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 (http://yellowcard.mhra.gov.uk/)

ANNEX 3

IMPORTANT INFORMATION FOR WOMEN ABOUT RISK OF BLOOD CLOTS WITH COMBINED HORMONAL CONTRACEPTIVES

All combined hormonal contraceptives (CHC) increase the rare but important risk of having a blood clot. The overall risk of a blood clot is small but clots can be serious and may in very rare cases even be fatal.

It is very important that you recognise when you might be at greater risk of a blood clot, what signs and symptoms you need to look out for and what action you need to take.

In which situations is the risk of a blood clot highest?

- in the first year of CHC use (including if you are re-starting use after a break of 4 weeks or more)
- if you are very overweight
- if you are older than 35 years
- if you have a close family member (eg parent or sibling) who has had a blood clot at a relatively young age (ie below 50)
- if you have given birth in the previous few weeks

If you smoke and are over 35 years old you are strongly advised to stop smoking or use a different method of contraception.

Seek medical attention immediately if you experience any of the following symptoms:

- Severe pain or swelling in either leg that may be accompanied by tenderness, warmth or changes in skin colour such as turning pale, red or blue. You may be experiencing a **deep vein thrombosis**.
- Sudden unexplained breathlessness or rapid breathing; severe chest pain which may increase with deep breathing; sudden cough without an obvious cause (which may bring up blood). You may be experiencing a serious complication of deep vein thrombosis called a **pulmonary embolism**. This occurs if the blood clot travels from the leg to the lung.
- Chest pain, often acute, but sometimes just discomfort, pressure, heaviness, upper-body discomfort radiating to the back, jaw, throat or arm; feeling of fullness, indigestion or choking; sweating, nausea, vomiting or dizziness. You may be experiencing a **heart attack**
- Weakness or numbness of the face, arm or leg, especially on one side of the body; trouble speaking, sudden confusion or lack of understanding; sudden loss of vision or blurred vision; severe headache or migraine that is worse than normal. You may be experiencing a **stroke**.

Watch out for symptoms of a blood clot, especially if you have:

- Just had an operation
- been off your feet for a long time (eg. because of an injury or illness, or if your leg is in a cast)
- a long journey (e.g. long-haul flight)

Remember to tell your doctor, nurse or surgeon that you are taking a CHC if you:

- Are due to or have recently had surgery
- Are asked by a healthcare professional if you are taking any medication

- For further information please read the accompanying Patient Information Leaflet for your CHC or go to http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/ .
- If you think you have a side effect from using your CHC you can report it to a healthcare professional.

Combined hormonal contraceptives: important information for women

Why have I been given this leaflet?

The person who prescribes your contraception has given you this sheet to give you a bit more information about the recommendations coming from a recent Europe-wide review of the safety of combined hormonal contraceptives, in particular the risk of blood clots.

The review recommended that all women should understand: the small risk of blood clots with combined hormonal contraceptives; what other conditions increase the risk of a blood clot; the signs and symptoms of a blood clot; and when you need to tell a healthcare professional that you are using a combined hormonal contraceptive. Although the risk is small, blood clots can be serious. This information will help you minimise your risk.

For all other information on the safe use of combined hormonal contraceptives please refer to the Information Leaflet that accompanies each pack of contraceptives (see below).

Key points to bear in mind

1. Combined hormonal contraceptives are highly effective in preventing unwanted pregnancy. They offer substantial benefits and these far outweigh the small risk of serious side effects.
2. No important new information on the safety of combined hormonal contraceptives has become available as a result of the recent review. The risk of blood clots with combined hormonal contraceptives has been known about for many years and much information has already been provided to prescribers and women.
3. There is no need for anyone who has been using a combined hormonal contraceptive without any problems to stop taking it on the basis of this review. If any woman has concerns, they should discuss them with their contraceptive provider at the next routine appointment, but should keep taking their combined hormonal contraceptive until they have done so. Suddenly stopping a combined hormonal contraceptive may result in accidental pregnancy.

Risk of a blood clot with combined hormonal contraception

4. It is important to remember that the overall risk of having a blood clot is small in most women for whom use of a combined hormonal contraceptive is appropriate.
5. The risk of a blood clot is greater during the first year of use and may also be higher after a break of 4 weeks or more.
6. The risk of a blood clot returns to normal within a few months of stopping taking combined hormonal contraception.
7. Blood clots usually occur initially in the legs (called a deep vein thrombosis), but may in some cases break off and travel to the blood vessels in the lungs (called a pulmonary embolism). This can be very serious and even fatal in rare cases. Blood clots can also form in the vessels of the heart (causing a heart attack) or the brain (causing a stroke) or in very rare cases in other parts of the body.
8. There is good evidence that the risk of a blood clot may vary between combined hormonal contraceptives, depending on the type of progestogen hormone it contains. Those that are considered to have the lowest risk of blood clots contain the progestogens levonorgestrel, norgestimate or norethisterone. The risk with other progestogens may be slightly higher.

What to expect when getting a contraceptive prescription

9. The person who prescribes your contraceptive should discuss the benefits and risks of combined hormonal contraceptives with you. In particular, they should highlight: the small risk of blood clots; the conditions that increase the risk of clots: and some of the key signs and symptoms to be aware of. They may also go through a short checklist with you to make sure that a combined hormonal contraceptive is right for you. This is because some women may have a condition that means they should not take a combined hormonal contraceptive.
10. If your prescriber thinks you are suitable for a combined hormonal contraceptive but your circumstances mean you have a naturally higher risk of a blood clot—eg, if you are older than about 35 years, or you are very overweight, or have a family history of a blood clot, then they may advise you to start on one of the lower-risk products (see 8). If you have more than one of the above risk factors, your contraceptive provider may consider that you should use a different method of contraception.
11. If you smoke you are at increased risk of the type of blood clots that may cause a heart attack or stroke and your doctor may recommend that you stop smoking if you wish to use a combined hormonal contraceptive. If you smoke and are also over 35 years old you may be strongly advised to consider using a different form of contraception.

What signs and symptoms of a clot should I look out for?

- It is important to watch out for symptoms of a blood clot, especially if you have:
  - just had an operation
  - been off your feet for a long time (eg, because of injury or illness or if your leg is in a cast)
  - been on a long journey (eg a long haul flight)

Seek medical attention immediately if you experience any of the following symptoms:

Are you experiencing any of these signs?	What are you possibly suffering from?
Severe pain or swelling in either leg that may be accompanied by tenderness, warmth or changes in skin colour such as turning pale, red or blue.	Deep vein thrombosis
Sudden unexplained breathlessness or rapid breathing; sudden cough without an obvious cause (which may bring up blood); severe chest pain which may increase with deep breathing.	Pulmonary embolism
Chest pain, discomfort, pressure, heaviness, upper-body discomfort extending to the back, jaw, throat or arm; feeling of fullness, indigestion or choking; sweating, nausea, vomiting or dizziness.	Heart attack
Weakness or numbness of the face, arm or leg, especially on one side of the body; trouble speaking, sudden confusion, or lack of understanding; sudden loss of vision or blurred vision; severe headache or migraine that is worse than normal.	Stroke

Remember to tell your doctor, nurse or surgeon that you are taking a combined hormonal contraceptive if you:

- are due to have, or have recently had, surgery
- are asked by a healthcare professional if you are taking any medicines

For further information, read the Patient Information Leaflet that is in every packet of combined contraceptives. Information is also available at http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/Hormonalcontraceptives/index.htm