The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

February 2004
CPMP/1390/04

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)
OPINION FOLLOWING AN ARTICLE 7(5) REFERRAL

Laurina and related invented names

International non-proprietary name (INN): Desogestrel/ ethinlestradiol

BACKGROUND INFORMATION

Laurina (and related invented names), which contains the active ingredients desogestrel and ethinylestradiol is a triphasic combined oral contraceptive.

Combined oral contraceptives have been subject to major scrutiny because of concerns regarding the adverse effects of these products and their use in essentially healthy women. In September 2001, the CPMP issued a public assessment report on the relative risks of VTE and made recommendations on the wording of warnings about VTE which should be included in the Summaries of Product Characteristics (SPCs) of all combined oral contraceptives. This public assessment report, although it specifically reviewed the risk of VTE in "3rd generation" COCs compared with "2nd generation" COCs, included a section on acute myocardial infarction as at one time it had been thought that the 3rd generation COCs might be less prone to cause this than earlier COCs. The Public Assessment Report concluded that there was no evidence that 3rd generation COCs significantly altered the risk of acute myocardial infarction compared with earlier COCs.

The Marketing Authorisation Holder (MAH) of Laurina applied for a renewal of the Marketing Authorisation in September 2001 before the release of the CPMP Public Assessment Report. During this renewal procedure, the MAH made the commitment to add, in a separate Type II variation, the VTE warnings according to the recommendations of the CPMP. The resulting Type II variation, which was the subject of this referral, requested a wording on VTE risk which was not strictly in accordance with that proposed by the CPMP. In addition, the MAH requested the inclusion of the results of recent epidemiological findings on arterial thrombosis, and in particular acute myocardial infarction (AMI) which they thought suggested that there was not a significantly increased risk of AMI in users of "third generation" combined oral contraceptives compared with non-users. During the procedure, the MAH revised the wording to suggest that the risk of AMI with 3rd generation COCs may be lower than in users of 2nd or 1st generation COCs. The Reference Member State (Finland) was prepared to accept the modified wordings agreed with the MAH at the end of the variation procedure, however Germany had strong objections and referred the issue to the CPMP.

The referral procedure started on 21 November 2002. The Rapporteur and Co-Rapporteur appointed were Dr. F. Lekkerkerker and Dr P. Arlett, respectively. Written explanations were provided by the Marketing Authorisation Holders on 13th February and 18th July 2003 with an addendum on 24th July 2003.

Based on evaluation of the currently available data and the Rapporteurs' assessment reports, the CPMP considered that the variation with respect to a differential risk of acute myocardial infarction could not be granted. However, changes to the information in the SPC on the risk of venous thrombo-embolism and arterial thrombosis were accepted. The CPMP therefore adopted an opinion on 25 September 2003 recommending the above variation to the Marketing Authorisations together with an amended Summary of Product Characteristics.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

The competent authorites of the Member States will continue to keep the product under regular review.

A list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II, together with the amended Summary of Product Characteristics in Annex III.

The final opinion was converted into a Decision by the European Commission on 5th February 2004

* Notes: The information given in this document and Annexes reflect only the CPMP Opinion dated 25 September 2003. The Member States' competent authorities will continue to keep the product under regular review.

ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS, PACKAGING AND PACKAGE SIZES IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
AUSTRIA	Organon GesmbH Siebenbrunnengasse 21/D/IV A-1050 Wien Austria	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
AUSTRIA	Organon GesmbH, Siebenbrunnengasse 21/D/IV A-1050 Wien Austria	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
BELGIUM	Organon Europe B.V. Kloosterstraat 6 5349 AB Oss, The Netherlands	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
BELGIUM	Organon Europe B.V. Kloosterstraat 6 5349 AB Oss, The Netherlands	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
DENMARK	N.V. Organon, Kloosterstraat 6 P.O. Box 20 5340 BH Oss The Netherlands	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
DENMARK	N.V. Organon, Kloosterstraat 6 P.O. Box 20 5340 BH Oss The Netherlands	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
FINLAND	N.V. Organon, Kloosterstraat 6 P.O. Box 20 5340 BH Oss The Netherlands	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
FINLAND	N.V. Organon, Kloosterstraat 6 P.O. Box 20 5340 BH Oss The Netherlands	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
GERMANY	Organon GmbH Mittenheimer Str. 62 D-85764 Oberschleissheim, Munich Germany	Novial	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
GERMANY	Organon GmbH Mittenheimer Str. 62 D-85764 Oberschleissheim, Munich Germany	Novial 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
GREECE	Organon Hellas SA 122 Vouliagmenis Av. Helliniko 16777 Athens Greece	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
GREECE	Organon Hellas SA 122 Vouliagmenis Av. Helliniko 16777 Athens Greece	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
IRELAND	Organon (Ireland) Limited PO Box 2857 Drynam Road Swords Co. Dublin Ireland	Novial	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
IRELAND	Organon (Ireland) Limited PO Box 2857 Drynam Road Swords Co. Dublin Ireland	Novial 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
LUXEMBOURG	Organon Europe B,V, Kloosterstraat 6 5349 AB Oss, The Netherlands	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets
PORTUGAL	Organon Portuguesa - Produtos Químicos e Farmacêuticos, Lda. Avenida Conde de Valbom, n.º 30 - 2º 1069-037 Lisboa Portugal	Laurina	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets 6 sachets x 1 blister x 21 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
PORTUGAL	Organon Portuguesa - Produtos Químicos e Farmacêuticos, Lda. Avenida Conde de Valbom, n.º 30 - 2º 1069-037 Lisboa Portugal	Laurina 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets 6 sachets x 1 blister x 28 tablets
SPAIN	Organon Española, S.A Ctra. De Hospitalet, 147-149 Cityparc Ronda de Dalt Edf. Amsterdam 08940 Cornella de Llobregat, Barcelona, Spain	Novial	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 21 tablets 3 sachets x 1 blister x 21 tablets

Member State	Marketing Authorisation Holder	Invented name	Strengths	Pharmaceutical form	Route of administration	Packaging	Package Sizes
SPAIN	Organon Española, S.A Ctra. De Hospitalet, 147-149 Cityparc Ronda de Dalt Edf. Amsterdam 08940 Cornella de Llobregat, Barcelona, Spain	Novial 28	Yellow tablets: 50 micrograms desogestrel, 35 micrograms ethinylestradiol Red tablets: 100 micrograms desogestrel, 30 micrograms ethinylestradiol White tablets: 150 micrograms desogestrel, 30 micrograms ethinylestradiol Placebo tablets: (no active substance)	Film coated tablets	Oral use	Blister (PVC/Alu)	1 sachets x 1 blister x 28 tablets 3 sachets x 1 blister x 28 tablets

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LAURINA AND ASSOCIATED NAMES (SEE ANNEX 1)

Laurina (Laurina/Laurina 28 and associated names) is a triphasic combined oral contraceptive (COC) containing ethinylestradiol and desogestrel (DSG). Laurina is licensed in several European countries on a national basis and also through the Mutual Recognition Procedure on 11th October 2000, with Finland acting as Reference Member State.

Combined oral contraceptives have been subject to major scrutiny because of concerns regarding the adverse effects of these products and their use in essentially healthy women. In 1995 the CPMP established an ad hoc expert group on oral contraceptives following the publication of three papers suggesting an increased risk of venous thrombo-embolism (VTE) in users of "third generation" COCs, which contain the progestagens desogestrel or gestodene, compared with "second generation" COCs containing the progestogen levonorgestrel. In September 2001, the CPMP issued a public assessment report on the relative risks of VTE and made recommendations on the wording of warnings about VTE which should be included in the Summaries of Product Characteristics (SPCs) of all COCs.[1] This public assessment report, although it specifically reviewed the risk of VTE, also included a section on acute myocardial infarction (AMI) as at one time it had been thought that the 3rd generation COCs might be less prone to cause this than earlier COCs. The public assessment report concluded that there was no evidence that the 3rd generation COCs significantly altered the risk of AMI compared with earlier COCs.

The Marketing Authorisation Holder (MAH) of Laurina applied for a renewal of the marketing authorisation in September 2001, prior to the release of the public assessment report. They committed to add, in a separate variation, the VTE warnings according to the wording of the CPMP. The resulting Type II variation, which is the subject of this referral, requested a wording which was not strictly in accordance with that proposed by the CPMP. In addition the MAH requested the inclusion of the results of recent epidemiological findings on arterial thrombosis, and in particular AMI, which they thought suggested that there was not a significantly increased risk of AMI in users of 3rd generation COCs compared with non-users. During the MRP, the MAH revised the wording to suggest that compared with no use, the risk of AMI with 3rd generation COCs may be lower than in users of 2nd or 1st generation COCs.

