NOTIFICATION TO THE PRAC OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC as amended
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 107i of Directive 2001/83/EC as amended to the PRAC made by FRANCE - ANSM

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	Diane 35 µg, coated tablets and all combinations of ethinylestradiol (0.035 mg)/cyproterone acetate (2mg)
Active Substance(s)/Therapeutic class	Ethinylestradiol: 0.035 mg/Cyproterone acetate: 2mg ATC code: G03HB01
Marketing Authorisation Holders in the referring Member State	Bayer Santé (originator product) and other MAHs for the combinations of ethinylestradiol (0.035 mg)/cyproterone acetate (2mg)

Following the announcement of its intention to suspend the marketing authorisation for Diane 35 and its generics at national level, France decided to initiate an Urgent Union procedure and to refer the matter to the PRAC.

In France, the combination cyproterone acetate (2 mg) and ethinylestradiol (0.035 mg) has a marketing authorisation in the treatment of acne but not as a contraceptive.
Diane 35 was authorised in France in 1987 and the therapeutic indication currently approved is: "Treatment of acne in women: the efficacy is moderate and is observed only after several months of treatment".

The French Agency – ANSM performed a benefit-risk review of Diane 35 and its generics in the context of a process of reviewing the national MAs granted before 2005.

Safety Data
The analysis of ADRs reported since 1987, in the French pharmacovigilance database with Diane 35 and its generics showed 125 reports of thromboembolism: 113 reports of venous thromboembolic events (VTE) and 12 reports of arterial thromboembolic events. This includes 4 fatal cases of which 3 pulmonary embolisms and 1 venous cerebral thrombosis.

The analysis of literature regarding venous thromboembolism risk *(Lidegaard and all., 2011)* showed that :

- In women without oral contraceptives, the risk of VTE was 3.7 cases per 10 000 women followed for 1 year ;
- In women taking Diane 35, this risk is multiplied by 4: RR = 4.10 [3.37-4.99].

This risk of 3.7 cases per 10 000 women without oral contraceptives followed for 1 year is multiplied by 4 in women receiving Diane 35.

Taking into account the wide use of Diane exposing an important number of women to this risk with potential fatal consequences, the situation has been considered as not acceptable by the French Agency.

Data on drug utilisation in France
In 2012, the sales figures of Diane 35 and its generics are approximately 4.1 millions of blisters: generics represent 79% of the total sales volume.
This corresponds to the estimated number of 315 000 women treated with Diane 35 and its generics in France in 2012.

Sales data by prescribers in France are distributed as follows:
- General practitioners (GP) : 60%
- Gynecologists: 37%
- Dermatologists: 3%

Prescription data in France are distributed as follows:
- GP: 40% of prescriptions in acne and 54% in contraception
- Gynecologists: 7% of prescriptions in acne and 75% in contraception
- Dermatologists: 95.5 % of prescriptions in acne.

Thus, the majority of the prescriptions concern the use in women for contraception which reveals an important off-label use despite 2 recommendations published in France in 2004 and 2007 on this topic.

Efficacy

Several clinical studies show that Diane 35 is an effective treatment of acne. In 2012, the Cochrane Collaboration published a review of COC pills for treatment of acne. This review identified 7 studies with Diane 35 out of which 4 were randomized and double-blind.
The Cochrane conclusion is that Diane 35 is as effective as COC in acne. There is no clear data to reserve Diane 35 in severe or refractory acne.

Although there is a presumption of efficacy for Diane 35 as a contraceptive, data provided by the MAH do not allow to accurately assess the contraceptive efficacy. The design of the study provided does not meet the current European guidelines for assessing the contraceptive efficacy of a drug. It is therefore not possible to calculate the Pearl Index according to the official requirements.

Conclusion

Following the evaluation of available data, the French Agency – ANSM estimates that the benefit / risk ratio of Diane 35 and its generic is negative in the treatment of acne, especially in view of the risk of venous and arterial thromboembolism with fatal cases and considering that acne is usually a non severe disease that can be treated by other medicines. In addition, the extensive use of these drugs as contraceptives is not consistent with the marketing authorisation and their efficacy as a contraceptive has not been demonstrated by appropriate clinical studies.
Therefore, the French Agency has decided to initiate a national procedure to suspend the marketing authorisation for Diane 35 and its generics.
This suspension of marketing authorisation will be effective within the next three months in order to give enough time to patients to be switched under an alternative product. In the meantime, healthcare professionals in France are asked not to initiate a new treatment or renew one with Diane 35 or its generics.

In view of the above, the French Agency – ANSM requests the PRAC to give a recommendation under the Urgent Union procedure in accordance with article 107i of the Directive 2001/83/EC, as amended on whether the marketing authorisations for Diane 35 and its generics in all indications approved in Europe should be maintained, varied, suspended or revoked, in the interest of all patients in the EU.

Signed Le Directeur Général [redacted]

Date 04 FEV. 2013