Direct Healthcare Professional Communication

Combined hormonal contraceptives: be aware of the difference in risk of thromboembolism between products, the importance of individual risk factors and remain vigilant for signs and symptoms

Dear Healthcare Professional,

This letter is to inform you of the results of a Europe-wide review and the latest evidence on the risk of thromboembolism in association with certain combined hormonal contraceptives[1] (CHCs). The letter is intended for all prescribers of contraception and any healthcare professional that may be presented with a possible thromboembolism due to CHCs and has been agreed with the European Medicines Agency (EMA), the marketing authorisation holders and the MHRA.

Summary

- **This review confirmed previous understanding that the level of VTE risk with all low dose CHCs (ethinylestradiol <50µg) is small.**
- **There is good evidence that the risk of venous thromboembolism (VTE) may vary between CHCs, depending on the type of progestogen they contain. Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE among combined hormonal contraceptives (see table 1 below).**
- **When prescribing CHCs, careful consideration should be given to the individual woman's current risk factors, particularly those for VTE, and the difference in risk of VTE between products.**
- **A woman who has been using her combined contraceptive without any problems does not need to stop using it.**
- **There is no evidence for differences between low dose CHCs (ethinylestradiol <50µg) in their risk of arterial thromboembolism (ATE).**
- **The benefits associated with using a CHC far outweigh the risk of serious side effects in most women. The focus is now on emphasising the importance of an individual woman's risk factors and the need to regularly reassess them, and raising awareness of the signs and symptoms of VTE and ATE which should be described to women when a CHC is prescribed.**
- **Always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.**
- **Additional guidance documents have been developed to help facilitate consultations, including: a checklist that prescribers may go through with the woman to ensure a CHC is suitable. A user card and information sheet that provides the important signs and symptoms of VTE and ATE for women to be aware of has also been developed.**

[1] Combined hormonal contraceptives containing ethinylestradiol or estradiol associated with chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate.

Further information on the safety concern and the recommendations

Many studies have evaluated the risk of VTE (deep vein thrombosis, pulmonary embolism) among users of different CHCs. Based on the totality of the data it is concluded that VTE risk differs between products - with the lower risk products being those containing the progestogens levonorgestrel, norethisterone and norgestimate. For some products there are currently insufficient data to know how the risk compares with the lower risk products.

Best estimates of the risk of VTE with a number of ethinylestradiol/progestogen combinations compared with the risk associated with levonorgestrel-containing pills are shown in table 1.

Compared with pregnancy and the postpartum period, the risk of VTE associated with using CHCs is lower.

Table 1: Risk of VTE with combined hormonal contraceptives

Progestogen in CHC (combined with ethinylestradiol, unless stated)	**Relative risk vs levonorgestrel**	**Estimated incidence (per 10,000 women per year of use)**
Non-pregnant non-user	-	2
Levonorgestrel	Ref	5-7
Norgestimate / Norethisterone	1.0	5-7
Gestodene / Desogestrel / Drospirenone	1.5-2.0	9-12
Etonogestrel / Norelgestromin	1.0-2.0	6-12
Chlormadinone[2] / Dienogest/ Nomegestrel acetate (E2)	TBC[1]	TBC[1]

E2 – estradiol; TBC – to be confirmed

[1] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products

[2] Not currently available in the UK

Prescribers should be aware of current product information and clinical guidance when discussing the most suitable type of contraceptive for any woman. The risk of VTE is highest during the first year of using any CHC, and may also be higher upon re-starting CHCs after a break of 4 or more weeks. The risk of VTE is also higher in the presence of intrinsic risk factors. Risk factors for VTE change over time and an individual's risk should be re-evaluated periodically. To facilitate earlier diagnosis all women with signs and symptoms should be asked if they are "taking any medicines *or if they are using a combined hormonal contraceptive*". You are reminded that a significant proportion of thromboembolisms are not preceded by any obvious signs or symptoms.

It is known that the risk of ATE (myocardial infarction, cerebrovascular accident) is also increased with use of CHCs, however there are insufficient data to demonstrate whether this risk varies between different products.

The decision about which product to use should be taken only after a discussion with the woman that includes: the level of VTE risk associated with different products; how her current risk factors influence the risk of VTE and ATE; and exploration of her preferences.

A prescribing checklist and a sheet for women have been developed to help guide this discussion (and are attached). Further information for women has also been developed and can be accessed at the following website:

http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/Hormonalcontraceptives/index.htm

Product information will be updated to reflect our current understanding of the available evidence and to make information as clear as possible. We have also taken this opportunity to update baseline VTE rates to reflect current evidence. These increased rates are likely due to improvements in VTE diagnosis and reporting and an increase in obesity over time.

