VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Approximately 85 among 100 women get pregnant within a year without using any contraceptive method. After a single act of intercourse, the expected pregnancy rate is 6 to 8% with no contraception. [i,ii] Between 11 and 54% of unintended pregnancies are terminated artificially.[iii]

Averagely, 46 million abortions take place every year, out of which 20 million are performed under unsafe conditions.[iv]

VI.2.2 Summary of treatment benefits

Contraceptive pills that contain two hormones are called "combination" pills. Gestodene + Ethinylestradiol 0.06 mg + 0.015 mg film-coated tablets are combined oral contraceptive pills indicated for prevention of pregnancy in women.

The contraceptive effect of Gestodene + Ethinylestradiol 0.06 mg + 0.015 mg film-coated tablets are based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.

Non-contraceptive health benefits

It is generally accepted that combination oral contraceptives have substantial health benefits unrelated to their contraceptive use.

OCs significantly reduce the incidence of ovarian and endometrial cancer within 6 months of use, and the incidence is decreased 50% after two years of use. Furthermore, this protective effect persists for up to 15 years after oral contraceptive use is discontinued. These agents also decrease the incidence of ovarian cysts and benign fibrocystic breast disease.

OCs have major benefits related to menstruation in many women. These include more regular menstruation, reduced menstrual blood loss and less iron-deficiency anaemia, less premenstrual tension, and decreased frequency of dysmenorrhoea. There is also a decreased incidence of pelvic inflammatory disease and ectopic pregnancies, and endometriosis may be ameliorated.[v]

VI.2.3 Unknowns relating to treatment benefits

Treatment benefits have been well established in the target population, so there are no unknowns relating.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Blood clots in veins and arteries (venous	*{Invented name}* is a combined oral contraceptive, also called „the pill". It contains two types of female	*{Invented name}* is a prescription-only medicine and should be used

Risk	What is known	Preventability
thromboembolic diseases: blood clots in the vessels (veins) in the legs (which can travel to the lung) or in other organs) **(arterial thromboembolic diseases: blood clots in the blood vessels of the brain, in the heart or in other organs)** (*Thromboembolism (venous and arterial))*	hormones: an estrogen, *ethinylestradiol* and *gestodene* in a low dose. The use of any combination pill, including *{Invented name}* increases the risk of developing a blood clot in the vessels compared to women who do not use the pill. Blood clots can develop in veins (such a condition is called a „venous thrombosis" or „venous thromboembolism", VTE) or they can develop in the arteries („arterial thrombosis", or „arterial thromboembolism", ATE). In either case these blood clots can cause a serious problem, and very rarely, they may be fatal. **<u>Blood clots in a vein (venous thromboembolism, VTE)</u>** If a blood clot forms in a vein of the leg or foot it can cause a deep vein thrombosis (DVT). If this clot breaks away from the vein where it is formed, the clot can travel to the lung, where it might block an artery of the lungs, causing a so-called "pulmonary embolism (PE)". Very rarely a clot may form in a vein in another organ such as the brain, eye, the bowels, kidney or liver. The risk of developing a blood clot in a vein is highest during the first year *{Invented name}* is used for the first time. The risk may also be higher if the woman restarts 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 the woman was not using a combined hormonal contraceptive. The risk is not as	only after consultation with a doctor. As a precaution measure, *{Invented name}* should not be used in the following cases: - if the woman has or has ever had a blood clot in a blood vessel of the legs (deep vein thrombosis), in the lung (pulmonary embolus) or in other organs, - if the patient has a disorder affecting her blood clotting, such as antitrombin III.-, protein C, -S-deficiency, Factor V Leiden, antiphospolipid antibodies - if the patient notice the first stages or signs of a blood clot - if the patient need an operation or if she is off her leg for a long time - if the patient has or has ever had a heart attack or stroke, - if the woman has or has ever had a disease that can be a predictor of a heart attack (for example, angina pectoris, which causes severe pain in the chest) or of a stroke (for example, a transient slight stroke with no residual effects), - if the patient has a disease that may increase the risk of a clot in the arteries, such as hyperhomocyteinaemia (a medical condition characterized by an abnormally high level of homocysteine in the blood) - if the patient has or has ever had migraine along with perception disorder, paraesthesia (a