The RMS was prepared to accept the wordings agreed with the MAH at the end of the variation procedure, however, Germany had strong objections and referred the issue to the CPMP on 23rd October 2002 with additional background information to the referral submitted on 6th November 2002.

The CPMP considered the documentation provided by the MAH and came to the following conclusions:

Acute Myocardial Infarction

The evidence submitted by the MAH was based primarily on published epidemiological studies with some supporting data from lipid analyses in clinical trials. The pivotal paper was a meta-analysis by Spitzer[2] with the epidemiological studies which were the subject of the meta-analysis providing additional evidence; along with a second meta-analysis by Khader[3].

Of the seven studies which were the basis of the Spitzer meta-analysis, only three, the Transnational (TNS)[4], MICA[5] and Ratio[6] were specifically designed and powered to address the differential risk of 3rd and 2nd generation COCs. Of the other studies in the Spitzer meta-analysis, the Lidegaard[7] study was in the form of an abstract of intermediate results, the GPRD[8] study was also in an abstract form and directly compared 3rd versus 2nd generation COC users, the Dunn study[9] was a subset of the MICA study population and had a different definition of cases and controls, whilst the WHO study[10] provided a small number of cases as AMI was not the primary objective of the study.

Table 1:Adjusted OR (95% CI) for the risk of myocardial infarction compared with non-users (except GPRD study)

	TNS[4]	MICA[5]	RATIO[6]	Danish[7]	WHO[10]	GPRD[8]	Dunn[9]
2nd generation	2.99 (1.51-5.91)	1.10 (0.52-2.30)	2.5 (1.5-4.1)	1.9 (0.7-4.9)	1.64 (0.49-5.54)	1.0[a]	2.88 (1.22-6.77)
3rd generation	0.85 (0.30-2.39)	1.96 (0.87-4.39)	1.3 (0.7-2.5)	0.96[b] (0.4-2.29)	0.97 (0.14-6.96)	0.7 (0.1-8.2)	0.83 (0.25-2.81)

[a] GPRD compared users of 3rd vs 2nd generation COCs
[b] Spitzer estimation as OR presented by duration of use in published paper

The MAH argued that in all these studies there was no significant difference between users of 3rd generation COCs and non-users and that, with the exception of the MICA study, the risk was always lower than that for 2nd generation users. The CPMP considered that although the Odds Ratios (OR) for users of 2nd generation COCs was above 1, this was not significant in 3 of the studies and the confidence intervals overlapped those of the 3rd generation COCs. The CPMP was also concerned that the results of the MICA study, which contributed the largest number of cases, were contrary to the other studies and this anomalous result had not been satisfactorily explained.

The CPMP also had concerns regarding the meta-analysis of Spitzer[2]. These concerns related to the inclusion and exclusion of studies from the meta-analysis, the heterogeneity between studies, the possibility of bias and the lack of adjustment for risk factors in some of the studies. The CPMP queried the use of 2 year data rather than 5 year data from the Danish study and also thought that the Dunn study, which was on a subset of the MICA study population, should not have been included. The CPMP felt that given the degree of heterogeneity, a random-effects rather than a fixed effects model should have been used for the analysis.

Table 2 shows the effect of including/excluding studies and changing from a fixed effects to a random-effects model on the results of comparisons between the risk of AMI in users of 3rd vs 2nd generation COCs. The comparison between 3rd and 2nd generation COCs was thought to be most clinically relevant. This shows that the data is affected by inclusion or exclusion of studies and whether a fixed or random effects model is used. This suggests that the results are not robust and depend upon the analysis model used.

Table 2: Effect of including/excluding studies and changing models on the results of comparisons between the risk of AMI in users of 3rd vs 2nd generation COCs.

