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EMEA COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

CPMP PUBLIC ASSESSMENT REPORT

Combined oral contraceptives and venous thromboembolism

PRODUCTS: **Third generation oral contraceptives**

NAMES OF ACTIVE SUBSTANCES:

Ethinylestradiol (at least 20 µg), and Desogestrel or Gestodene (mono-, bi- or tri-phasic)

PHARMACOTHERAPEUTIC CLASSIFICATION:

Hormonal contraceptives for systemic use

BACKGROUND INFORMATION

Combined oral contraceptives (COCs) are very effective and give almost 100% protection against pregnancy if properly used. In addition, common disorders such as dysmenorrhea, premenstrual syndrome, menorrhagia, iron deficiency anaemia and salpingitis are less frequent in women when they use COCs, and COCs decrease the risk for endometrial as well as ovarian cancer.

Minor, often transient, adverse reactions associated with the use of COCs such as nausea, oedema, weight gain and mood changes are common. However, serious adverse reactions are rare. In fact, about 99.95% of women using COCs for one year will not experience any serious problems. Well-known serious but rare adverse reactions are venous thromboembolism (VTE), myocardial infarction and stroke.

The 3rd generation COCs discussed in this report are oral contraceptives containing at least 20 µg ethinylestradiol combined with the progestins desogestrel or gestodene as mono-, bi- or tri-phasic formulation. This report summarizes the present knowledge concerning VTE related to the use of 3rd generation COCs compared to the use of 2nd generation COCs containing less than 50 µg of ethinylestradiol combined with certain other progestins, the most widely used being levonorgestrel.

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ASSESSMENT

Risk of venous thromboembolism (VTE)

The incidence of VTE in women not using COCs and aged 15-44 years is 5-10 cases per

100 000 women-years. In pregnancy, the incidence is estimated as 60 cases per 100 000 pregnancies. It is expected that 20 % of the women affected by a VTE will develop a disabling post-thrombotic syndrome. The most serious complication of VTE is pulmonary embolism which occurs in about 10 % of the cases. 1 - 2 % of VTE cases result in death [1].

The use of all COCs confers an increased risk of VTE. The magnitude of the absolute risk increase is small. In users of 2nd generation COCs the incidence of VTE is estimated to be about 20 cases per 100 000 women-years of use. This translates into a mortality rate of 2-4 deaths per million women-years of use in users of 2nd generation COCs.

Comparing 3rd generation and 2nd generation COCs, epidemiological studies [2-20] - in particular original studies [2-13, 20] (rather than re-analyses [14-19]) - showed an increased relative risk of VTE for women using a 3rd generation COC. Although the studies presented a wide range of relative risk estimates (0.8 - 4.2), it has been found after thorough scientific evaluation that women using a 3rd generation COC have a significantly increased risk of VTE compared with women using a 2nd generation COC, and that the best estimate of the magnitude of the relative risk is in the range of 1.5 to 2.0. This means that in users of 3rd generation COCs the incidence of VTE is estimated to be about 30 to 40 cases per 100 000 women-years of use.

A recent meta-analysis of pertinent epidemiological studies revealed a significantly increased summary relative risk of 1.7, for 3rd as compared with 2nd generation COCs [21].

The magnitude of the differential risks should be considered through their effects on incidence and mortality in absolute terms. In women using 3rd generation COCs, an additional number of 10 to 20 cases of VTE per 100 000 women-years of use would occur compared to 2nd generation COCs. This increase of incidence of VTE would translate into an additional 20 to 40 cases of disabling post-thrombotic syndrome, 10 to 20 cases of pulmonary embolism and 1 to 4 deaths per million women-years of use. The excess risk of VTE is highest during the first year a woman ever uses any COC. Therefore, the impact of the relative risk for users of 3rd generation COCs will be greatest in absolute terms (number of new cases of VTE) during the first year a woman ever uses a COC.

This information should be taken into account when any COC is used by a woman for the first time.

Haemostatic factors

The suggestion of a differential risk between levonorgestrel containing and desogestrel or gestodene containing COCs is supported by studies demonstrating changes in haemostatic factors. The 3rd generation COCs induce a stronger response in pro-thrombotic factors that may be associated with VTE including levels of resistance against activated protein C (APC) (as measured by endogenous thrombin production (ETP) based methods), protein S, and possibly prothrombin fragments (1+2), when compared to the 2nd generation COCs.

Risk of acute myocardial infarction and stroke

Analyses of acute myocardial infarction risk in two large epidemiological studies [22, 23] did not show evidence that 3rd generation COCs significantly altered the risk, or that the risk differed between the COC types, in young women below the age of 35 years. The risk of ischemic stroke increased slightly in an oestrogen-dose dependent way for users of COCs according to five of the recent epidemiological reports [24-28] and a meta-analysis of 16 epidemiological studies. There was no clear difference in effect between the various types of progestins in the COCs.

Tolerability

Experience from medical practice indicates that 3rd generation COCs differ in their tolerability compared to 2nd generation COCs. However there are no systematic scientific data supporting this clinical experience. A prospective comparative study to document relevant differences is not available.

