ANNEX 1

January 2014

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**

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

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.

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:
https://www.gov.uk/drug-safety-update/combined-hormonal-contraceptives-and-venous-thromboembolism-review-confirms-risk-is-small#further-information

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
Please report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card scheme. You can report via:

- the Yellow Card website www.mhra.gov.uk/yellowcard
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible. By reporting side effects, you can help provide more information on the safety of this medicine.

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/).