Analysis	Spitzer	MAH using Spitzer model[a]	MAH using Cochrane model[b]	MAH using Cochrane model[b]	CPMP analysis	CPMP analysis
Model	Fixed – effects			Random - effects		
Studies included	All	TNS, WHO, Ratio MICA	TNS, WHO, Ratio MICA	TNS, WHO, Ratio MICA	All except Danish[7]	All except Dunn with Danish 5yr[11]not 2yr[7] data
3rd vs 2nd generation OR (CI)	0.62 (0.38-0.99)	0.64 (0.38-1.09)	0.64 (0.38-1.10)	0.62 (0.26-1.48)	0.67 (0.35-1.27)	0.77 (0.41-1.44)
Chi^2 (p value)	NR	6.95c (p=0.07)	6.86[c] (p=0.08)	6.86[c] (p=0.08)	NR	8.81[d] p>0.1

[a]Reanalysis by MAH using model and OR employed by Spitzer
[b]Reanalyis by MAH using Review Manager software of the Cochrane collaboration
[c]Q statistic for heterogeneity; df=3 for all comparisons
[d]Qstatistic for heterogeneity; df=4

In addition, although the point estimates are in favour of the 3rd generation COCs, the confidence intervals are too large for a definite conclusion.

The meta-analysis by Khader[3] had results broadly in line with that of the Spitzer[7] meta-analysis but there were concerns over methodology and inclusion of data.

The CPMP therefore considered that the current data did not support the MAH's claim that there was a differential risk for AMI between 2nd and 3rd generation COCs and that the variation with respect to this could not be granted.

Venous thrombo-embolism
The CPMP agreed that the SPC should be changed to reflect the wording of the CPMP public assessment report with regard to the warnings regarding venous thrombo-embolism. The SPC should also be updated with respect to risk factors for venous thrombo-embolism and acute myocardial infarction.

The CPMP supported the proposed changes, agreed during the referral procedure, to strengthen the wording of section 4.3 to prevent use in women with a history of, or predisposition towards arterial or venous thrombosis.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CPMP considered the referral made under article 7(5) of Commission Regulation EC No 541/95, for Laurina and associated names (see Annex 1),
- the CPMP agreed that the current data did not support the finding of a differential risk for AMI between users of 3rd and 2nd generation COCs and that this aspect of the variation should be refused.
- the CPMP agreed that the warnings and contraindications regarding venous thrombo-embolism and risk factors for this and AMI should be included in the SPC

the CPMP has recommended the granting of the variation of the Marketing Authorisation for which the Summary of Product Characteristics is set out in Annex III for Laurina and associated names.

References

1. EMEA Committee for proprietary medicinal products (CPMP). CPMP public assessment report. Combined oral contraceptives and venous thromboembolism. EMEA/CPMP/2201/01 28 September 2001
2. Spitzer WO, Faith J, MacRae K. Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. Hum Reprod 2002; 17: 2307-2314.
3. Khader YS, Rice J, John L, Abueita O. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. Contraception 2003; 68: 11-17
4. Lewis MA, Heinemann LA, Spitzer WO, MacRae KD, Bruppacher R. The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Contraception 1997; 56: 129-140.
5. Dunn NR, Thorogood M, Faragher B, Caestecker de L, MacDonald TM, McCollum C, Thomas S, Mann R. Oral contraceptives and myocardial infarction: results of the MICA case-control study. Mr Med J. 1999; 318: 1579-1584.
6. Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, van der Graaf Y, Rosendaal FR. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001; 345: 1787-1793.
7. Lidegaard O, Edstrom B. Oral contraceptives and acute myocardial infarction: a case control study. Eur J Contracept Reprod Health Care 1996; 1: 74
8. Jick H, Jick SS, Wald Myers M, Vasilakis C. Risk of acute myocardial infarction and low dose combined oral contraceptives. Lancet 1996; 347: 627-628.
9. Dunn NR, Arscott A, Thorogood M. The relationship between use of oral contraceptives and myocardial infarction in young women with fatal outcome, compared with those who survive: results from the MICA case-control study. Contraception 2001; 63: 65-69.
10. Poulter NR, Meirik O, Chang CL, Farley TMM, Kelaghan J, Marmot MG, et al. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multi centre case control study. Lancet 1997; 349: 1202-1209.
11. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and myocardial infarction. A five year nation-wide case-control study. Eur J. Contraception Reprod Health Care 2000; 5(suppl 1): 29

ANNEX III

AMENDED SUMMARY OF PRODUCT CHARACTERISTICS OF THE REFERENCE MEMBER STATE

Note: This SPC is the one that was annexed to the Commission Decision on this Article 7(5) referral for Laurina and related names. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC may not necessarily represent the current text.

