

QUESTIONS AND ANSWERS ON COMBINED HORMONAL CONTRACEPTIVES: LATEST INFORMATION FOR WOMEN

The contents of the letter have been agreed with the European Medicines Agency (EMA), the marketing authorisation holders and the Malta Medicines Authority.

Why is new information being made available now?

- Previously, a Europe wide review looked at the benefits and risks of combined hormonal contraceptives and in particular at the risk of blood clots associated with the use of these medicines. This information is now updated with the latest evidence on the risk of blood clots with the use of combined hormonal contraceptives that contain the progestogen dienogest in combination with ethinylestradiol.
- This document is intended to give you more information about the risk of blood clots with combined hormonal contraceptives; including which conditions increase your risk of a 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 a lot of information on blood clots is provided here, this is because the review focused specifically on this risk. It is important to remember that combined hormonal contraceptives are highly effective medicines for preventing unwanted pregnancy and the overall risk of a blood clot is small. For most women, these medicines offer benefits which far outweigh the small risk of serious side effects.
- This information does not apply to any products that contain only a progestogen (no ethinylestradiol or estradiol).

What are the conclusions and recommendations of the review?

- The risk of blood clots with combined hormonal contraceptives has been known for many years and much information has already been provided to prescribers and women. The review confirmed our previous understanding of the risk as being small and so the focus is now on ensuring that you receive helpful information about this risk.
- If you have been using your combined hormonal contraceptive without any problems there is no need to stop taking it on the basis of this review. If you have any concerns, you should discuss them with your contraceptive provider at your next routine appointment, but keep taking your combined hormonal contraceptive in the meantime. Remember that suddenly stopping a combined hormonal contraceptive may result in unintended pregnancy.

What are combined hormonal contraceptives?

- Combined hormonal contraceptives are highly effective at preventing unintentional pregnancy. They contain two hormones: an estrogen and a progestogen. The estrogen in most products is called ethinylestradiol, but some products contain a different estrogen called estradiol. A wide range of progestogens are available.

What are the benefits of taking a combined hormonal contraceptive?

- In addition to preventing unintentional pregnancy, in the longer-term combined hormonal contraceptives have other advantages such as reducing the risk of cancer of the endometrium (lining of the womb) and cancer of the ovaries.
- Combined hormonal contraceptives can sometimes have other benefits such as improving menstrual cycle control, endometriosis (a disorder of the lining of the womb), pelvic inflammatory disease and, in some women, acne. Few studies have compared the beneficial effects of different combined hormonal contraceptives with each other, and so it is not clear if there are any meaningful differences between them.
- For most women, these medicines offer benefits which far outweigh the small risk of serious side effects.

What are the risks of combined hormonal contraceptives?

- As with all medicines, combined hormonal contraceptives are associated with some risks. The most common risks include breast discomfort, mood changes, and weight changes. Large studies have also found a very small increase in risk of breast cancer and cervical cancer.
- Perhaps the most important risk with combined hormonal contraceptives use is having a blood clot.

What can happen if I have a blood clot?

- 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). Blood clots can also form in the blood vessels of the heart, causing heart attacks, or the brain, causing strokes. Blood clots can therefore be very serious and, in very rare cases, can be fatal.

How high is the risk of a blood clot with combined hormonal contraceptives?

- All combined hormonal contraceptives slightly increase your risk of a blood clot; however, it is important to remember that this risk is small.
- Your risk of having a blood clot in association with the use of a combined hormonal contraceptive is highest in the first year of use – this applies if you have never used a combined hormonal contraceptive before or if you have had a break from taking your contraceptive (of 4 weeks or longer). The risk of a blood clot is also greater if you are naturally at higher risk (please see **“What other factors may increase my risk of a blood clot?”**).
- The risk of having a blood clot with a combined hormonal contraceptive falls after the first year of use but remains higher than if you were not using one. The risk goes back to normal a few months after you stop taking it.

Is my risk of a blood clot the same with all combined hormonal contraceptives?

- Large studies done over many years have provided good evidence that the risk of a blood clot may vary between the combined hormonal contraceptives. The difference is thought to depend on the dose of estrogen it contains and the type of progestogen. Remember that the overall risk of a blood clot with any combined hormonal contraceptive product is small for most women.
- Combined hormonal contraceptives that contain ethinylestradiol plus one of the following progestogens levonorgestrel, norgestimate, or norethisterone tend to have a lower risk compared with combined hormonal contraceptives that contain other progestogens.

How many women will have a blood clot?

- It is thought that:
 - About 2 out of 10 000 healthy women who do not use a combined hormonal contraceptive will have a blood clot during a year.

By comparison:

- About 5-7 out of 10 000 healthy women who use a combined hormonal contraceptive that contains ethinylestradiol plus levonorgestrel, norgestimate or norethisterone will have a blood clot during a year
- About 8-11 out of 10 000 healthy women who use a combined hormonal contraceptive that contains ethinylestradiol plus dienogest will have a blood clot during a year
- About 9-12 out of 10 000 healthy women who use a combined hormonal contraceptive containing ethinylestradiol plus gestodene, desogestrel or drospirenone will have a blood clot during a year
- About 6-12 out of 10 000 healthy women who use a combined hormonal contraceptive containing ethinylestradiol plus etonorgestrel or norelgestromin will have a blood clot during a year

- For estradiol valerate plus dienogest the risk of developing a blood clot during a year is about the same as with other combined hormonal contraceptives including combined hormonal contraceptives containing levonorgestrel
- The number of women who may develop a blood clot is not yet known for some combined hormonal contraceptives. These include products containing ethinylestradiol plus chlormadinone and estradiol plus nomegestrel.

