The European Agency for the Evaluation of Medicinal Products
Technical Co-ordination Unit

London, 27 October 1995
CPMP/PhV/690/95, Rev.5

CPMP Assessment on the Basis of the ad hoc Expert Working Group concerning Gestodene or Desogestrel-containing products and the risk of cardio-vascular disorders

Summary of Facts

The attention of the CPMP was drawn by the British and German Members to three independently conducted epidemiological studies about to be completed or published.

- a multinational study carried out by Dr Farley, Dr Meirik, Dr Poulter *et al* (World Health Organisation): Effect of Different Progestogens in Low Oestrogen Dose Oral Contraceptives on Venous Thromboembolic Disease
- a cohort study based on record linkage carried out by Prof H. Jick *et al* (Boston University Medical Center): Risk of Idiopathic Nonfatal Venous Thromboembolism Comparing Combined Oral Contraceptive Preparations with Differing Progestogen Components
- a transnational study carried out by Prof W.O. Spitzer *et al* (Potsdam Institut of Pharmacoepidemiology and Technology Assessment): Oral Contraceptives and the Health of Young Women

Thus on 18 October 1995, the CPMP held a hearing with the investigators involved in the three studies.

As a consequence the CPMP members were asked to analyse the data circulated and forward their comments to the CPMP Secretariat (H/CPMP/657/95) and national competent authorities were asked to wait until common agreement be reached by the CPMP before taking any national position.

The three main companies concerned were asked to provide EMEA with any scientific material related to the risk of "third generation" oral contraceptive use (containing gestodene or desogestrel) (H/CPMP/658/95) and were invited for a hearing in the afternoon of 26 October to the CPMP ad hoc Working Group.

An ad hoc working party meeting with national experts in pharmacovigilance took place on 26 October 1995 including a presentation by the investigators of the studies and the hearing of the companies (Organon, Schering, Wyeth) to continue the analysis of the data.

Results of the CPMP ad hoc Expert Working Group

The scientific discussion of the European experts in pharmacovigilance (clinical and experimental pharmacology, pharmacoepidemiology, special clinical experts and experts in regulatory affairs) reported to the CPMP can be summarised as follows :

1. to date there is no evidence to draw conclusions that the cardiovascular mortality is different for desogestrel- or gestodene-containing combined oral contraceptives compared to levonorgestrel-containing combined oral contraceptives;

2. the three epidemiological studies indicate a somewhat greater risk of non-fatal venous thromboembolic events (close to a 2-fold increase) for desogestrel- or gestodene-containing products compared to levonorgestrel-containing products or other combined oral contraceptives: this would correspond to an excess of about 10 cases of thromboembolism per hundred thousand women per year. It cannot be excluded that inherent biases contribute to the differences. Selective prescribing was a potential confounder in all three studies but attempts were made in the analysis to eliminate this effect. There is no plausible biological explanation for the differences;

3. the risk of venous thromboembolic events with all combined oral contraceptives is still substantially less than the risk of venous thromboembolic events in pregnancy;

4. there is no apparent difference in the risk of stroke between the desogestrel- or gestodene- containing products and levonorgestrel-containing products or other combined oral contraceptives;

5. a lesser risk for acute myocardial infarction has been suggested for gestodene- or desogestrel-containing products but to date the information is insufficient to draw conclusions. Further work is in progress. Data coming from the investigator teams will include further analyses of the data. Furthermore results are awaited from one on-going study;

there is no evidence that from a public health point of view the other major benefits or risks (e.g. reliability of contraception) are different for these products. For the individual there may, however, be benefits in quality of life.

Annex

In their detailed scrutiny of the results of the investigators the experts conclude:

- there is no evidence that differential misclassification is operating in the WHO study and is unlikely to be relevant in the others;
- differential ascertainment of venous thromboembolic events could lead to an apparent increased relative risk for combined oral contraceptives as a whole. It would not explain the observed differences between desorgestrel- or gestodene-containing products compared to levonorgestrel-containing products or other combined oral contraceptives;
- the differences between the products remained even after restriction of the analysis to first ever users.