,5
	Unk.	127	86,4	109	89,3	10	100	14	93,3	260	88,4
Thrombosis in direct Family	Yes	12	8,2	12	9,8	1	10	1	6,7	26	8,8
	No	44	29,9	28	23	3	30	5	33,3	80	27,2
	Unk.	91	61,9	82	67,2	6	60	9	60	188	63,9

Immobilization	Yes	23	15,6	17	13,9	0	0	2	13,3	42	14,3
	No	40	27,2	24	19,7	3	30	4	26,7	71	24,1
	Unk.	84	57,1	81	66,4	4	40	9	60	178	60,5
Malignancies	Yes	1	0,7	0	0	0	0	0	0	1	0,3
	No	48	32,7	32	26,2	4	40	6	40	90	30,6
	Unk.	98	66,7	90	73,8	6	60	9	60	203	69
Phlebitis or varices	Yes	7	4,8	3	2,5	1	10	0	0	11	3,7
	No	42	28,6	29	23,8	3	30	6	40	80	27,2
	Unk.	98	66,7	90	73,8	6	60	9	60	203	69
Hypertension	Yes	5	3,4	0	0	0	0	2	13,3	7	2,4
	No	44	29,9	31	25,4	4	40	4	26,7	83	28,2
	Unk.	98	66,7	91	74,6	6	60	9	60	204	69,4
Migraine	Yes	12	8,2	5	4,1	3	30	2	13,3	22	7,5
	No	38	25,9	26	21,3	3	30	4	26,7	71	24,1
	Unk.	97	66	91	74,6	4	40	6	40	198	67,3
Hyperchol-esterolaemia	Yes	2	1,4	1	0,8	0	0	1	6,7	4	1,4
	No	42	28,6	26	21,3	2	20	4	26,7	74	25,2
	Unk.	103	70,1	95	77,9	8	80	10	66,7	216	73,5
Cardiac Disorder	Yes	1	0,7	0	0	0	0	0	0	1	0,3
	No	48	32,7	31	25,4	3	30	6	40	88	29,9
	Unk.	98	66,7	91	74,6	7	70	9	60	205	69,7
Factor V Leiden deficiency	Yes	6	4,1	6	4,9	1	10	1	6,7	14	4,8
	No	6	4,1	4	3,3	0	0	0	0	10	3,4
	Unk.	135	91,8	112	91,8	9	90	14	93,3	270	91,8
Decreased Protein S or C	Yes	1	0,7	0	0	0	0	0	0	1	0,3
	No	2	1,4	1	0,8	0	0	0	0	3	1
	Unk.	144	98	121	99,2	10	100	15	100	290	98,6
Homocysteine	Yes	0	0	0	0	0	0	0	0	0	0
	No	3	2	1	0,8	0	0	0	0	4	1,4
	Unk.	144	98	121	99,2	10	100	15	100	290	98,6

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has received a total of 309 reports on thromboembolic adverse drug reactions associated with the use of cyproterone/ethinylestradiol.
In literature specific risk factors have been described for the development of venous and arterial thromboembolic adverse drug reactions, namely increasing age, a positive family

history, immobilisation 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 tried to obtain a complete picture for the reported cases. However the risk factors, like hereditary predisposition, are not always completely documented for each case. In respect to reports submitted to the Netherlands Pharmacovigilance Centre, no differences in risk factors seem to exist between labelled and off-label indications.

The number of reports in which the presence of hereditary factors like Factor-V-Leiden deficiency or Activated Protein C (APC) resistance, decreased Protein S or C levels, or increased homocysteine level has been mentioned is relatively low. For instance, it is known that approximately 8% of the population has a Factor-V-Leiden deficiency, whereas in our dataset only 14 (4.8%) out of 294 reports with a known indication mention this factor. Factor V Leiden is the most common cause of inherited thrombophilia in Caucasian populations, accounting for 40 to 50 percent of cases. The prothrombin gene mutation, deficiencies in protein S, protein C, and antithrombin account for most of the remaining cases. The total incidence of an inherited thrombophilia in subjects with a deep vein thrombosis ranges from 24 to 37 percent overall, compared with about 10 percent in controls [7].

In 31 (10%) out of 309 cases a delay between the onset of the first symptoms and first diagnosis has been mentioned, meaning the thromboembolic ADR was initially not recognized as such by either the patient or their healthcare professional.

Over time there have been changes in the reimbursement status of oral contraceptives on the Dutch market. For instance, since January 1st 2004 contraceptives where no longer reimbursed for women older than 21 years in the Netherlands. Because cyproterone/ethinylestradiole is indicated for the treatment of acne and not primary as a contraceptive, this drug was still reimbursed. In October 2005 Stichting Farmaceutische Kengetallen (SFK) reported that since the reimbursement change for the contraceptives, the use of cyproterone/ethinylestradiole had increased by 3% [7]. Although this could possibly entail that more women used cyproterone/ethinylestradiole for the off-label indication contraception, it is not possible to make a direct link between this information and the number of reports in the Lareb database.

In the SmPC [3] is advised to stop treatment 3 to 4 months after the condition for which cyproterone/ethinylestradiol was prescribed has disappeared. In the reports Lareb received, women have sometimes used cyproterone/ethinylestradiol for a period of years while it is unknown if the use was still indicated according to the SmPC.

Media attention for the association between cyproterone/ethinylestradiol and thromboembolism, has an effect on the rate of adverse drug reaction reporting, leading to a so called 'notoriety-bias' [8]. Following the extensive media attention concerning this association, the number of reports increased rapidly.

For a proportion of the reported cases, the actual ADR occurred years in the past. Recall bias could therefore be present. This is shown in figure 2, in which the year in which the ADR occurred is shown, corrected for the number of prescriptions. The latter data origin from the council of health insurances (CVZ) in the Netherlands and is only available from 1995 till 2011. The analysis shown is based on all data present in the database at March 31 2013, including the high number of reports submitted in the last two months. The relative number of report is higher in recent years, which is indicative for the existence of recall bias. ADRs who occurred in het past are less likely to be reported.

The reported thromboembolic ADRs are a known risk related to the use of cyproterone/ethinylestradiol. Cyproterone/ethinylestradiole is only authorised for the *treatment of acne, seborrhea or light hirsutism in women of childbearing age if hormonal treatment is considered necessary* [3], however from the reports that Lareb received it is evident that there is a lot of off-label use.

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This signal has been raised on May 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).

Nederlands Bijwerkingen Centrum Lareb
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