Risk	What is known	Preventability
	high as the risk of developing a blood clot during pregnancy. When the woman stops *{Invented name}*, her risk of a blood clot returns to normal within a few weeks. The risk depends on the patient's natural risk of VTE and the type of combined hormonal contraceptive she is taking. The overall risk of a blood clot in the leg or lung (DVT or PE) with *{Invented name}* is small. - 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 about 9-12 will develop a blood clot in a year. The risk of having a blood clot will vary according to the patient's personal medical history. The risk of a venous thrombosis in women, who are taking combined pills, increases in the following cases: - with increasing age (particularly above about 35 years), - if the woman is overweight (body mass index over 30kg/m²), - if one of the woman's close relatives has had a blood clot	tingling/ tickling sensation) or movement disorder, - if the patient has very high, uncontrolled blood pressure (values constantly above 140/90 mm Hg), - if the patient has severe diabetes with blood vessel damage or her blood sugar fluctuates uncontrollably, - if the patient has a very high level of fat in the blood (cholesterol or triglycerides) There are several diseases/conditions, when *{Invented name}* must be used only under close medical supervision, because such diseases/conditions may increase the risk of the development of blood clots in the vessels. Therefore it is very important that women always inform their doctor about their past and current diseases/ medical conditions, especially in the following cases: - if the patient smokes - if the patient suffers from a disorder of the blood fat (lipid) metabolism, - if the patient has high blood pressure, - if the woman has diabetes (diabetes mellitus), - if the patient is overweight - if the woman suffers from migraine, - if the patient suffers from Crohn's disease or ulcerative colitis (inflammatory bowel disease).

Risk	What is known	Preventability
	(thrombosis) in the leg, lung, or other organ at a young age, - if the patient needs to have an operation, or if she is off her feet for a long time because of an injury or illness, or she has her leg in a cast. It is important to tell the patient's doctor in advance that the patient is using *{Invented name}* as the treatment may have to be stopped before the operation or if the patient becomes bedridden for a longer period. The patient's doctor will tell her when to start again. - air travel (>4 hours) may temporarily increase the risk of a blood clot, particularly if the patient has some of the other listed risk factors - if the patient previously had blood clots in her veins - if the patient has a blood clotting disorder (such as a genetic disorder called "Leyden mutation"); - if the woman gave birth less than a few weeks ago - there are some other diseases, which may increase the risk for a VTE, e.g. if the woman has • cancer • a blood disorder known as haemolytic uremic syndrome – (HUS) (a blood disease where blood clots cause the kidneys to fail) • systemic lupus erythaematosus – (SLE) (an inflammatory disease, which can affect many parts of the body, including skin, joints and inner organs)	- if the woman has sickle cell anaemia (an inherited disease of the red blood cells) - if the patient has a blood disorder known as haemolytic uremic syndrome – HUS (a blood disease where blood clots cause the kidneys to fail), - if the woman has systemic lupus erythaematosus – SLE (an inflammatory disease, which can affect many parts of the body, including skin, joints and inner organs). - if the patient has varicose veins or an inflammation of a vein under the skin- usually in the legs - (superficial thrombophlebitis), - if the patient need an operation or she is are off her feet for a long time - if she has just given birth If the patient has increased risk for developing blood clots, the doctor should be informed about it before starting the treatment, and the patient should see her doctor more often for checkups. In some cases, if the patient has severe or multiple risk factors, alternative contraceptive methods should be considered to prevent the risk of blood clot formation. If any of the above listed conditions change while the woman is using *{Invented name}*, she should inform her doctor, as these changes may increase the risk of a thrombosis and therefore re-assessment of the woman's status may be necessary. The following healthy lifestyle can help to prevent blood clots:

