

**NOTIFICATION TO THE PRAC OF A REFERRAL UNDER ARTICLE 31 OF
DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051**

This notification is an official referral under Article 31 of Directive 2001/83/EC to the PRAC made by France- ANSM

<Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)>	Oral contraceptives : - desogestrel, gestodene, norgestimate containing products - drospirenone, chlormadinone, dienogest, nomegestrol as progestins containing products - etonorgestrel (vaginal ring) - norelgestromine (patch)
<Applicant(s)/Marketing Authorisation Holder(s)> <In the referring Member State>	

France considers that it is in the interest of the Union to refer the above mentioned range of medicinal products to the PRAC.

Venous thromboembolism (VTE) is a rare (about 20 cases per 100,000 women in one year of use for levonorgestrel-containing COCs to 40 cases per 100,000 women in one year of use for desogestrel/gestodene/drospirenone-containing COCs) and well-known effect of combined oral contraceptives (COC) since their approvals. VTE is fatal in 1-2% of cases.

Since 2001, VTE has been identified as more frequent for the desogestrel, gestodene, norgestimate containing products of oral contraceptives compared to levonorgestrel containing products. In 2011, a similar increase VTE risk was identified for the drospirenone-containing products. The SPC of these products reflects this risk.

Although the absolute risk remains small, the relative risk of VTE is however doubled for the desogestrel, gestodene, norgestimate containing products and those containing drospirenone comparing with levonorgestrel containing products.

For drospirenone, chlormadinone, dienogest, nomegestrol as progestins containing products, the level of risk of VTE compared with levonorgestrel containing products is not yet characterized in the SPC due to their recent marketing authorizations.

After the PhVWP 2011 risk assessment for the oral contraceptives containing drospirenone, the French agency performed a market analysis showing that :

- COC remain in France the first contraceptive for women, with 5 millions of users
- Half of them are taking a second generation COC
- The other half are taking a - desogestrel, gestodene, norgestimate or drospirenone, chlormadinone, dienogest, nomegestrol containing products although the majority of these products is not reimbursed and despite the recommendations provided to the prescribers.

Therefore, considering:

- The doubling in the incidence of venous thrombosis and thus the doubling in the incidence of pulmonary embolism fatal events.
- The similar arterial risk (i.e. myocardial infarction and stroke) across the various types of progestins in the COC as demonstrated in a recent pharmaco-epidemiological study

(Lidegaard 2012).

- The absence of scientific data supporting that desogestrel, gestodene, norgestimate or drospirenone, chlormadinone, dienogest, nomegestrol as progestins containing products differ in their efficacy and/or tolerability versus second generation COC.

and despite the fact that :

- the information is clearly stated in section 4.4 (special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC of these products.

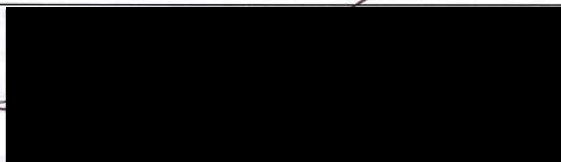
- the information of users and health care professionals through press releases, DHPC and recommendations have been sent or posted since 2001 by National and European authorities.

VTE and arterial risk should be further considered and discussed in the assessment of benefit/risk ratio of desogestrel, gestodene, norgestimate or drospirenone, chlormadinone, dienogest, nomegestrol as progestins containing products compared for VTE risk to levonorgestrel containing products. In addition, this assessment should also be extended to etonorgestrel containing product (vaginal ring) and to norelgestromine (patch)

France considers that the benefit-risk of desogestrel, gestodene, norgestimate and drospirenone, chlormadinone, dienogest, nomegestrol as progestins containing products used in a first line indication as contraceptive is clearly negative and hence the indication of these products should be restricted to second line (i.e. after the use of levonorgestrel containing products).

In view of the above and as some preliminary information provided by other MS shows that our situation of high prescribing volumes is not isolated and hence, in the interest of the Union, the ANSM requests the PRAC to give a recommendation under Article 31 of Directive 2001/83/EC on whether the indication of these products should be restricted and/or any other regulatory measures taken.

Signed:



05 FEB. 2013

Date:

Pr Dominique MARANINCHI