Call for reporting

Any suspected adverse reactions should be reported to the MHRA through the Yellow Card Scheme online at http://yellowcard.mhra.gov.uk/. Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail: "FREEPOST YELLOW CARD"
- at the back of the British National Formulary (BNF)
- by telephoning the Commission of Human Medicines free phone line: 0800-731-6789
- or by electronic download through the MHRA website (http://yellowcard.mhra.gov.uk/)

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Company contact point

Reports of suspected adverse reactions can also be made to the relevant marketing authorisation holder. Contact point details for further information are given in the product information of the medicine (SmPC and Package Leaflet at: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/).

CHECKLIST FOR PRESCRIBERS – COMBINED HORMONAL CONTRACEPTIVES

Please use this checklist in conjunction with the Summary of Product Characteristics during combined hormonal contraceptive (CHC) consultations.

- Thromboembolism (e.g. deep vein thrombosis, pulmonary embolism, heart attack and stroke) is a rare but important risk with use of a CHC.
- A woman's risk will also depend on her baseline risk of thromboembolism. The decision to use a CHC should therefore take into consideration the contraindications and a woman's risk factors, particularly those for thromboembolism – see boxes below and the Summary of Product Characteristics.
- The risk of a thromboembolism with a CHC is higher:
    - during the first year of use
    - when re-starting use after an intake break of 4 or more weeks.
- CHCs that contain ethinylestradiol in combination with levonorgestrel, norgestimate or norethisterone are considered to have the lowest risk of venous thromboembolism (VTE).
- The decision to use any CHC should be taken only after a discussion with the woman to ensure she understands
    - the effect of any intrinsic risk factors on her risk of thrombosis
    - the risk of thromboembolism with her CHC
    - that she must be alert for signs and symptoms of a thrombosis

Do not prescribe a CHC if you tick any of the boxes in this section. Does the woman have:	
☐	Current or personal history of a thromboembolic event e.g. deep vein thrombosis, pulmonary embolism, heart attack, stroke, transient ischaemic attack, angina pectoris?
☐	Knowledge of predisposition for a blood clotting disorder?
☐	History of migraine with aura?
☐	Diabetes mellitus with vascular complications?
☐	Very high blood pressure eg systolic ≥160 or diastolic ≥100mm Hg?
☐	Very high blood lipids?
☐	Major surgery or a period of prolonged immobilisation coming up? If so, advise to use a different method of contraception for at least 4 weeks beforehand and two weeks after full ambulation.

Discuss the suitability of a CHC with the woman if you tick any of the boxes in this section:	
☐	Is her BMI over 30 kg/m²?
☐	Is she aged over 35 years?
☐	Is she a smoker? If yes and also over the age of 35 she should be strongly advised to stop smoking or use a different method of contraception.
☐	Does she have high blood pressure eg systolic 140-159 or diastolic 90-99mm Hg?

☐	Does she have a close relative (eg parent or sibling) who has had a thromboembolic event (see above list) at a young age (eg before 50)?
☐	Does she or someone in her immediate family have high blood lipids?
☐	Does she get migraines?
☐	Does she have a cardiovascular condition such as atrial fibrillation, arrhythmia, coronary heart disease, cardiac valve disease?
☐	Does she have diabetes mellitus?
☐	Has she given birth in the last six weeks?
☐	Does she travel for more than 4 hours per day?
☐	Does she have any other medical conditions that might increase the risk of thrombosis (eg. cancer, systemic lupus erythematosus, sickle cell disease, Crohn's disease, ulcerative colitis, haemolytic uraemic syndrome)?
☐	Is she taking any other medicines that can increase the risk of thrombosis (eg. corticosteroids, neuroleptics, antipsychotics, antidepressants, chemotherapy etc)?
More than one of the above risk factors may mean a CHC should not be used. **Don't forget, a woman's <u>risk factors may change over time</u> and should be revisited at regular intervals.**	

Please make sure your patient understands that she should tell a healthcare professional she is taking a combined hormonal contraceptive if she:

- Needs an operation
- Needs to have a period of prolonged immobilisation (eg because of an injury or illness, or if her leg is in a cast)

➢ <u>In these situations it would be best to discuss whether a different method of contraceptive should be used until the risk of VTE returns to normal.</u>

Please also tell your patient that the risk of a blood clot is increased if she:

- Travels for extended periods (eg during long-haul flights)
- Develops one or more of the above risk factors for VTE
- Has given birth within the last few weeks

➢ <u>In these situations your patients should be particularly alert for any signs and symptoms of a thromboembolism.</u>

Please **advise your patient to tell you** if any of the above situations change or get much worse.

Please strongly encourage women to read the Patient Information Leaflet that accompanies each pack of CHC. This includes the symptoms of blood clots that she must watch out for.

Please report any adverse events suspected to be caused by a combined contraceptive to the company or the MHRA (<u>http://yellowcard.mhra.gov.uk/</u>)