The European Agency for the Evaluation of Medicinal Products
Human Medicines Evaluation Unit

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CPMP/374/96

POSITION STATEMENT OF THE CPMP ON ORAL CONTRACEPTIVES CONTAINING DESOGESTREL OR GESTODENE

Background Summary

At the October 1995 CPMP meeting Committee members from the UK and Germany addressed the issue of combined oral contraceptives, especially Gestodene- and Desogestrel-containing oral contraceptives and deep vein thrombosis, based on data from three independently conducted epidemiological studies which were published in December 1995 and January 1996.

During its plenary session the CPMP held a preliminary discussion and heard investigators involved in these studies. An ad hoc group was set up and a meeting was convened for 26 October 1995, when the three main companies concerned which were invited for a hearing gave their joint point of view.

On 27 October 1995 the CPMP, following an extra meeting, released their position statement on oral contraceptives containing Desogestrel or Gestodene (CPMP/PhV/696/95) requesting the three companies to provide further data for review no later than six months from the date of the position statement.

On 16 December 1995 a further study on the risk of deep vein thrombosis associated with oral contraceptive use was published by an investigator team of the Netherlands.

On 31 January 1996 the companies concerned (Wyeth, Schering, Organon) submitted a joint report assessing the safety of Desogestrel- or Gestodene-containing oral contraceptives with regard to venous thromboembolism and acute myocardial infarction.

On 11 April 1996 the three companies mentioned above presented supplementary information on Desogestrel- or Gestodene-containing oral contraceptives and cardiovascular effects.

The CPMP discussed the matter during its plenary meeting on 16, 17 and 18 April 1996. Following discussion the Committee agreed the following.

Position Statement

Venous thromboembolism is a serious but rare risk associated with the use of oral contraceptives. Because this complication is rare it is difficult to study and estimates of its incidence are not precise.

All studies hitherto presented to the CPMP indicate that the risk for venous thromboembolism is higher in users of Desogestrel- or Gestodene-containing oral contraceptives than in users of Levonorgestrel-containing oral contraceptives. The impact of biases and confounders on the difference still can not be fully evaluated.

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Data from studies of haemostatic factors indicate differences between Levonorgestrel-containing oral contraceptives (so called second generation) and Desogestrel- or Gestodene-containing oral contraceptives (so called third generation) but these are of unknown clinical relevance as yet.

The requested pooled analyses of acute myocardial infarction have not yet been performed and currently available data do not allow a conclusion that Desogestrel- or Gestodene-containing oral contraceptives have an advantage over Levonorgestrel-containing oral contraceptives in this respect.

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 Desogestrel- or Gestodene-containing oral contraceptives. For the individual there may, however, be benefits in quality of life.

Factors other than the 'generation' of pill used, such as heredity and immobilisation also have an important role for the occurrence of venous thromboembolic events.

To further evaluate to what extent biases and confounding have contributed to the difference in risk of venous thromboembolic events in users of Desogestrel- or Gestodene-containing oral contraceptives and Levonorgestrel-containing oral contraceptives respectively and to clarify whether there are differences in effect on myocardial infarction rates the CPMP will request further analysis of the data presented and carefully follow the ongoing studies.

The following message to Doctors/Users is still relevant:

- Contraindications of combined oral contraceptives include a history of, or existing venous thromboembolic, cerebrovascular or cardiovascular diseases.

- Known risk factors for venous thromboembolism include a family history of venous thrombosis, obesity (as defined as a body mass index greater than thirty - measured as weight in Kg/m^2) or varicose veins.

- The risk of venous thromboembolic events with all combined oral contraceptives is still substantially less than in pregnancy.

In addition Doctors/Users should also be reminded of:

- Discontinuation of oral contraceptives should be seriously considered in situations that are associated with an increased risk of venous thromboembolic events, such as immobilisation, major trauma and major surgery.

- Due to the vague symptomatology of many venous thromboembolic events, discontinuation of oral contraceptives should be considered in cases of suspected thrombosis in patients on oral contraceptives, while diagnostic interventions are being pursued.

- In cases of an uncertain diagnosis of venous thromboembolic events, alternative contraceptive strategies should be discussed with the patient, since the event may represent a first signal of oral contraceptive associated thrombophilia.

The CPMP asked the EMEA Secretariat to communicate this position statement to the 15 national competent authorities responsible for the marketing authorisation of these products, the three companies mentioned above, and the European Commission.