1. NAME OF THE MEDICINAL PRODUCT

<*Name of product*>, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<*Name of product*> is a triphasic oral contraceptive of which:

- each yellow tablet contains 0.050 mg desogestrel and 0.035 mg ethinylestradiol;
- each red tablet contains 0.100 mg desogestrel and 0.030 mg ethinylestradiol;
- each white tablet contains 0.150 mg desogestrel and 0.030 mg ethinylestradiol.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The tablets are round, biconvex and 5 mm in diameter. They are coded on one side VR4 (yellow tablets), VR2 (red tablets), TR5 (white tablets) and on the reverse side Organon and a star.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

4.2 Posology and method of administration

How to take *<Name of product>*
Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 21 consecutive days, starting with the yellow tablets for 7 days, followed by the red for 7 days and finally the white for 7 days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

How to start *<Name of product>*
No preceding hormonal contraceptive use [in the past month]
Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from another combined oral contraceptive (COC)
The woman should start with <*Name of product*> preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

Changing from a progestagen-only-method (minipill, injection, implant)
The woman may switch any day from the minipill (from an implant on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion
For breastfeeding women see Section 4.6

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets
If the user is **less than 12 hours late** in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time. If she is **more than 12** hours **late** in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- **Week 1 (yellow tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

- **Week 2 (red tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3 (white tablets)**

The risk of reduced reliability is imminent because of the forthcoming tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the current pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.

Advice in case of vomiting
If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets (see above) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to delay a period
Delaying a period is not an indication for the product. However, if in exceptional cases a period needs to be delayed, the woman should continue with the white tablets from another pack of <*Name of product*> without a tablet-free interval. The extension can be carried on for a maximum of 7 days, until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of <*Name of product*> is then resumed after the usual 7-day tablet-free interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during COC use, the product should be stopped immediately.

- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism)
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, and antiphospholipid antibodies.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under 'Special Warnings and Special Precautions for Use').
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the active substances of <*Name of product*> or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings
If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

1. Circulatory Disorders

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The incidence of VTE is considered to be 5-10 per 100,000 woman years in non-OC users. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.
- In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30 µg, and a progestin such as

desogestrel have an increased risk of VTE compared with those using combined oral contraceptives containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel.

- For brands containing 30 µg ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg ethinylestradiol and levonorgestrel, the overall relative risk of VTE has been estimated to range between 1.5 and 2.0. The incidence of VTE for levenorgestrel containing combined oral contraceptives with less than 50 µg of ethinylestradiol is approximately 20 cases per 100,000 women-years of use. For <*Name of product*> the incidence is approximately 30-40 per 100,000 women-years of use: i.e. additional 10-20 cases per 100,000 women-years of use. The impact of the relative risk on the number of additional cases would be greatest in women during the first year they ever use a combined oral contraceptive when the risk for VTE with all combined oral contraceptives is highest**.**
- The risk of venous thromboembolism increases with:
- increasing age;
- a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
- obesity (body mass index over 30 kg/m^2);
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
- and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.
- The use of COCs in general has been associated with an increased risk of acute myocardial infarction (AMI) or stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely. It has not been studied how <*Name of product*> modifies the risk of AMI.
- The risk of arterial thromboembolic complications increases with:
- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m^2);
- hypertension;
- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/ or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen.
- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (for information on “Pregnancy and Lactation” see Section 4.6).
- An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.
- Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia,

antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

2. Tumours

- An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behavior and other factors such as human papilloma virus (HPV).
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

3. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.
- Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using COCs. However, diabetic women should be carefully observed while taking COCs.
- Crohn' s disease and ulcerative colitis have been associated with COC use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

All this information should be taken into account when prescribing this COC. When counselling the choice of contraceptives method(s) all the above information should be taken into account.

Medical Examination/Consultation
Prior to the initiation or reinstitution of <*Name of product*> a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (section 4.3) and warnings (section 4.4). The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy
The efficacy of COCs may be reduced in the event of missed tablets (Section 4.2), vomiting (Section 4.2) or concomitant medication (Section 4.5).

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking <*Name of product*> due to the risk of decreased plasma concentrations and reduced clinical effects of <*Name of product*> (see Section 4.5 Interactions)

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions
Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbamazepine and rifampicin; oxcarbazepine, topiramate, felbamate, ritonavir and griseofulvin are also suspected. The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Contraceptive failures have also been reported with antibiotics, such as ampicillins and tetracyclines. The mechanism of this effect has not been elucidated.

Women on short-term treatment with any of the above-mentioned classes of drugs or individual drugs should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation. If concomitant drug administration runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual tablet-free interval.

In women on long-term treatment with hepatic enzyme-inducing drugs, experts have recommended to increase the contraceptive steroid doses. If a high contraceptive dosage is not desirable or appears to

be unsatisfactory or unreliable, e.g. in the case of irregular bleeding, another method of contraception should be advised.

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be taken concomitantly with oral contraceptives as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of drug metabolising enzymes by St. John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort.

Laboratory Tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

The use of COCs during pregnancy is not indicated. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Serious undesirable effects
There is an increased risk for venous thrombo-embolism for all women using a combined oral contraceptive. For information on differences in risks between combined oral contraceptives, and for other serious undesirable effects, see section 4.4.

Other possible undesirable effects
The following undesirable effects have been reported in users of COCs:

Breast:	breast tenderness, pain, secretion;
Central Nervous System:	headache, migraine, changes in libido, depressive moods;
Eyes:	contact lens intolerance;
Gastro-intestinal tract:	nausea, vomiting;
Uro-genital:	changes in vaginal secretion;
Skin:	various skin disorders (e.g. erythema nodosum, erythema multiforme, photosensitivity, rash);
Various:	fluid retention; change in body weight; hypersensitivity reaction.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification G03AB05

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, with the higher-dosed COCs (50 μg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.

In clinical studies it has been shown that <*Name of product*> significantly reduced the androgenic parameters 3-α androstenediol-glucuronide, androstenedione, DHEA-S and free testosterone.

5.2 Pharmacokinetic properties

Desogestrel
Absorption
Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Peak serum concentrations of approximately 1.5 ng/ml (first week) to 5 ng/ml (third week) are reached at about 1.5 hours. Bioavailability is 62 - 81 %.

Distribution
Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 - 4 % of the total serum drug concentrations are present as free steroid, 40 - 70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 l/kg.

Metabolism
Etonogestrel is completely metabolized by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction was found with the co-administered ethinylestradiol.

Elimination
Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

Steady-state conditions
Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1-2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5l/kg was determined.

Metabolism
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans when COCs are used as recommended. This is based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
α-Tocopherol; lactose monohydrate; potato starch; povidone; silica, colloidal anhydrous; stearic acid

Film-coating
Ferric oxide red (E 172)*; ferric oxide yellow (E 172)**; hypromellose; macrogol 400; talc, titanium dioxide (E 171)

* only in 0.100 mg desogestrel/0.030 mg ethinylestradiol tablets
** only in 0.050 mg desogestrel/0.035 mg ethinylestradiol tablets

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package.

6.5 Nature and contents of container

The push-through pack is a PVC/Al blister, consisting of aluminium foil with a heat-seal coating and a PVC film. Each blister contains 21 tablets and is packed in a printed aluminium sachet. The sachet is packed in a printed cardboard box together with the package leaflet (1, 3 or 6 sachets per box).

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<*Name of product*>, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<*Name of product*> is a triphasic oral contraceptive of which:

- each yellow tablet contains 0.050 mg desogestrel and 0.035 mg ethinylestradiol;
- each red tablet contains 0.100 mg desogestrel and 0.030 mg ethinylestradiol;
- each white tablet contains 0.150 mg desogestrel and 0.030 mg ethinylestradiol;
- the green tablets do not contain active substances (placebo tablets).

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

The tablets are round, biconvex and 5 mm in diameter. They are coded on one side VR4 (yellow tablets), VR2 (red tablets), TR5 (white tablets) or KH above 2 (green tablets). On the reverse side all tablets are coded Organon and a star.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

4.2 Posology and method of administration

How to take <Name of product>
Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days, starting with the yellow tablets for 7 days, followed by the red for 7 days, the white for 7 days and finally the green (inactive or placebo tablets) for 7 days. Each subsequent pack is started immediately following the last placebo tablet. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last active tablet and may not have finished before the next pack is started.

How to start <Name of product>
No preceding hormonal contraceptive use [in the past month]
Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from another combined oral contraceptive (COC)
The woman should start with <*Name of product*> preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.

Changing from a progestagen-only-method (minipill, injection, implant)
The woman may switch any day from the minipill (from an implant on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion
For breastfeeding women see Section 4.6

Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of missed tablets
If the user is **less than 12 hours late** in taking any tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time. If she is **more than 12 hours late** in taking any active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
1. active tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

- **Week 1 (yellow tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular placebo tablet interval, the higher the risk of a pregnancy.

