VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Combined oral contraceptive pills are widely used by women of child bearing potential across globe.

Unintended pregnancy is a major problem in the United States. Approximately 3 million pregnancies per year —50% of all pregnancies — are unintended, and this rate is significantly higher than that in other developed countries. Unintended pregnancy in the United States results in 1.2 million abortions per year, has negative effects on women's health and education and the health of newborns, and imposes a considerable personal burden as well as a financial burden on families and society. **(Winner B. *et al* 2012)**

Millions of women use birth control pills for contraceptive and non-contraceptive purpose. The oral contraceptive pill (OCP) remains the most popular form of contraception among young women in the UK with 54% of women who use contraception between the ages of 20–24 years using the OCP. **(Killey J 2007; Molloy G. J. *et al,* 2012)**

VI.2.2 Summary of treatment benefits

The Gestodene /Ethinylestradiol film-coated tablet is a combined oral contraceptive pill. It is used to prevent pregnancy. It contains two types of female sex hormones, oestrogen and progestogen.

The pill changes the body's hormonal balance so that the ovaries do not ovulate (produce an egg). It also causes the mucus made by the neck of the womb (cervix) to thicken and form a mucous plug. This makes it difficult for sperm to get through to the womb (uterus) to fertilise an egg. Gestodene/ Ethinylestradiol film-coated tablets also make the lining of the womb thinner. This makes it less likely that a fertilised egg will be able to attach to the uterus.

Gestodene / Ethinylestradiol tablet can be found in the following presentations:

a) 24/4 day
b) 21/7 day or
c) 21 day active only pill.

The 24/4 day pill blister contains 24 active yellow tablets of Gestodene 60 / ethinylestradiol 15 mcg and 4 white placebo tablets.
In the case of Gestodene 75 / ethinylestradiol 20 and 30 mcg, the presentation can contain 21 active white tablet only or 21 active plus 7 placebo green tablet.

For the presentations with placebo, the two differently coloured tablets are arranged in order, first the active and then the placebo tablets.
In the case of Gestodene 75 /ethinylestradiol 20 and 30 mcg the appearance of the active tablets is different. In the case of Gestodene 75 /ethinylestradiol 20, tablets are debossed with 'C' on one side and '34' on the other. In the case of Gestodene 75 /ethinylestradiol 30, tablets are debossed with 'C' on one side and '33' on the other.

Benefits of taking this tablet include:

- It is very effective
- It does not interfere with sex
- It makes periods lighter, less painful and more regular
- It relieves premenstrual tension for some women

[http://www.nhs.uk/Conditions/contraception-guide/Pages/combined-contraceptive-pill.aspx**, accessed on 04 July 2013]**

In the leaflets also appear advise about how to proceed when the woman forget to take one or more tablets. In summary the advice is similar when the forgotten tablet is the active one, but some differences are found when the missed tablet is the inactive one (placebo).

VI.2.3 Unknowns relating to treatment benefits

Lactation may be influenced by contraceptive pills since they may reduce the amount of breast milk and change its composition. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the infant. This pill is generally not recommended when woman is breast-feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Blood clots and related problems (Arterial and venous thrombotic and thromboembolism)	Use of Gestodene / Ethinylestradiol film-coated tablets increases the risk of developing a venous blood clot. Its use is also associated with an increase of the risk of an arterial blood clot.	Patients should not take these pills if: • They have (or have ever had) a blood clot in a blood vessel of the leg (thrombosis), lung (pulmonary embolism) or other organs • They have (or have ever had) a heart attack or a stroke • They have (or have ever

Risk	What is known	Preventability
		had) a disease that can be an indicator of a heart attack in the future • They have a disease that may increase the risk of a clot in the arteries. This applies to the following diseases: - diabetes with damaged blood vessels - very high blood pressure - a very high level of fat in the blood (cholesterol or triglycerides) • They have a disturbance of blood clotting • They have history of migraine The use of the pill increases the risk of developing a venous blood clot (venous thrombosis) as well as the risk of an arterial blood clot (arterial thrombosis). The risk of an venous blood clots and arterial blood clot in women using combination pills increases: • With increasing age • If one of the patient's close relatives ever had a blood clot in the leg, lung (pulmonary embolism), or other organs at a young age