Limitations of the scope of the present assessment report

It is important to recognise that differences in VTE risk between COCs observed in the epidemiological studies almost entirely concern the mono-phasic COCs. Most but not all of these study data relate to COCs with 30µg ethinylestradiol combined with desogestrel, gestodene or levonorgestrel**.** It was considered reasonable to extrapolate the conclusions on a differential risk to bi- or tri-phasic COCs. For COCs containing desogestrel with 20µg of ethinylestradiol, the available epidemiological data do not suggest a lower VTE risk than for those containing 30µg of ethinylestradiol. A meta-analysis of epidemiological studies presenting information separately for 3rd generation COCs containing desogestrel and 20 or 30µg of ethinylestradiol compared to 2nd generation COCs yielded similar risk estimates, i.e. odds ratios of 2.1 and 2.2 respectively [29]. There are currently no epidemiological studies comparing COCs containing gestodene and 20µg of ethinylestradiol to 2nd generation COCs. However, since no difference in VTE risk between desogestrel and gestodene was observed in studies investigating formulations with 30µg of ethinylestradiol, by analogy it can be expected that there will be no difference in VTE risk in COCs containing gestodene with 20µg of ethinylestradiol compared to COCs containing gestodene with 30µg of ethinylestradiol. There are no data on VTE risk in COCs containing desogestrel or gestodene and less than 20µg of ethinylestradiol, and since the dose of the estrogen may be relevant to the VTE risk, no conclusion can be drawn for these products. Due to insufficient data related to VTE risk, no firm conclusions can be drawn for COCs with progestins other than desogestrel, gestodene and levonorgestrel.

SUMMARY AND RECOMMENDATIONS

- **Venous thromboembolism (VTE) is a rare side effect of all COCs. The level of this risk is low, and overall the balance of benefits and risks remains favourable with all available COCs. Thus, there is no reason for women currently using any brand of COCs to stop taking it on basis of these findings.**
- **On the basis of a careful scientific evaluation, it has been found that women using a 3rd generation COC with 30µg of ethinylestradiol have a small increased risk of VTE compared to women using 2nd generation COCs. For 3rd generation COCs with 20µg of ethinylestradiol the epidemiological data do not suggest a lower VTE risk than for those containing 30µg of ethinylestradiol.**
- **There is an excess risk of VTE during the first year a woman ever uses any COC. The impact of the relative risk of VTE of 3rd generation compared to 2nd generation COCs on the number of additional cases would be greatest in the first year a woman ever uses a COC. This should be taken into account when a COC is prescribed for and used by a woman for the first time.**
- **The increased risk of VTE associated with COCs is less than the risk of VTE associated with pregnancy.**

Consequently, the CPMP, after having considered all options for safety measures, recommends that differences in risk should be reflected in Summaries of Product Characteristics and User Package Leaflets for the relevant products and should be communicated to prescribers of COCs, as well as to the women in need of contraceptive advice.

PROPOSALS FOR CHANGES TO THE SUMMARIES OF PRODUCT CHARACTERISTICS (SPCs)

These proposals concern the elements which should be included in the SPCs and it will be up to national regulatory authorities to express it appropriately.

SPC Section 4.4 on Special warnings and special precautions for use:

For all COCs *except* those COCs further specified below:

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a women 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.
- It is not known how <name of product> influences the risk of VTE compared with other combined oral contraceptives.

For all COCs containing 50µg or more ethinylestradiol

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. 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.
- <name of product> carries a higher risk of VTE than combined oral contraceptives containing a lower dose of ethinylestradiol.

For all COCs containing less than 50µg ethinylestradiol and levonorgestrel

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. 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.
- The overall absolute risk (incidence) of VTE for levonorgestrel containing combined oral contraceptives with 30µg ethinylestradiol is approximately 20 cases per 100,000 women-years of use.

For all COCs containing 20µg or more of ethinylestradiol and desogestrel or gestodene (mono-, bi- or tri-phasic formulation)

- The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. 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 30µg, and a progestin such as <name of progestin> have an increased risk of VTE compared with those using combined oral contraceptives containing less than 50µg of ethinylestradiol and the progestin levonorgestrel.
- For brands containing 30µg of ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg of 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 levonorgestrel 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 cases 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 the 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.

  Additional statement for formulations with 20µg ethinylestradiol:

  For combined oral contraceptives containing desogestrel or gestodene with 20µg of ethinylestradiol the epidemiological data do not suggest a lower VTE risk than for those containing 30µg of ethinylestradiol.
- All this information should be taken into account when prescribing this combined oral contraceptive. When counselling the choice of contraceptive method(s) all the above information should be considered.

SPC Section 4.8 on Undesirable effects:

For all COCs containing 20µg or more of ethinylestradiol and desogestrel or gestodene (mono-, bi- or tri-phasic formulation)

- There is an increased risk of venous thromboembolism for all women using a combined oral contraceptive. For information on differences in risk between combined oral contraceptives, see Section 4.4.

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