Information kit on combined hormonal contraceptives

In February 2013, the European Medicines Agency (EMA) started a review of certain combined hormonal contraceptives (CHCs) authorised in the European Union (EU) following concerns in France about the known risk of venous thromboembolism (VTE or blood clots in veins) and possible pulmonary embolism fatal events with these medicines. The review also covers the risk of arterial thromboembolism (blood clots in arteries), which can potentially cause a stroke or heart attack.

CHCs contain two types of hormones, an oestrogen and a progestogen. The review includes contraceptives containing the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate. The CHCs being reviewed are sometimes referred to as ‘third generation’ or ‘fourth generation’ contraceptives (see below) and are available as pills, skin patches and vaginal rings. The current review assesses the risk of thromboembolism with each progestogen individually.

Key messages (to be updated at the time of the PRAC recommendation)

- Combined hormonal contraceptives (CHCs) are an effective method of preventing pregnancy.
- All CHCs are associated with a small increase in risk of VTE compared to no use.
- The absolute risk of VTE is low for all CHCs. Information and advice about the different risks of VTE with the various products is already included in the summary of product characteristics and patient information leaflet to support informed decision-making by prescribers and women. The differences in risks between these products are being discussed as part of the ongoing review.
- The absolute risk of arterial thromboembolism (ATE) is very low and is currently thought to be similar for all progestogens.
- If a woman has concerns, careful discussion with her doctor should help her decide which contraceptive may suit her best. The ongoing review in itself presents no reason for a woman to stop taking her CHC.
- Women using CHCs should seek immediate medical advice if they think they have symptoms of VTE or ATE, which include:
  - Severe pain and swelling in either of the legs or more rarely in the arms;
  - an unusual sudden cough;
  - sudden sharp pain in the chest which may reach the left arm;
  - breathlessness;
  - any unusual, severe, or long-lasting headache or worsening of migraine;
- partial or complete loss of vision, or double vision;
- slurring of speech or speech disability;
- sudden changes to hearing, sense of smell, or taste;
- dizziness or fainting;
- weakness or numbness in any part of the body;
- severe pain in the abdomen.
Generations of hormonal contraceptive products – a history

Hormonal contraceptives are sometimes classified by ‘generations’, reflecting at what point in time they were developed and authorised for use.

The first generation of contraceptive pills, developed in the 1960s, used a high concentration of oestrogen (no progestogen component). Later, a second generation of hormonal contraceptive was introduced. These medicines combined lower levels of oestrogens with various progestogens in different concentrations, often levonorgestrel. Since the 1990s, further combined hormonal contraceptive products have been developed. They contain different progestogens from those used in second generation products, with similar contraceptive effect. These newer products are sometimes referred to as third and fourth generation contraceptives.

This classification is not science-based and not standardised, and may differ between institutions and publications.

There are also hormonal contraceptives that contain a progestogen only, and these products fall outside the scope of this referral.

Background on the current review of CHCs

The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing all available data on the risk of VTE and ATE with the above mentioned CHCs, and will issue a recommendation on the matter.

Previous EMA reviews of combined oral contraceptives (see more details below) concluded that their absolute risk of VTE is low, and information on the risk and its management is included in their product information. Previous reviews did not examine the risk of ATE associated with these medicines. This risk is very low and is currently considered to be similar for all progestogens.

The PRAC is examining data gathered from marketing authorisation holders, drug utilisation studies, and published literature, as well as cases of thromboembolism reported by patients and healthcare professionals. Experts have been convened specifically to discuss this issue and have presented their views to the PRAC. All information will be fed into the current review.

The PRAC recommendations will be shared with the Committee for Medicinal Products for Human Use (CHMP) which will adopt an opinion. This opinion will then be sent to the European Commission for a legally-binding decision.

For more information on the current review of CHCs, please click on the following link:


Previous EMA reviews

Oral combined hormonal contraceptives: reviewed in 2001

In 2001, the EMA’s scientific committee then called the Committee for Proprietary Medicinal Products (CPMP) concluded an assessment on the risk of VTE associated with the use of so-called third generation combined oral contraceptives containing the progestogens desogestrel or gestodene.

The review began in 1995 and was based on three independent epidemiological studies that indicated an increased risk of VTE for these products, compared to combined oral contraceptives containing the progestogen levonorgestrel. The EMA issued public statements in 1995, and also, taking into account newly-emerging data, in 1996 and 1997. Further to the initial studies, the 2001 review evaluated additional epidemiological studies and studies on blood clotting mechanisms, and concluded the following on the small increased VTE risk of the so-called third generation products:
Drospirenone-containing CHCs: last reviewed in 2012

In 2012, the CHMP Pharmacovigilance Working Party (PhVWP) – now superseded by the PRAC – completed an informal review of two new epidemiological studies regarding the risk of VTE associated with oral drospirenone-containing CHCs. As these products only became available after 2001, they were not included in the 2001 review.

The findings of these studies confirmed the conclusion of a review of these products by PhVWP in May 2011 that the risk of VTE with any oral CHC (including those containing drospirenone) is low. The risk for drospirenone-containing products is higher than for those containing levonorgestrel and may be similar to the risk for those containing desogestrel or gestodene (so-called third generation CHCs).

For more information on the conclusions of the PhVWP to national competent authorities, please click on the following link:


Diane 35 and generics

The PRAC has also recently conducted a separate review of Diane 35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms) and its generics – a treatment for acne and other hormone related conditions. The progestogen content of Diane 35, cyproterone, suppresses ovulation and therefore also has a contraceptive effect, although it is not authorised as a contraceptive in its own right.

In May 2013, the PRAC concluded that the benefits of Diane 35 and its generics outweigh the risks, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism (excessive unwanted growth of hair in women) in women of reproductive age. Furthermore, Diane 35 should only be used for the treatment of acne when alternative treatments, such as topical therapy and oral antibiotic treatment, have failed.

Since Diane 35 and its generics acts as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

For more information on the review of Diane 35 and its generics, please see here: