The European Agency for the Evaluation of Medicinal Products
Post-authorisation evaluation of medicines for human use

London, 28 September 2001
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Dear Health Care Professional Letter on 3rd Generation COCs

Re: Combined oral contraceptives containing desogestrel or gestodene

The Committee for Proprietary Medicinal Products (CPMP), the scientific committee for medicines for human use of the European Agency for the Evaluation of Medicinal Products (EMEA), has today published the outcome of its assessment on the risk of venous thromboembolism associated with the use of so-called "third generation" combined oral contraceptives (COCs) containing as progestin desogestrel or gestodene (mono-, bi- or tri-phasic formulation).

The CPMP assessment is the result of an ongoing review which began in 1995, based on three independent epidemiological studies that indicated an increased risk of venous thromboembolism associated with the use of COCs containing desogestrel or gestodene, compared to COCs containing the progestin levonorgestrel.

The EMEA previously issued CPMP position statements in 1995 and, taking into account newly emerging data, in 1996 and 1997. Further to the initial studies, the CPMP has evaluated additional epidemiological studies and studies on haemostatic mechanisms. The CPMP has taken into account all available new information up to mid-September 2001 in preparing this assessment.

On the basis of the overall information, the CPMP concludes in its public assessment report that:

Venous thromboembolism (VTE) is a rare, but serious side effect associated with any type of COCs.

The level of risk of VTE is low and overall the balance of benefits and risks remains favourable with all available COCs.

This risk is highest within the first year a woman ever uses a COC of any type.

- Evidence suggests there is a small increased risk of VTE after taking COCs containing at least 30µg of ethinylestradiol in combination with desogestrel or gestodene compared with those COCs containing levonorgestrel with the same amount of ethinylestradiol. The estimates of the overall relative risk for VTE for these COCs, compared with levonorgestrel containing COCs, varied considerably between epidemiological studies. On the basis of a careful evaluation of all available data, the best estimate of the relative risk is in the range of 1.5 to 2.0.

- For COCs containing desogestrel with 20µg of ethinylestradiol, the available epidemiological data do not suggest a lower VTE risk than for those containing 30µg of ethinylestradiol.

- There are currently no epidemiological studies comparing COCs containing gestodene and 20µg of ethinylestradiol to COCs containing levonorgestrel. However, since no difference in VTE risk between desogestrel and gestodene was observed in studies investigating formulations with 30µg of ethinylestradiol, by analogy it can be expected

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that there will be no difference in VTE risk between COCs containing gestodene and either 20 or 30µg of ethinylestradiol.

- There are currently no data on the VTE risk for COCs containing less than 20µg of ethinylestradiol.

- There are currently insufficient data on the risk of venous thromboembolism for COCs containing progestins other than levonorgestrel, desogestrel or gestodene.

The risk of VTE can be usefully expressed as follows:

- Healthy women between 15 and 44 years old not taking COCs: 5 to 10 cases per 100,000 women-years

- Women taking COCs containing less than 50µg ethinylestradiol with levonorgestrel: 20 cases per 100,000 women-years of use

- Women taking COCs containing at least 20µg of ethinylestradiol in combination with desogestrel or gestodene (mono-, bi- or tri-phasic formulation): 30 to 40 cases per 100,000 women-years of use.

- It should however be noted that the risk associated with all COCs is lower than in pregnancy which is around 60 per 100,000 pregnancies.

There is no consistent evidence showing a difference in the tolerability between the different types of COCs.

There is no evidence for a difference in the risk of myocardial infarction (women below the age of 35 years) or in the risk of stroke between COCs containing desogestrel or gestodene compared to COCs containing less than 50µg of ethinylestradiol with levonorgestrel.

Therefore, the CPMP recommends:

There is no reason for women currently using any brand of a COC to stop taking it on the basis of these findings.

When prescribing a COC for a woman for the first time, the following should be taken into account: The impact of the relative risk of VTE of COCs containing at least 20µg of ethinylestradiol in combination with desogestrel or gestodene (mono-, bi- or tri-phasic formulation) compared to COCs containing less than 50µg ethinylestradiol with levonorgestrel on the number of additional cases would be greatest in the first year a woman ever uses a COC.

Please let us remind you that:

Concerning the risk of VTE, contraindications for use of COCs include a history of, or existing venous thromboembolic diseases. COCs are also contraindicated in case of a history of, or recent myocardial infarction or stroke.

Known risk factors to take into account when prescribing COCs include obesity, the post-partum period, recent surgical operation and family history of venous thrombosis. Furthermore, discontinuation of COCs should be considered in the event of surgical operation or immobilisation for any reason.

Following consideration of all options for safety measures, changes to the relevant sections of the Summary of Product Characteristics (i.e. product information) of the national marketing authorisations for COCs are recommended by the CPMP.

For more details, please connect to the website of your national agency or the EMEA website http://www.emea.eu.int .

Annex: List of website addresses:

Austria http://www.bmsg.gv.at

Belgium http://www.afigp.fgov.be

Denmark http://www.laegemiddelstyrelsen.dk

Finland http://www.nam.fi

France http://agmed.sante.gouv.fr

Germany http://www.bfarm.de

Greece http://www.ypyp.gr

Ireland http://www.imb.ie

Italy http://www.sanita.it/sanita

Luxembourg http://www.etat.lu/MS

The Netherlands http://www.cbg-meb.nl

Portugal http://www.infarmed.pt

Spain http://www.msc.es

Sweden http://www.mpa.se

United Kingdom http://www.mca.gov.uk

Iceland http://www.lyfjastofnun.is

Norway http://www.legemiddelverket.no