Outcome of review of Combined Hormonal Contraceptives (CHCs) results in an opinion to update the product information to help women make informed decisions about their choice of contraception.

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Information on CHCs

Combined Hormonal Contraceptives are medicinal products which contain two types of hormones, an oestrogen and a progestogen. As described in Medicines Authority Circular P05/2013, the review included all contraceptives containing low-dose oestrogen and the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate. These are sometimes referred to as 'third generation' or 'fourth generation' contraceptives and are available as pills, skin patches and vaginal rings. During the review, the risk of Venuos Thrombo Embolism (VTE) with these medicines was compared with that of CHCs containing levonorgestrel and norethisterone (also known as 'second generation' contraceptives).

The classification as 'second, third or fourth generation' is however not science-based and not standardised, and may differ between institutions and publications.

With the exception of Zoely (nomegestrol acetate/estradiol), Ioa (nomegestrol acetate/estradiol) and Evra (norelgestromin/ethinylestradiol), which have been authorised centrally through the EMA, all other combined contraceptives in the EU have been authorised via national procedures.

Information from European Medicines Agency about the safety concern

The product information of CHCs will be updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman's individual risk factors when prescribing a contraceptive. Doctors should also consider how the risk of VTE with a particular CHC compares with other CHCs (see table below).

The review also looked at the risk of arterial thromboembolism (ATE, blood clots in arteries, which can potentially cause a stroke or heart attack). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen.

Medicines Authority
203 Level 3, Rue D'Argens, Gzira, GZR 1368 – Malta.
Tel. (+356) 23439000 Fax. (+356) 23439161 www.medicinesauthority.gov.mt

The CHMP opinion will now be sent to the European Commission for the adoption of a legally binding decision to update the product information of all CHCs throughout the EU.

In Malta

Information to patients

- If you have been taking CHCs without any problem, there is no reason for you to stop taking them on the basis of this review. But it is important that you are aware of the risk of blood clots associated with these medicines, even though it is very low.
- The risk of blood clots in the veins varies between CHCs, depending on the type of progestogen (a hormone) they contain, and ranges from 5 to 12 cases of blood clots per 10,000 women who use them for a year (see table below). This compares with 2 cases of blood clots in the veins each year per 10,000 women who are not using CHCs.
- You should also be aware of the factors that increase your risk of a clot and be aware of how these may change over time. Risk factors include being very overweight, increasing age, having a member of your family who has had a blood clot at a relatively young age (e.g. below 50), having migraine or being immobilised for a long time (e.g. because of an illness or injury). Your risk of a blood clot is also higher in the first year of using a CHC.
- When taking CHCs, you should be alert for the signs and symptoms of blood clots, which may include severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and weakness or numbness of the face, arm or leg. If you develop any of these signs and symptoms you should seek medical advice immediately.
- If you have any questions or concerns, speak with your doctor, pharmacist or nurse. Your doctor can help you decide what the most appropriate type of contraception for you is.

Information to healthcare professionals

- Healthcare professionals should always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.
- Differences exist between CHCs in their risk of VTE 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 (see table below).
- When prescribing a CHC, 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. CHCs are contraindicated if a woman has one serious or multiple risk factors that put her at high risk of blood clots.

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- There is no evidence for differences between low-dose CHCs in their risk of arterial thromboembolism (ATE).
- Because a woman's individual risk factors will change over time, there is a need to regularly re-assess the suitability of her contraceptive.
- It is also important to raise awareness of the signs and symptoms of VTE and ATE when prescribing a CHC.

Risk of developing a blood clot (VTE) in a year	
Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a CHC containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using a CHC containing **etonogestrel or norelgestromin**	About 6-12 out of 10,000 women
Women using a CHC containing **drospirenone, gestodene or desogestrel**	About 9-12 out of 10,000 women
Women using a CHC containing **chlormadinone, dienogest or nomegestrol**	Not yet known[1]

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

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on combined hormonal contraceptives. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority ADR form or online at **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Dr John Joseph Borg

Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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