Scenario	Risk of developing a blood clot in a year
Not using a combined hormonal contraceptive (pill, patch or ring) and not pregnant	About 2 out of 10,000 women
Using a combined hormonal contraceptive containing <u>ethinylestradiol plus</u> levonorgestrel, norgestimate or norethisterone	5-7 out of 10,000 women
Using a combined hormonal contraceptive containing <u>ethinylestradiol plus</u> dienogest	8-11 out of 10,000 women
Using a combined hormonal contraceptive containing <u>ethinylestradiol plus</u> gestodene, desogestrel or drospirenone	9-12 out of 10,000 women
Using a combined hormonal contraceptive containing <u>ethinylestradiol plus</u> etonorgestrel or norelgestromin	6-12 out of 10,000 women
Using a combined hormonal contraceptive containing <u>estradiol valerate plus</u> dienogest	About the same as with other combined hormonal contraceptives including contraceptives containing levonorgestrel
Using a combined hormonal contraceptive containing <u>ethinylestradiol plus chlormadinone or estradiol plus nomegestrel</u>	Not known

What other factors may increase my risk of a blood clot?

- Even without using a combined hormonal contraceptive the likelihood of a blood clot occurring differs between individuals. A number of conditions mean you will have a naturally higher risk of a blood clot — e.g.:
 - you are older than about 35 years
 - you are very overweight
 - you have a brother, sister or parent who had a blood clot at a relatively early age (e.g. younger than about 50)
 - you have a medical condition that increases the risk of a blood clot, such as cancer
 Women who smoke are at increased risk of blood clots causing heart attacks and strokes, particularly if they are over 35 years old.
- You may have none of the above factors in which case your risk of developing a blood clot with use of a combined hormonal contraceptive is extremely low.
- If you have several of these factors your risk of a blood clot with use of a combined hormonal contraceptive is higher. In some cases having several risk factors may mean that you should not use a combined hormonal contraceptive and you should discuss another form of contraception with your prescriber.
- Your risk of a blood clot will change over time — for example if you gain a lot of weight, change your smoking status, have major surgery, it is important that you tell the person who prescribes your contraception.

What should I look out for?

- It is important to watch out for symptoms of a blood clot, especially if you:
 - Just had an operation
 - have been off your feet for a long time (e.g. because of an injury or illness) or have been on a long 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 of your legs that may be accompanied by tenderness, warmth or changes in the skin colour such as turning pale, red or blue.	Deep vein thrombosis
Sudden unexplained breathlessness or rapid breathing; severe pain in the chest which may increase with deep breathing; sudden cough without an obvious cause (which may bring up blood).	Pulmonary embolism
Chest pain, discomfort, pressure, heaviness, upper body discomfort radiating to the back, jaw, throat, arm together with a 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 understanding; sudden loss of vision or blurred vision; severe headache/migraine that is worse than normal.	Stroke

What should I expect when I see my doctor?

- The doctor will discuss the benefits and risks of the combined hormonal contraceptives with you. In particular they should highlight the small risk of blood clots, the conditions that increase your risk of blood clots and go through some of the key signs and symptoms to be aware of.

What do I need to do if I take a combined hormonal contraceptive?

- There is no need for anyone who has been using their combined hormonal contraceptive without any problems to stop taking it on the basis of this review. If you have concerns about your contraception you should discuss them with your contraceptive provider at the next routine appointment. You should keep taking your contraceptive until you have done so.
- Remember that suddenly stopping your combined hormonal contraceptive may result in unintended pregnancy. The risk of a blood clot during pregnancy and immediately after birth is higher than the risk associated with combined hormonal contraceptive use.
- It is important that you remember to tell the healthcare professional who is treating you (for example if you are going to have a surgery) that you are taking a combined hormonal contraceptive.

Where can I find further information?

- If you use a combined hormonal contraceptive you should carefully read the patient information leaflet. It includes information on the risk of blood clots and the signs and symptoms of a blood clot (e.g. deep vein thrombosis, pulmonary embolism, heart attack or stroke), and guidance what to do if you think you have any of these.

- Further information is available at the following websites:
www.medicinesauthority.gov.mt
www.ema.europa.eu

Suspected Adverse Drug Reactions (side effects) or medication errors may be reported using the Medicines Authority ADR reporting form, which is available online at <http://www.medicinesauthority.gov.mt/adrportal>, and sent by post or email to; P: Pharmacovigilance Section at Post-Licensing Directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000
E: postlicensing.medicinesauthority@gov.mt

More information is available on the [**Guidance Notes for Pharmaceutical Companies on Pharmacovigilance Obligations for Medicinal Products for Human Use**](#) which can be found on the Medicines Authority's website following this link: <http://www.medicinesauthority.gov.mt/adrindustry?l=1>