- **Week 2 (red tablets)**

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- **Week 3 (white tablets)**

The risk of reduced reliability is imminent because of the forthcoming placebo tablet interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.
1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next pack must be started as soon as the active tablets in the current pack are finished, i.e., no placebo tablets should be taken. The user is unlikely to have a withdrawal bleed until the placebo tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on active tablet-taking days.
2. The woman may also be advised to discontinue ‘active tablet’-taking from the current pack. She should then immediately continue with the placebo tablets. The total number of missed tablets and placebo tablets must never exceed seven. Subsequently she should continue with the next pack.

- **Week 4 (green tablets)**

Contraceptive protection is not reduced, the woman should take further tablets at the usual time.

If the woman missed active tablets and subsequently has no withdrawal bleed in the first normal placebo tablet interval, the possibility of a pregnancy should be considered.

Advice in case of vomiting

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets (see above) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to delay a period

Delaying a period is not an indication for the product. However, if in exceptional cases a period needs to be delayed, the woman should continue with the white tablets from another pack of *<Name of product>* without having a placebo tablet interval. The extension can be carried on for a maximum of 7 days (the white tablets in the second pack). During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of *<Name of product>* is then resumed after the usual 7-day placebo tablet interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

4.3 Contraindications

Combined oral contraceptives (COCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear during COC use, the product should be stopped immediately.

- Presence or history of venous thrombosis (deep venous thrombosis, pulmonary embolism)
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g. transient ischaemic attack, angina pectoris).
- Known predisposition for venous or arterial thrombosis, such as Activated Protein C (APC) resistance, antithrombin-III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, and antiphospholipid antibodies.
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see under 'Special Warnings and Special Precautions for Use').
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the active substances of *<Name of product>* or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

1. Circulatory Disorders

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The incidence of VTE is considered to be 5-10 per 100,000 woman years in non-OC users. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.
- In several epidemiological studies it has been found that women using combined oral contraceptives with ethinylestradiol, mostly with a dose of 30 µg, and a progestin such as desogestrel have an increased risk of VTE compared with those using combined oral contraceptives containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel.
- For brands containing 30 µg ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg ethinylestradiol and levonorgestrel, the overall relative risk of VTE has been estimated to range between 1.5 and 2.0. The incidence of VTE for levenorgestrel containing combined oral contraceptives with less than 50 µg of ethinylestradiol is approximately 20 cases per 100,000 women-years of use. For <*Name of product*> the incidence is approximately 30-40 per 100,000 women-years of use: i.e. additional 10-20 cases per 100,000 women-years of use. The impact of the relative risk on the number of additional cases would be greatest in women during the first year they ever use a combined oral contraceptive when the risk for VTE with all combined oral contraceptives is highest.
- The risk of venous thromboembolism increases with:
- increasing age;
- a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use;
- obesity (body mass index over 30 kg/m^2);
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.
- and possibly also with superficial thrombophlebitis and varicose veins. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.
- The use of COCs in general has been associated with an increased risk of acute myocardial infarction (AMI) or stroke, a risk that is strongly influenced by the presence of other risk factors (e.g. smoking, high blood pressure, and age) (see also below). These events occur rarely. It has not been studied how <*Name of product*> modifies the risk of AMI.
- The risk of arterial thromboembolic complications increases with:
- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m^2);
- hypertension;
- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.
- Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.
- Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/ or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal

seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

- Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
- The increased risk of thromboembolism in the puerperium must be considered (for information on "Pregnancy and Lactation" see Section 4.6).
- An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.
- Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).
- When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COC use.

2. Tumours

- An increased risk of cervical cancer in long-term users of COCs has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behavior and other factors such as human papilloma virus (HPV).
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

3. Other conditions

- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
- Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. A relationship between COC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
- The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

- Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using COCs. However, diabetic women should be carefully observed while taking COCs.
- Crohn' s disease and ulcerative colitis have been associated with COC use.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

All this information should be taken into account when prescribing this COC. When counselling the choice of contraceptives method(s) all the above information should be taken into account.