Risk	What is known	Preventability
		• If the patient has to have surgery, if patients have had a serious accident or if patients are immobilized for a long time • If the patient smokes • If the fat content of patient's blood is increased (cholesterol or triglycerides) • If the patient is overweight • If one of patients' close relatives ever had a heart attack or stroke at a young age • If the patient has high blood pressure • If the patient suffers from migraine • If the patient has a problem with heart (valve disorder, a disturbance of the cardiac rhythm) Patient should stop taking the pills and contact doctor immediately in case of any possible signs of a blood clot, such as: • Severe pain and/or swelling in one of patients' legs • Sudden severe pain in the chest which may reach the left arm • Sudden breathlessness • sudden cough without an obvious cause

Risk	What is known	Preventability
		• Unusual, severe or long-lasting headache or worsening of migraine • Partial or complete blindness or double vision • Difficulty in speaking or inability to speak • Giddiness or fainting • Weakness, strange feeling or numbness in any part of the body
Benign and malign liver tumours	In rare cases, benign liver tumours and in even fewer cases malignant liver tumours have been reported in women using pills.	Patients should not take Gestodene + Ethinylestradiol film-coated tablets: • If the patient has (or have ever had) a tumour in the liver Patients should contact their doctor if they have unusually severe abdominal pain.
Breast cancer, cervical cancer	Breast cancer has been observed slightly more often in women using combination pills, but it is not known whether this is caused by the treatment. The occurrence of breast tumours gradually decreases after stopping the combination hormonal contraceptives. Cervical cancer has been observed in long term users of these pills.	Patients should not take Gestodene + Ethinylestradiol film-coated tablets: • If the patient has (or have ever had) or if patients are suspected of having breast cancer or cancer of the genital organs; If a close relative of the patient has or has ever had breast cancer, special care of the patients should be taken while using Gestodene 60 + Ethinylestradiol film-coated tablets. Doctor may need to examine patients regularly.

Risk	What is known	Preventability
		Patients should regularly check their breasts. Patients should contact the doctor if they feel any lump. Patients should contact their doctor if they have unusually severe abdominal pain.
Effect on hereditary angioedema	In women with hereditary angioedema products containing estrogens may induce or worsen symptoms of angioedema.	Doctors to be aware of worsen symptoms of angioedema.
Disturbances of liver function	Use of COC is contraindicated in cases of severe disturbances of liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.	Doctors to be aware of any disturbance in liver function
Pancreatitis	Use of COC is contraindicated in patients with pancreatitis or previous pancreatitis associated with severe hypertriglyceridaemia In women with hypertriglyceridaemia or with a family history of hypertriglyceridaemia, an increased risk of pancreatitis can occur when using oral contraception.	Doctors to check patients with hypertriglyceridaemia.
Increased blood pressure	Increased blood pressure is a risk factor for stroke and	If sustained hypertension develops during the use of a COC, antihypertensive

Risk	What is known	Preventability
	myocardial infarction. Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare.	treatment should normally be instigated at a level of 160/100 mm Hg in uncomplicated patients or at 140/90 mm Hg in those with target organ damage, established cardiovascular disease, diabetes or with increased cardiovascular risk factors. Decisions about the continued use of the COC should be made at lower BP levels, and alternative contraception may be advised.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Worsening of endogenous depression/depressed mood	Some conditions have been reported to occur or deteriorate with COC use. Consideration should be given to stopping COC therapy if worsening of endogenous depression/depressed mood occur during use.
Crohn's disease and ulcerative colitis	Some conditions have been reported to occur or deteriorate with COC use. Consideration should be given to stopping COC therapy if any of the following occur during use.

VI.2.5 Summary of risk minimization measures by safety concern

Summary of Product Characteristics (SmPC) of Gestodene / Ethinylestradiol film-coated tablets provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the

package leaflet (PL). All these risk minimization measures are given in SmPC and PL of Gestodene / Ethinylestradiol film-coated tablets.

This medicine has no additional risk minimisation measures. However, Notification to the Pharmacovigilance risk assessment committee (PRAC) of referral under article 31 of directive with regard to 3rd and 4th generation combined oreal contraceptives has impact on the RMP and SmPC/PL of this product.

Article 31 of Directive 2001/83/EC regarding Combined hormonal contraceptives (EMEA/H/A-31/1356).

[For all gestodene containing products listed in Annex I, *the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]*

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

[The wording below should be inserted at the end of this section]

[...]

The decision to prescribe [invented name] should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with [invented name] compares with other CHCs (see sections 4.3 and 4.4).

Section 4.3 - Contraindications

[This section should be amended to include the following contraindications]
Combined hormonal contraceptives (CHCs) should not be used in the following conditions.

[...]

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilisation (see section 4.4)

- A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)

- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms.
  - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia

[...]

Section 4.4 - Special warnings and precautions for use

[This section should be amended to reflect the following wording]

Warnings

[...]

If any of the conditions or risk factors mentioned below is present, the suitability of [invented name] should be discussed with the woman.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of [Invented name] should be discontinued.

Risk of venous thromboembolism (VTE)

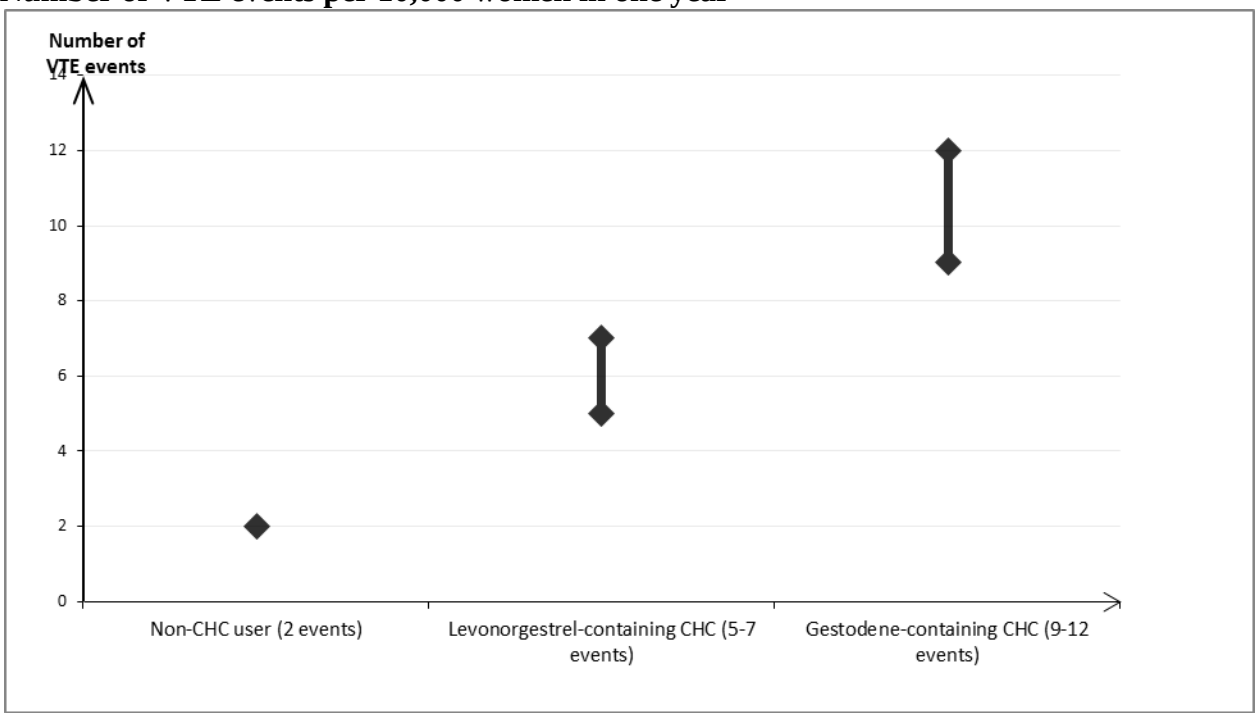
[The wording below should be inserted at the top of this section]

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as [invented name] may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with [invented name], how her current risk factors influence this risk, and**

that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

[The wording below should be inserted in this section]
In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).
It is estimated[7] that out of 10,000 women who use a CHC containing gestodene between 9 and 12 women will develop a VTE in one year; this compares with about 6[8] in women who use a levonorgestrel-containing CHC.
In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.
VTE may be fatal in 1-2% of cases.

[The following graph should be inserted here.]
Number of VTE events per 10,000 women in one year



[The following wording to be kept/added (as appropriate)]

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries.

[The following should be deleted (where applicable)]

[7] These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.
[8] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

There is no consensus as to whether the occurrence of these events is associated with the use of CHCs.

[This following wording should be inserted in this section]

Risk factors for VTE

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table).

[Invented name] is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if [invented name] has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.
Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking,
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).
Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.
If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). [Invented name] is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	

Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.
Symptoms of a cerebrovascular accident can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).
Symptoms of myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

[…]

Medical examination/consultation

Prior to the initiation or reinstitution of [invented name] a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of [invented name] compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.
The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

[...]

Section 4.6 - Fertility, pregnancy and lactation

Pregnancy
[The following wording should be added to this section]

The increased risk of VTE during the postpartum period should be considered when re-starting [invented name] (see section 4.2 and 4.4).

Section 4.8 – Undesirable effects

[This following wording should be reflected in this section]

[…]

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

[…]

[VTE or ATE should be listed in the adverse events table, under the frequency "Rare".]

II. Package Leaflet

[The wording below should be inserted at the top of the package leaflet]

Important things to know about combined hormonal contraceptives (CHCs):

- They are one of the most reliable reversible methods of contraception if used correctly
- They slightly increase the risk of having a blood clot in the veins and arteries, especially in the first year or when restarting a combined hormonal contraceptive following a break of 4 or more weeks
- Please be alert and see your doctor if you think you may have symptoms of a blood clot (see section 2 "Blood clots")

[…]

Section 2. What you need to know before you use [Invented name]

[The wording below should be inserted at the top of this section]

General notes

Before you start using [invented name] you should read the information on blood clots in section 2. It is particularly important to read the symptoms of a blood clot – see Section 2 "Blood clots").

[…]

When you should not use [Invented name]

[This section should be amended to include the below wording]

You should not use [Invented name] if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.

- if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs;
- if you know you have a disorder affecting your blood clotting – for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, Factor V Leiden or antiphospholipid antibodies;
- if you need an operation or if you are off your feet for a long time (see section 'Blood clots');
- if you have ever had a heart attack or a stroke;
- if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms);

- if you have any of the following diseases that may increase your risk of a clot in the arteries:
  - severe diabetes with blood vessel damage
  - very high blood pressure
  - a very high level of fat in the blood (cholesterol or triglycerides)
  - a condition known as hyperhomocysteinaemia
- if you have (or have ever had) a type of migraine called 'migraine with aura';

[…]

When to take special care with [Invented name]

[The below wording should be inserted in this section]

When should you contact your doctor?
Seek urgent medical attention

- if you notice possible signs of a blood clot that may mean you are suffering from a blood clot in the leg (i.e. deep vein thrombosis), a blood clot in the lung (i.e. pulmonary embolism), a heart attack or a stroke (see 'Blood clot' (thrombosis) section below.

For a description of the symptoms of these serious side effects please go to "How to recognise a blood clot".

[...]

Tell your doctor if any of the following conditions apply to you.
If the condition develops, or gets worse while you are using [invented name], you should also tell your doctor.
[...]

- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease);
- if you have systemic lupus erythematosus (SLE –; a disease affecting your natural defence system);
- if you have haemolytic uraemic syndrome (HUS - a disorder of blood clotting causing failure of the kidneys);
- if you have sickle cell anaemia (an inherited disease of the red blood cells);
- if you have elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);

- if you need an operation, or you are off your feet for a long time (see in section 2 'Blood clots ');
- if you have just given birth you are at an increased risk of blood clots. You should ask your doctor how soon after delivery you can start taking [invented name];
- If you have an inflammation in the veins under the skin (superficial thrombophlebitis);
- If you have varicose veins.

BLOOD CLOTS
Using a combined hormonal contraceptive such as [invented name] increases your risk of developing a blood clot compared with not using one. In rare cases a blood clot can block blood vessels and cause serious problems.
Blood clots can develop

- in veins (referred to as a 'venous thrombosis', 'venous thromboembolism' or VTE)
- in the arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.
It is important to remember that the overall risk of a harmful blood clot due to [invented name] is small.

HOW TO RECOGNISE A BLOOD CLOT
Seek urgent medical attention if you notice any of the following signs or symptoms.

Are you experiencing any of these signs?	What are you possibly suffering from?
• swelling of one leg or along a vein in the leg or foot especially when accompanied by: • pain or tenderness in the leg which may be felt only when standing or walking • increased warmth in the affected leg • change in colour of the skin on the leg e.g. turning pale, red or blue	Deep vein thrombosis
• sudden unexplained breathlessness or rapid breathing; • sudden cough without an obvious cause, which may	Pulmonary embolism

bring up blood; • sharp chest pain which may increase with deep breathing; • severe light headedness or dizziness; • rapid or irregular heartbeat • severe pain in your stomach; If you are unsure, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').	
Symptoms most commonly occur in one eye: • immediate loss of vision or • painless blurring of vision which can progress to loss of vision	Retinal vein thrombosis (blood clot in the eye)
• chest pain, discomfort, pressure, heaviness • sensation of squeezing or fullness in the chest, arm or below the breastbone; • fullness, indigestion or choking feeling; • upper body discomfort radiating to the back, jaw, throat, arm and stomach; • sweating, nausea, vomiting or dizziness; • extreme weakness, anxiety, or shortness of breath; • rapid or irregular heartbeats	Heart attack
• sudden weakness or numbness of the face, arm or leg, especially on one side of the body; • sudden confusion, trouble speaking or understanding; • sudden trouble seeing in one or both eyes; • sudden trouble walking, dizziness, loss of balance or	Stroke

coordination; • sudden, severe or prolonged headache with no known cause; • loss of consciousness or fainting with or without seizure. Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke..	
• swelling and slight blue discolouration of an extremity; • severe pain in your stomach (acute abdomen)	Blood clots blocking other blood vessels

BLOOD CLOTS IN A VEIN

What can happen if a blood clot forms in a vein?

- The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.
- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?

The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more

After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.

When you stop [invented name] your risk of a blood clot returns to normal within a few weeks.

What is the risk of developing a blood clot?

The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are taking.
The overall risk of a blood clot in the leg or lung (DVT or PE) with [invented name] is small.

[The below wording should be inserted in this section]

- […]
- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains gestodene such as [invented name] between about 9 and 12 women will develop a blood clot in a year.
- The risk of having a blood clot will vary according to your personal medical history (see "Factors that increase your risk of a blood clot" below)
- […].

	Risk of developing a blood clot in a year
Women who are **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive pill containing **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using [Invented name]	About 9-12 out of 10,000 women

Factors that increase your risk of a blood clot in a vein
The risk of a blood clot with [invented name] is small but some conditions will increase the risk. Your risk is higher:

- if you are very overweight (body mass index or BMI over 30kg/m^2);
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g. below the age of about 50). In this case you could have a hereditary blood clotting disorder;
- if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of [invented name] may need to be stopped several weeks before surgery or while you are less mobile.

If you need to stop [invented name] ask your doctor when you can start using it again.

- as you get older (particularly above about 35 years);
- if you gave birth less than a few weeks ago

The risk of developing a blood clot increases the more conditions you have.
Air travel (>4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.
It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that [invented name] needs to be stopped.
If any of the above conditions change while you are using [invented name], for example a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

BLOOD CLOTS IN AN ARTERY
What can happen if a blood clot forms in an artery?
Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery
It is important to note that the risk of a heart attack or stroke from using [invented name] is very small but can increase:

- with increasing age (beyond about 35 years);
- **if you smoke.** When using a combined hormonal contraceptive like [invented name] you are advised to stop smoking. If you are unable to stop smoking and are older than 35 your doctor may advise you to use a different type of contraceptive;
- if you are overweight;
- if you have high blood pressure;
- if a member of your immediate family has had a heart attack or stroke at a young age (less then about 50). In this case you could also have a higher risk of having a heart attack or stroke;
- if you, or someone in your immediate family, have a high level of fat in the blood (cholesterol or triglycerides);
- if you get migraines, especially migraines with aura;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation)
- if you have diabetes.

If you have more than one of these conditions or if any of them are particularly severe the risk of developing a blood clot may be increased even more.
If any of the above conditions change while you are using [invented name], for example you start smoking, a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

[…]
Section 4. Possible side effects

[The following text should be inserted in this section]
Like all medicines, [Invented name] can cause side effects, although not everybody gets them. If you get any side effect, particularly if severe and persistent, or have any change to your health that you think may be due to [invented name], please talk to your doctor.
An increased risk of blood clots in your veins (venous thromboembolism (VTE)) or blood clots in your arteries (arterial thromboembolism (ATE)) is present for all women taking combined hormonal contraceptives. For more detailed information on the different risks from taking combined hormonal contraceptives please see section 2 "What you need to know before you use [invented name]".

[The below wording should be added and the frequency of the adverse events should be aligned to that of the SmPC]
- harmful blood clots in a vein or artery for example:
    - in a leg or foot (i.e. DVT)
    - in a lung (i.e. PE)
    - heart attack
    - stroke
    - mini-stroke or temporary stroke-like symptoms, known as a transient ischaemic attack (TIA)
    - blood clots in the liver, stomach/intestine, kidneys or eye.

The chance of having a blood clot may be higher if you have any other conditions that increase this risk (See section 2 for more information on the conditions that increase risk for blood clots and the symptoms of a blood clot)
[…]

VI.2.6 Planned post authorisation development plan

No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time

This section is not applicable as this is version 01 of RMP.