Risk	What is known	Preventability
	• sickle cell anaemia (an inherited disease of the red blood cells) • inflammatory bowel disease (Crohn's disease or ulcerative colitis) The risk of developing a blood clot increases the more conditions the woman has. Symptoms of a venous thrombosis can be the following: • *Deep vein thrombosis (when the blood clot develops in a vein of the legs):* - severe pain or swelling in either of the legs or feet (which may be felt only when standing or walking), especially when accompanied by increased warmth in the affected leg or change in colour of the skin on the leg (e.g. turning pale, red or blue) • *Pulmonary embolism (if the clot breaks away from the veins where it is formed and travels to the lung where it blocks the arteries of the lungs):* - sudden unexplained breathlessness or rapid breathing; - an unusual sudden cough (which may bring up blood); - severe pain in the chest which may increase with deep breathing; - severe light headedness or dizziness; - rapid or irregular heartbeat - severe pain in the abdomen	- regular physical activity - maintaining healthy body weight - controlling blood sugar, blood pressure and cholesterol levels - avoiding smoking: Women are strongly advised to stop smoking when they use **{***Invented name}*, especially if they are older than 35 years. If the woman is a smoker and she is older than 35 years, other methods of contraception should be considered. Early detection of the symptoms helps the correct diagnosis in time and improves the clinical outcome. *{Invented name}* should be stopped and the patient should seek medical advice immediately if any of the following signs of a blood clot are noticed during treatment with *{Invented name}*: - severe pain or swelling in either of the patient's legs or feet that may be accompanied by tenderness, warmth or discoloured skin; - an unusual sudden cough, which may bring up blood; - sudden chest pain which may increase with deep breathing; - sudden unexplained breathlessness or rapid breathing; - pain in chest that spreads to the arm or neck; - discomfort radiating to the back, jaw, throat, arm and stomach; - rapid or irregular heartbeat; - severe pain in the abdomen;

Risk	What is known	Preventability
	<u>Blood clots in an artery (arterial thromboembolism, ATE)</u> If the blood clot forms in an artery, it can also cause serious problems, for example heart attack (if the clot forms in the blood vessels of the heart) or stroke (if the clot forms in the vessels of the brain). The risk of an arterial thrombosis in women who are taking combined pills, increases in the following cases: - with increasing age (particularly above about 35 years), - if the patient is smoking - she is strongly advised to stop smoking when she uses *{Invented name}*, especially if the patient is older than 35 years, - if the patient is overweight (her body mass index is over 30 kg/m²), - if a member of the woman's immediate family has had a heart attack or stroke at a young age (less than about 50) - in this case the woman could also have a higher risk of having a heart attack or stroke - if the patient has high blood pressure (also called hypertension), - if the patient, or someone in her immediate family, has a high level of fat in the blood (cholesterol or triglycerides); - if the woman has migraine, especially migraines with aura - if the woman has a problem with her heart (valve disorder, heart rhythm disturbance), - if the woman has diabetes	- severe light headedness or dizziness; - severe sweating, nausea, vomiting; - extreme weakness and anxiety; - any sudden changes to the eyesight (such as loss of vision, blurred vision or double vision); weakness or numbness of the face, arm or leg, especially on one side of the body; - sudden confusion, slurred speech or any other difficulties affecting the patient's speech or trouble understanding; - sudden trouble walking, dizziness, loss of balance or coordination; - unexplained migraine like headaches which happen for the first time, or any unusual, severe or long-lasting headache; - loss of consciousness or fainting with or without seizure. As a further precaution measure as a general rule in all patients who are undergoing major surgeries or who become bedridden for a longer period, the patients doctor might stop the treatment with *{Invented name}* and/or consider other preventive measures to prevent the development of blood clots following the patients surgery/ during the immobilisation. In such cases, treatment should not be restarted until the woman is completely mobilised, which is usually about two weeks after she is back on her

Risk	What is known	Preventability
	If the patient has 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. The following signs and symptoms can suggest a blood clot formation in an artery: • *Heart attack (if the clot forms in the blood vessels of the heart):* - pain, discomfort, pressure, heaviness; - sensation of fullness in the chest which may reach the left arm; - fullness, indigestion or choking feeling; - discomfort radiating to the back, jaw, throat, arm and stomach; - severe sweating, nausea, vomiting or dizziness; - extreme weakness, anxiety, or shortness of breath - rapid or irregular heartbeats • *Stroke (if the clot forms in the vessels of the brain):* - 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 coordination; - sudden, severe or prolonged headache with no known cause;	feet. The therapy should be restarted only after consultation with the patient's doctor. In order to mitigate the risk of blood clots in veins and arteries, some communication and educational materials have been distributed at the beginning of 2014 to healthcare professionals, and through them to patients as well. In some countries, these materials may be re-distributed in the future upon agreement between the manufacturer and the national authorities.

Risk	What is known	Preventability
	- loss of consciousness or fainting with or without seizure.	

Risk	What is known	Preventability
Liver tumours *(Liver tumours)*	In rare cases benign (non-cancerous), and even more rarely malignant (cancerous) liver tumours have been reported in patients taking oral contraceptives, like *{Invented name}*. Non-cancerous tumours of the liver caused by the Pill can be e.g. haaemangioma, hepatic adenoma or focal nodular hyperplasia. Haemangiomas are benign tumours consisting of blood vessels. Most haemangiomas of the liver never cause symptoms or health problems and they may only be detected accidentally, e.g. during a routine ultrasound examination of the abdomen. Rarely, larger haemangiomas can rupture, causing severe pain and bleeding into the abdomen that may be severe or even life threatening. They may need to be removed surgically if they cause pain, bleeding, or if there is chance to transform to malignant tumours. There are no specific symptoms of liver cancer. The following symptoms can refer to liver tumours: • abdominal fluid and swelling (ascites) • pain in the tummy (in the abdomen) that does not disappear on its own • unexplained weight gain	Oral contraceptive-induced liver cell adenomas are reversible if the pill is discontinued within a certain time period. Because an adenoma has a risk of bleeding and it can transform to a cancerous type, surgical excision is usually done for solitary liver adenomas. Liver tumours can be detected by Ultrasound, CT, (computer-tomography) or MRI (Magnetic resonance imaging) examinations, but only a biopsy will distinguish a benign tumour from a malignant one. As a precaution measure, *{Invented name}*.should not be taken by patients with liver tumour.

Risk	What is known	Preventability
	• jaundice (yellow colour of the skin and of the whites of the eyes)	

Risk	What is known	Preventability
Breast cancer, Cervical cancer	Breast cancer is a type of cancer originating from the breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Breast cancer has been found slightly more often in women who take the pill than in women of the same age who do not take the pill. Cervical cancer, or cancer of the cervix, is cancer of the entrance to the uterus (womb). The cervix is the narrow part of the lower uterus, often referred to as the neck of the womb. There are some data, which show an increased risk of cervical cancer in women who use the pill, like *{Invented name}* for a longer period. However, it is uncertain whether this increased risk is caused by the pill, or by other factors, since development of the disease depends on many different factors such as sexual behaviour. For example, frequent change of partners increases the risk of a sexually transmitted virus infection called HPV (human papilloma virus), which is associated with a higher risk for the development of cervical cancer.	As a precaution measure, the woman should not take *{Invented name}* if she has malignant breast tumour, or undiagnosed genital bleeding. If women stop taking the pill, this reduces the risk so that 10 years after stopping the pill, the risk of finding breast cancer is the same as for women who have never taken the pill. It is not certain whether the pill causes the increased risk of breast cancer. It may be that women taking the pill are examined more often, so that breast cancer is noticed earlier. Lifestyle changes have been shown to decrease breast cancer risk, e.g. maintaining a healthy body weight, getting regular physical activity, avoiding or limiting alcohol intake and quitting smoking. Early detection will not prevent breast cancer, but it can help find it when the likelihood of successful treatment is greatest. Therefore it is important to regularly check the woman's breasts and she should contact her doctor if she feels any lump. Breast cancer screening is recommended regularly in

Risk	What is known	Preventability
		accordance with the national guidelines. Since the most common form of cervical cancer starts with pre-cancerous changes, there are two ways to stop this disease from developing. The first way is to find and treat pre-cancers before they become true cancers. The second one is to prevent the pre-cancers by avoiding being exposed to human papilloma virus (HPV, a sexually transmittable virus) as much as possible (e.g. frequent change of partners increases the risk of HPV infection), getting HPV vaccine and avoiding smoking. Cervical cancer screening is recommended regularly in accordance with the national guidelines.