Medical Examination/Consultation
Prior to the initiation or reinstitution of *<Name of product>* a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (section 4.3) and warnings (section 4.4) The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy
The efficacy of COCs may be reduced in the event of missed tablets (Section 4.2), vomiting (Section 4.2) or concomitant medication (Section 4.5).

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking *<Name of product>* due to the risk of decreased plasma concentrations and reduced clinical effects of *<Name of product>* (see Section 4.5 Interactions).

Reduced cycle control
With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the placebo tablet interval. If the COC has been taken according to the directions described in Section 4.2, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions
Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbamazepine and rifampicin; oxcarbazepine, topiramate, felbamate, ritonavir and griseofulvin are also suspected. The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2-3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Contraceptive failures have also been reported with antibiotics, such as ampicillins and tetracyclines. The mechanism of this effect has not been elucidated.

Women on short-term treatment with any of the above-mentioned classes of drugs or individual drugs should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation. If concomitant drug administration runs beyond the end of the tablets in the COC pack, the next COC pack should be started without the usual placebo tablet interval.

In women on long-term treatment with hepatic enzyme-inducing drugs, experts have recommended to increase the contraceptive steroid doses. If a high contraceptive dosage is not desirable or appears to be unsatisfactory or unreliable, e.g. in the case of irregular bleeding, another method of contraception should be advised.

Herbal preparations containing St. John's wort (Hypericum perforatum) should not be taken concomitantly with oral contraceptives as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of drug metabolising enzymes by St. John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort.

Laboratory Tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6 Pregnancy and lactation

The use of COCs during pregnancy is not indicated. Most epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

Serious undesirable effects
There is an increased risk for venous thrombo-embolism for all women using a combined oral contraceptive. For information on differences in risks between combined oral contraceptives, and for other serious undesirable effects, see section 4.4.

Other possible undesirable effects

The following undesirable effects have been reported in users of COCs:

Breast:	breast tenderness, pain, secretion;
Central Nervous System:	headache, migraine, changes in libido, depressive moods;
Eyes:	contact lens intolerance;
Gastro-intestinal tract:	nausea, vomiting;
Uro-genital:	changes in vaginal secretion;
Skin:	various skin disorders (e.g. erythema nodosum, erythema multiforme, photosensitivity, rash);
Various:	fluid retention; change in body weight; hypersensitivity reaction.

4.9 Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification G03AB05

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency. Apart from this, with the higher-dosed COCs (50 μg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs remains to be confirmed.
In clinical studies it has been shown that <*Name of product*> significantly reduced the androgenic parameters 3-α androstenediol-glucuronide, androstenedione, DHEA-S and free testosterone.

5.2 Pharmacokinetic properties

Desogestrel
Absorption
Orally administered desogestrel is rapidly and completely absorbed and converted to etonogestrel. Peak serum concentrations of approximately 1.5 ng/ml (first week) to 5 ng/ml (third week) are reached at about 1.5 hours. Bioavailability is 62 - 81 %.

Distribution
Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 - 4 % of the total serum drug concentrations are present as free steroid, 40 - 70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 l/kg.

Metabolism
Etonogestrel is completely metabolized by the known pathways of steroid metabolism. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction was found with the co-administered ethinylestradiol.

Elimination
Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

Steady-state conditions
Etonogestrel pharmacokinetics are influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

Ethinylestradiol
Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1-2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5l/kg was determined.

Metabolism
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted, ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions
Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans when COCs are used as recommended. This is based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core active tablets
α-Tocopherol; lactose monohydrate; potato starch; povidone; silica, colloidal anhydrous; stearic acid

Tablet core placebo tablets
Lactose monohydrate; magnesium stearate; maize starch

Film-coating
Ferric oxide red (E 172)*; ferric oxide yellow (E 172)**; hypromellose; indigo carmine lake (E 132)***; macrogol 400; talc, titanium dioxide (E 171)

* only in 0.100 mg desogestrel/0.030 mg ethinylestradiol tablets
** only in 0.050 mg desogestrel/0.035 mg ethinylestradiol tablets and placebo tablets
*** only in placebo tablets

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C
Store in the original package.

6.5 Nature and contents of container

The push-through pack is a PVC/Al blister, consisting of aluminium foil with a heat-seal coating and a PVC film. Each blister contains 28 tablets and is packed in a printed aluminium sachet. The sachet is packed in a printed cardboard box together with the package leaflet (1, 3 or 6 sachets per box).

6.6 Instructions for use and handling and disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT