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

CPMP/045/97
24-01-97

PRESS RELEASE

The Committee for Proprietary Medicinal Products (CPMP) held its 23rd plenary meeting on 21-22 January 1997 at the EMEA.

Centralised Procedures

The Committee adopted by consensus a positive opinion for a medicinal product (Part B) containing a new active substance for substitution maintenance treatment of opiate addiction. This now concludes the centralised review of the 18 ex-concertation procedures which were transfered to the EMEA in January 1995. The Opinion will be forwarded to the Commission in due time.

The Committee also adopted by consensus a positive Opinion for a centralised Type II Variation procedure concerning a recent Community Marketing Authorisation.

The European Commission, since the December 1996 meeting, granted a marketing authorisation for Evotopin (topotecan). The corresponding European Public Assessment Report (EPAR) will be made available by the EMEA.

Nine new applications for 8 active substances have been assigned to Rapporteurs and Co-Rapporteurs under the Centralised Procedure (3 List A and 6 List B).

Detailed figures are given in Annex I+II.

Pharmacovigilance

Following the report of an Ad-Hoc Working Group the CPMP adopted a Position Statement on oral contraceptives containing desogestrel or gestodene which modifies the previous statement which was issued on 17 April 1996 (Annex III).

Mutual Recognition

The Committee noted that 7 new mutual recognition procedures have been recently finalised as well as 11 type I and 4 type II variation procedures.

There were no new arbitration referrals.

The current status as at 20 January 1997 of procedures under mutual recognition is as follows:

New applications finalised	New applications pending	Type I variations finalised	Type I variations pending	Type II variations finalised	Type II variations pending	Arbitrations referred to CPMP*
101	23	78	7	95	62	3

* two for full applications, one for variations

Scientific Advice

The CPMP adopted 2 new scientific advice by consensus.

Working Parties

The CPMP heard reports from its Quality, Biotechnology, Safety, Efficacy and Pharmacovigilance Working Parties.
The ICH Guideline Q5D "Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (CPMP/ICH/294/95) was released to interested parties for consultation until July 1997.

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This press release and other documents are available on the Internet (http://www.eudra.org/emea.html).

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ANNEX I to **CPMP - Jan. 97**
Press Release
Rev. 1

	EX - CONCERTATION		NEW CENTRALISED		TOTAL *
	Part A	***Part B***	***Part A***	***Part B***	
APPLICATIONS SUBMITTED SINCE 1.1.95	9	9	22	34	74
WITHDRAWN	0	4	0	2	6
REVIEW ONGOING	0	0	11	18	29
OPINIONS GIVEN BY CPMP	9	5	11	14	39
MARKETING AUTHORIZATION GRANTED BY COMMISSION	9	4	3	12	28

** 39 Opinions corresponding to 34 substances*

	PENDING		FINAL		TOTAL
	Part A	***Part B***	***Part A***	***Part B***	
VARIATIONS TYPE I	11	3	8	11	33
VARIATIONS TYPE II	1	8	3	7	19
SCIENTIFIC ADVICE	6		26		32

Updated 24 January 1997

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ANNEX II to **CPMP - Jan. 97**
Press Release

Medicinal Products granted a Community Marketing Authorisation under the Centralised Procedure
Status: 22 January 1997

Product) Brandname) INN) Part A/B	**Company** a) Name b) Origin	**Therapeutic Area** a) ATC b) Indication	**Presentation** a) Form b) Dose c) Number of Presentations	**EMEA/CPMP** a) Validation b) Opinion c) Active Time d) Clock stop	**Commission** a) Date of decision b) Date of notification c) OJ No.
) **Evotopin**) topotecan) Part B	a) Beecham Group b) USA	a) L01X X17 b) Ovary metastatic carcinoma	d) Powder for infusion e) 4 mg f) 2 Presentations	e) 16.01.96 f) 19.07.96 g) 154 Days h) 28 Days	d) 09.12.96 e) f)

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ANNEX III to **CPMP - Jan. 97**
Press Release

London, 22 January 1997
CPMP/073/97 Rev.2

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 subsequently 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 adhoc 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 a 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 involved (Wyeth Ayerst Ltd, Schering AG & NV 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.

On 16, 17 and 18 April 1996, the CPMP discussed the matter during its plenary meeting, and released a position statement (CPMP/374/96).

On 22 May 1996 at the CPMP's request, an ad-hoc expert meeting was organised to follow the ongoing studies and analysis.

In its position statement dated on 17 April 1996, the CPMP considered that data received at that time from studies of haemostatic factors indicate differences between oral contraceptives containing desogestrel or gestodene and those containing levonorgestrel but these are of unknown clinical significance. The available data on comparative haematological parameters consisted of a substantial number of small clinical trials which do not, individually, have adequate statistical power to detect significant differences in effect

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between the drugs studied. CPMP therefore requested that a large clinical trial should be initiated specifically to address the question of differences between combined oral contraceptives containing new "third generation" gestagens and older "second generation" gestagens.

The CPMP also requested a randomised double-blind study comparing combined oral contraceptives containing desogestrel or gestodene with combined oral contraceptives containing levonorgestrel aiming at illustrate differences in the profiles of common side effects.

Furthermore, after an Adhoc Expert Group held on 22 May 1996, a letter was sent (on 10 June 1996) to the investigators of the six publications listed hereafter in the reference documents (Dr NR Poulter, Dr W Spitzer, Dr O Lidegaard, Dr O Meirik and Dr H Jick) in order to obtain further information on the results of their studies considering:
- possible confounding variables;
- possible biases;
- further subgroup analyses (sub-groups of users taking [a] OCs containing norgestimate, [b] desogestrel and 20 micrograms of ethinyloestradiol, [c] tri-phasic OCs);
- follow-up of subjects excluded (numbers of subjects excluded from the study for each of the stated exclusion criteria).

On 17 December 1996, the Adhoc Expert Group met in order to discuss an update pharmacovigilance assessment report on cardiovascular risks and the use of the third generation oral contraceptives prepared by the Rapporteur country. The report included an assessment of newly submitted position papers of the companies and the responses from the investigators of the previous studies.
Following the letter sent to the Marketing Authorisation Holders on 16 July 1996, a protocol synopsis had been provided for a study of hemostatic parameters under different OCs. The protocol was discussed and feed back will be provided to the companies.

The conclusion of the Adhoc Expert Group was that the new data do not result in a need of major modifications on the CPMP position statement on 17 April 1996. However, the CPMP position statement needs to be updated.

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.

In the seven studies hitherto presented to the CPMP the risk was higher in women who used desogestrel or gestodene containing oral contraceptives (so called third generation) than in women using so-called second generation oral contraceptives containing levonorgestrel (the majority), lynestrol or norethisterone. The increase in the observed risk was about two-fold in the first four case-control studies, and statistically significant in three of them. In the three following studies, the difference in risk was less, one has been reported as an interim analysis, one reached statistical significance, the other not.

The CPMP and the investigator teams have made efforts to re-analyse the early studies seeking additional control of bias and confounders. This has not been fully possible since all relevant information were not available to the investigators. Hence, the impact of biases and confounding on the observed differences cannot be fully evaluated.

In Europe, there is no unequivocal evidence that the use of combined oral contraceptives containing 30-40 µg ethinyl-estradiol increases the risk of stroke in young women (<35 years) unless they smoke or have hypertension. There is no evidence that the risk of stroke is influenced by dose or type of progestagen in combined oral contraceptives.

The presently available analyses of the risk for acute myocardial infarction do not allow clear conclusions regarding differences between desogestrel/gestodene containing and levonorgestrel containing oral contraceptives.

Data from studies of haemostatic factors indicate differences between levonorgestrel-containing oral contraceptives and desogestrel- or gestodene-containing oral contraceptives but these are of unknown clinical relevance as yet.

A comparative study on haemostatic factors will be performed by the Marketing Authorisation Holders with the aim of identifying differences of possible clinical significance between desogestrel, gestodene, and levonorgestrel containing oral contraceptives.

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 than for levonorgestrel containing oral contraceptives. For the individual there may, however, be differences in the quality of life and the CPMP have requested a comparative study to investigate this further.

The following message to Prescribers/Users, agreed by all members of the CPMP, is still relevant:

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

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

In addition Prescribers/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.

- Alternative contraceptive strategies should be discussed in case of a discontinuation of oral contraceptives (because of an increased risk of venous thromboembolic events or because thrombosis is suspected), as the level of risk related to pregnancy is twice higher than the one related to oral contraceptives.

Additional measures have been taken in the Member States and may henceforth be taken. In such cases, the CPMP should be informed through the EMEA.

The CPMP asked the EMEA Secretariat to communicate this position statement to the fifteen National Competent Authorities responsible for the marketing authorisation of these products, the three companies mentioned above and the European Commission. The CPMP asked the EMEA Secretariat to make this position statement public.