Risk	What is known	Preventability
Induction or exacerbation of the symptoms of hereditary angioedema *(Aggravation of hereditary angioedema)*	Hereditary Angioedema is a very rare and potentially life-threatening genetic disorder (patients have a defect in the gene that controls a blood protein called C1 Inhibitor). Hereditary Angioedema symptoms include episodes of oedema (swelling) in various body parts including the hands, feet, face and airway. Airway swelling is particularly dangerous and can lead to death by drowning.[vi] Most Hereditary Angioedema attacks occur spontaneously with no apparent reason; however anxiety, stress, minor trauma, surgery, and	The patient should seek medical advice immediately if she experiences symptoms of angioedema such as swollen face, tongue and/or pharynx and/or difficulty swallowing or hives together with difficulty breathing.

Risk	What is known	Preventability
	illnesses such as colds and flu are triggers. Patients have also reported swelling in extremities following typing, prolonged writing, pushing a lawn mower, hammering, shoveling, and other physical activities. The trauma associated with dental procedures is particularly dangerous for Hereditary Angioedema patients because it increases vulnerability to airway attacks. In women, menstruation and pregnancy seem to have a major effect on disease activity. Many female patients report an increase in the number of attacks during their menstrual periods. During pregnancy, some women note an increase in the frequency of attacks, while others have reported a decrease. Many women report that oral contraceptives and hormone replacement therapy cause an increase in the frequency and severity of attacks. In women with Hereditary Angioedema estrogens, which is one component of *{Invented name}*, may induce or exacerbate symptoms of angioedema.	

Risk	What is known	Preventability
Liver disorders, elevations in some laboratory blood tests of the liver (*Liver function disturbances*)	During treatment with *{Invented name}* liver disturbances may occur. The classic symptoms of liver disturbances include the following: pale stools, dark urine, jaundice (yellowing eyes/skin), itching, swelling of the abdomen, ankles and feet, persistent nausea/vomiting,	As a precaution measure, the woman should not take *{Invented name}* in the following situations: - if the patient suffers from inflammation of the liver (e.g. due to a virus) or from jaundice and her liver function (as determined by laboratory investigation of the blood)

Risk	What is known	Preventability
	stomach/ abdominal pain, loss of appetite, fatigue, bruising. The patient's doctor should be contacted immediately if the patient experiences any of these symptoms. These symptoms can predict possible liver damage, which may need immediate medical help, as a suddenly occurring liver failure is a serious but often reversible medical condition. In several cases, liver function alterations might not be accompanied with any symptom and can be detected only with laboratory blood tests (called as asymptomatic liver function alteration). Liver function alterations can occur with a sudden onset or can have a prolonged course. Liver damages can be diagnosed by laboratory blood tests called liver function tests (like ALT (alanine transaminase), AST (aspartate transaminase), ALP (alkaline phosphatise), GGT (γ-glutamyl transpeptidase) or bilirubin), which show elevated values in these cases. If liver disturbances develop during the treatment with *{Invented name}*, the pill should be discontinued at least temporarily. In most of the cases, these liver function abnormalities disappear after the treatment is stopped.	values have not yet returned to normal. - if the patient experiences itching all over her body or if she suffers from cholestasis (when the bile flow is slowed or blocked) - particularly if this occurred in connection with a previous pregnancy or oestrogen treatment. - the patient's bilirubin (a degradation product of blood pigment) level in her blood is raised, e.g. due to an inborn excretion disorder (Dubin-Johnson or Rotor syndrome) If the patient has acute or chronic disturbances of liver function, or suffered from jaundice during a previous pregnancy or while using an oral contraceptive and this disorder reappears, the patient's doctor may tell her to stop taking *{Invented name}* until her liver values have returned to normal and the doctor may advise to use a non-hormonal method of birth control temporarily or permanently. Before starting the treatment with *{Invented name}* patients should always inform their doctors about their medical history (previous and current diseases/conditions) and if they take any other medicines, especially if those medicines are known to cause liver damages. In some cases, regular check-ups (e.g. laboratory blood tests for the evaluation of the liver function) may be necessary. The necessity and/or the frequency and type of these

Risk	What is known	Preventability
		check-ups should be determined by the patients' doctor.

Risk	What is known	Preventability
Inflammation of the pancreas *(Pancreatitis)*	Pancreatitis can be manifested with a sudden onset accompanied with intensive symptoms called 'acute pancreatitis, leading to a potentially life-threatening condition, or can occur over several years often with moderate and non-specific symptoms (especially in the first period), the latter called 'chronic pancreatitis'. In women who have a certain disorder of elevated blood fat values (hypertriglyceridaemia) or this has occurred in their family, there is an increased risk of an inflammation of the pancreas during the patient's treatment with *{Invented name}*. The most common symptoms of pancreatitis are severe upper abdominal burning pain radiating to the back, nausea, and vomiting worsening with eating. Diagnosis contains acquiring family history, physical examination (physician looks for signs of pancreatitis), imaging tests (like ultrasound) and other diagnostic tests from the patient's blood and/or urine, including measurement of the pancreatic enzyme levels (e.g. amylases, lipases), glucose (blood sugar), and white blood cell count. Risk factors of pancreatitis include woman gender, alcohol consumption, elevated blood fat (triglyceride) levels, gallbladder disease, genetic risk factors, history of or existing abdominal trauma and	As a precaution measure, if patients suffer or have suffered from inflammation of the pancreas and this is associated with severe increase in the patient's blood fats (triglycerides), they should not take *{Invented name}*. Patients receiving *{Invented name}* and their doctors should be aware of the possible risk of pancreatitis during the patient's treatment with this contraceptive pill. For this reason, before starting the treatment with *{Invented name}*, patients should always inform their doctors about their medical history. In some cases, regular check-ups (e.g. laboratory blood tests) may be necessary. The necessity and/or the frequency and type of these check-ups should be determined by the patients' doctor. If women experience symptoms typical for pancreatitis, they should immediately contact their doctors, as early diagnosis and treatment of this condition is essential for a better outcome.

Risk	What is known	Preventability
	viral infection (mumps, hepatitis) as well, but in most of the cases the reason for the development of pancreatitis is unknown.	

Risk	What is known	Preventability
Increased blood pressure *(Hypertension)*	High blood pressure is also known as hypertension. A blood pressure reading appears as two numbers. The first and higher of the two is a measure of systolic pressure, the second number measures diastolic pressure. Blood pressure is ideal and healthy at 120 over 80 values. A person is considered to be hypertensive when systolic pressure is over 140mmHg most of the time or when diastolic pressure is over 90mmHg most of the time, according to the National Institutes of Health. High blood pressure can threaten healthy arteries and lead to life-threatening conditions such as heart disease and stroke. High blood pressure (hypertension) does not usually cause any symptoms; in these cases, the problem can only be detected by the measurement of the blood pressure values. People with high blood pressure can experience headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), anxiety, irregular heartbeats, vision changes, dizzy spells, chest pain, nose-bleed and dyspnoe.	The treatment with *{Invented name}* means a moderately increased risk for the development of hypertension. In most of the cases, this increase in blood pressure is small and does not require any action. Such an increase in the blood pressure, which would require medical attention, is, however, rare. Stopping the treatment with *{Invented name}* is necessary only in these more severe cases. Having a high blood pressure in women taking the Pill may increase even the risk of a blood clot in the arteries. For this reason, it is necessary to lower the blood pressure to a healthy range or stop the Pill in those cases when a normal blood pressure cannot be achieved even by medicaments.

Risk	What is known	Preventability
	There are several factors which influence and increase blood pressure: • overweight • smoking • little or no exercise • too much salt in a diet • drinking too much alcohol • stress • history of high blood pressure in the family	

Important potential risks

Risk	What is known
Worsening of depression/depressed mood *(Worsening of depression/depressed mood)*	Depression is a serious mood disorder. Symptoms could be feelings of helplessness and hopelessness, loss of interest in daily activities, increased irritability, anger, sleep disturbances, including insomnia or sleeping too much, changes in appetite, weight loss or weight gain, suicidal thoughts, difficulty concentrating and social isolation. During taking birth control pills (like *{Invented name}*), the symptoms of depression can occur and there were also some reports about worsening of depression in woman taking the Pill. There are many factors, which can increase the risk of depression in women, including reproductive, genetic or other biological factors and personal characteristics. *{Invented name}* should not be used in women who suffer from severe depression. *{Invented name}* should be used with caution in women who have or have ever had depression. For this reason, patients should always inform their doctors about their medical history (previous and current diseases/conditions), before starting the treatment with this medicine.

Risk	What is known
Inflammatory bowel diseases (Crohn's disease and ulcerative colitis)	Crohn's disease and ulcerative colitis are chronic (long-lasting) inflammatory diseases of the digestive tract. The cause (aetiology) of these diseases is unknown. They can affect different parts of the bowels: ulcerative colitis usually affects only the innermost lining of the large intestine (colon) and rectum, while Crohn's disease causes inflammation anywhere along the lining of the digestive tract (from

(Crohn's disease and ulcerative colitis)	the gullet (oesophagus) to the rectum, affecting often the small intestines), and often spreads deep into the affected tissues. The most specific symptoms contain abdominal pain, severe internal cramps/muscle spasms and diarrhoea, sometimes bleeding. There are also other symptoms which affect other organs outside the bowels, like skin, eyes, joint or liver symptoms. Inflammatory bowel diseases may lead to one or more of the following complications: bowel obstruction, sores, fistula (an abnormal channel between different parts of bowel, between bowel and skin, or between bowel and another organs), malnutrition (as diarrhoea, abdominal pain and cramping may make it difficult to eat or to absorb enough nutrients from the bowels to keep the patient nourished), anemia, large bowel (colon) cancer and anal fissure (crack, or cleft, in the anus or in the skin around the anus where infections can occur). There are some data which suggest that combined hormonal birth control pills, like *{Invented name}* can worsen the patient's underlying inflammatory bowel disease. *{Invented name}* should be used with caution, always after a thorough assessment of the positive effects and possible risks of the treatment in women who have Crohn's disease or ulcerative colitis. For this reason, patients should always inform their doctors about their medical history (previous and current diseases/conditions), before starting the treatment with this medicine.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which 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) / patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

In 2013, the European Medicines Agency (EMA) completed a review of certain combined hormonal contraceptives (CHCs) authorised in the European Union (EU), including *{Invented name}*, particularly on the risk of thromboembolism (blood clots in vessels) associated with their use. This review was initiated in February 2013 at the request of France, under Article 31 of Directive 2001/83/EC. (Procedure No.: EMEA/H/A-31/1356). A review of the data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for all questions concerning medicines for human use, which adopted the Agency's final opinion. The CHMP opinion was forwarded to the European Commission, which issued a final decision on 16 January 2014.

The two committees involved in this procedure, the Pharmacovigilance Risk Assessment Committee (PRAC) and the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), both concluded that the benefits of CHCs in preventing unwanted pregnancies continue to

outweigh their risks, and that the well-known risk of venous thromboembolism (VTE or blood clots in veins) with all CHCs is small.

The review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.

The product information of CHCs has been updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is emphasized, 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.

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.

More details about this referral procedure can be found on the EMA website: *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Combined_hormonal_contraceptives/human_referral_prac_000016.jsp&mid=WC0b01ac05805c516f*

Based on the above, Product information documents (Summary of Product Characteristics and the Package Leaflet) of *{Invented name}* were created to help women make informed decisions about their choice of contraception.

In addition to the above mentioned amendments of the product information documents, as a result of the above mentioned Referral, there were recommendations for some special conditions and restrictions for the safe and effective use (called additional risk minimisation measures) connected to the Company's birth control pill of *{Invented name}*. These additional risk minimisation measures are linked to the product's safety concerns of **Thromboembolism (venous and arterial).**

The summary of these activities is presented in the following table:

Safety concern in lay terms: • **Blood clots in veins and blood clots in arteries *(venous thromboembolic diseases: blood clots in the vessels (veins) in the legs (which can travel to the lung) or in other organs and arterial thromboembolic diseases: blood clots in the blood vessels of the brain, in the heart or in other organs)*** (Venous thrombotic events and arterial tromboembolism)
Additional risk minimisation measure(s) • Direct Healthcare Professional Communication (DHPC) • Questions & Answers for women • Checklist for prescribers • Information cards for women.

Objective and rationale

To provide Healthcare Professionals and Patients with detailed and up-to-date information about the risk of blood clot formation in veins and arteries associated with the use of combined hormonal contraceptives (CHC) in order to make them understand this risk and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Summary description of main additional risk minimisation measures (key points of the proposed actions):

Key elements of the information about the risk of blood clot formation associated with the use of combined hormonal contraceptive include the following:

- It is important that patients and healthcare professionals are aware of the risk of blood clots associated with these medicines, even though this risk it is very low;
- The risk of blood clots in the veins (venous thromboembolism, VTE) varies between CHCs, depending on the type of progestogen component of the products, while there is no evidence for differences between CHCs in their risk of blood clot formation in arteries (arterial thromboembolism, ATE)
- Patients and their doctors should be aware of the factors that increase the women's risk of a clot and they should also be aware of how these may change over time;
- Women should always discuss with their doctors or nurses what is the most appropriate type of contraception for them. When prescribing a CHC, careful consideration should be given to the individual woman's current risk factors, and as a woman's individual risk factors will change over time, there is a need to regularly re-assess the suitability of her contraceptive.
- When taking CHCs, patients and their doctors should be alert for the signs and symptoms of blood clots (thromboembolism). Healthcare professionals should always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.

Brief description of the actions:

- ***Direct Healthcare professional communication (DHPC):*** to inform/remind healthcare professionals on the latest evidence on the risk of blood clots in vessels (in veins and arteries) in association with the use of combined hormonal contraceptives and the results of the review conducted in frame of the Referral.
- ***Questions & Answers for women:*** to provide women with answers to questions they may have on the outcome of the Referral procedure, to inform them on the risk of blood clots in vessels associated with the use of combined hormonal contraceptives, how the level of risk compares between products, on the known risk factors, signs and symptoms of these conditions and to provide women with answers to questions they may have on this topic.
- ***Checklist for prescribers***: to help the discussion between the prescriber and woman who is being treated with combined hormonal contraceptives. This checklist is intended to be used by healthcare professionals involved in prescribing hormonal contraceptives, to initiate a discussion with women about the suitability of a treatment with combined hormonal contraceptives.

- ***Information card for women***: to provide brief information for the women using CHCs on the important signs and symptoms of blood clot formation in vessels and when to seek medical attention.

After finalisation of the Referral on CHCs in January 2014, there were consultations with the National Competent Authorities about the need and the way of the implementation of these activities. As a result of these discussions, the above mentioned communication and educational materials have already been distributed in agreement with the National Competent Authorities at the beginning of 2014 in those countries, where any of the Company's CHC products were on the market.

Since the implementation of the requested additional risk minimisation actions at the beginning of 2014, there were not any relevant changes regarding either the knowledge about risk of thromboembolism associated with the use of CHCs or the target population for whom these materials were distributed, which would require new or repeated activities. For this reason, re-implementations of these actions at the time point when the current product is entered into the market (more than a year after the Referral has been closed) may be even confusing for Health Care Providers and for patients as well, therefore is considered not necessary.

VI.2.6 Planned post authorisation development plan (if applicable)

No post-authorisation studies/activities are planned by Gedeon Richter Plc. for its product of *{Invented name}*.

In connection with the safety concerns of **Blood clots in veins and arteries *(Thromboembolism (venous and arterial))***, Gedeon Richter Plc. agreed to participate in a joint survey, working together with other companies concerned with this issue, to measure the success of providing and understanding all core communication and educational materials regarding these safety concerns. Details of the joint survey-based study will be discussed with the National Competent Authorities in a further phase if such a survey will be initiated.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable, since this is the first RMP on Gedeon Richter Plc's product of *{Invented name}*.