

## **VI.2 Elements for a public summary**

### **VI.2.1 Overview of disease epidemiology**

The ability to control one's own reproduction is considered a human right that is already recognized in national laws and international human rights documents. Contraceptive use and need for family planning are keys to understanding changes in fertility and to improve reproductive health worldwide.

The distribution of specific contraceptive methods used have been similar between 1990 and 2011 even though contraceptive prevalence among married or in union women of reproductive age increased worldwide from 55 per cent in 1990 to 63 per cent in 2011. Women's choices are often imposed or limited by direct or indirect social, economic and cultural factors.

The pill has the widest geographic distribution of any method. However, adolescents and women of low socioeconomic status are at greater risk because of the lack of use and contraceptive failure. This conducts to greater risk for unintended conceptions.

### **VI.2.2 Summary of treatment benefits**

Both active substances, levonorgestrel and ethinylestradiol are well known substances which have complementary contraceptive effects. It has been established that combinations of ethinylestradiol with a suitable progestogen provide effective contraceptive protection. Levonorgestrel presents greater progestogen activity compared to the natural progesterone, allowing ovulation inhibition. Estrogens act synergistically with progestogens in suppressing the hormonal cycle. Additionally, they maintain the endometrium, improve the cycle control and act preventing the breakthrough bleeding.

Several studies have proven the efficacy in ovulation inhibition, and cycle control when comparing this formulation with a combination of norethisterone/ ethinylestradiol 0.5 mg/0.02 mg.

### **VI.2.3 Unknowns relating to treatment benefits**

Both active substances, levonorgestrel and ethinylestradiol, are well known substances which have complementary contraceptive effects. There are no doubts about the clinical and pharmacological effects of the active substances, with extensive experience in the proposed indication.

### **VI.2.4 Summary of safety concern**

**Important identified risks**

Risk	What is known	Preventability
<p>-Blood clot in a blood vessel of the leg, lung or other organs (Venous thromboembolism)</p>	<p>Blood clots in the veins (venous thrombosis) have been reported in women using combined oral contraceptives (COCs).</p> <p>COCs should not be used in the presence of blood clots in the veins (deep venous thrombosis, pulmonary embolism); or in the presence of a severe or multiple risk factor(s) such as diabetes mellitus with damaged blood vessels, very high blood pressure, and very high level of fat in the blood (cholesterol or triglycerides); hereditary or acquired increased risk of venous or arterial blood clots (thrombosis).</p> <p>The use of any COC increases the risk of venous thrombosis due to blood clots (venous thromboembolism) when compared with no use.</p> <p>The risk of venous blood clots in users of combinations pills increases with age, family history, hereditary predisposition, overweight, prolonged immobilization, major surgery, or any surgery of the legs or a serious accident.</p> <p>The risk of venous thrombosis due to blood clot (thromboembolism) may be increased after having a</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Patients should be advised to promptly report in case of: unusual unilateral leg pain and/or swelling; sudden severe chest pain which may or may not radiate to the left arm; sudden respiratory difficulty; sudden onset of coughing, unusual severe and prolonged headache; sudden partial or complete loss of vision; double vision; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or marked numbness suddenly affecting one side or one part of the body; motor disturbances; acute abdomen pain.</li> <li>•Early detection and monitoring.</li> </ul>

Risk	What is known	Preventability
	<p>baby.</p> <p>Other medical conditions that have been associated with circulatory problems include: diabetes mellitus, a disease affecting the immune system called systemic lupus erythematosus, disorder of blood clotting causing failure of the kidneys called haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and inherited disease of the red blood cells called sickle cell anaemia.</p>	
<p>- Blood clot in a blood vessel of the leg, lung or other organs (Arterial thromboembolism)</p>	<p>Blood clot in arterial blood vessel (arterial thrombosis) have been reported in women using combination pills.</p> <p>COCs should not be used in the presence or a history of arterial blood clots (arterial thrombosis) or heart problems such as heart attack or a condition that cause severe chest pain (angina pectoris); presence or history of stroke, presence of a severe or multiple risk factor(s) such as diabetes mellitus with damaged blood vessels, very high blood pressure, and a very high level of fat in the blood (cholesterol or triglycerides); hereditary or acquired increased risk of venous or arterial blood clots (thrombosis); or history of certain form of migraine with aura.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Patients should be advised to promptly report in case of: unusual unilateral leg pain and/or swelling; sudden severe chest pain, which may or may not radiate to the left arm; sudden respiratory difficulty; sudden onset of coughing, unusual severe and prolonged headache; sudden partial or complete loss of vision; double vision; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or marked numbness suddenly affecting one side or one part of the body; motor disturbances; acute abdomen</li> </ul>

Risk	What is known	Preventability
	<p>The risk factors for arterial blood clot (arterial thrombosis) include: increasing age; smoking (women over 35 years should be strongly advised to stop smoking if they wish to use a COC), very high level of fat in the blood (cholesterol or triglycerides), very high blood pressure; migraine, especially migraine with aura; heart problems (valve disorder or disturbance of the cardiac rhythm); overweight; if a close relative ever had a heart attack or stroke at a young age; hereditary predisposition.</p> <p>The risk of arterial blood clot (arterial thrombosis) may be increased after having a baby. Other medical conditions that have been associated with circulatory problems include: diabetes mellitus, a disease affecting the immune system called systemic lupus erythematosus, disorder of blood clotting causing failure of the kidneys called haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and inherited disease of the red blood cells called sickle cell anaemia.</p>	<p>pain.</p> <ul style="list-style-type: none"> <li>•Early detection and monitoring.</li> </ul>
<p>-Tumour in the liver (Benign and malign liver tumors)</p>	<p>In rare cases, benign, and even more rarely, malignant liver tumours have been reported in COC users.</p> <p>COCs should not be used in case of current liver</p>	<ul style="list-style-type: none"> <li>•Early detection and monitoring.</li> </ul>

Risk	What is known	Preventability
	tumours or history of liver tumours (benign or malignant).	
-Breast cancer	<p>The frequency of diagnosis of breast cancer is slightly increased among COC users, but it is not known whether this is caused by the treatment. As breast cancer is rare in women under 40 years of age, the excess number is small in relation to the overall risk of breast cancer.</p> <p>COCs should not be used in case of known or suspected sex-steroid influenced cancer (e.g. breast cancer).</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>
-Cancer of the genital organs (Cervical cancer)	<p>Some epidemiological studies have reported an increased risk of cancer of the genital organs (cervical cancer) in long-term COC users.</p> <p>COCs should not be used in case of known or suspected sex-steroid influenced cancer (e.g. of the genital organs).</p>	<ul style="list-style-type: none"> <li>•Early detection and monitoring.</li> </ul>
-Disturbances of liver function: Severe hepatic disease, as long as liver function values have not returned to normal.	<p>Disturbances of liver function have been reported in COC users.</p> <p>COCs should not be used in case of current severe liver disease or history of severe liver disease, as long</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>

Risk	What is known	Preventability
	<p>as liver function values have not returned to normal.</p> <p>Acute or chronic liver function disorders require discontinuation of COC use until liver function markers return to normal. Recurrence of liver function disorders requires discontinuation of COCs.</p>	
<p>-Disturbances of liver function: Liver tumours (benign or malignant)</p>	<p>Disturbances of liver function have been reported in COC users.</p> <p>COCs should not be used in case of current liver tumours or history of liver tumours (benign or malignant).</p> <p>Acute or chronic liver function disorders require discontinuation of COC use until liver function markers return to normal. Recurrence of liver function disorders requires discontinuation of COCs.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>
<p>-Inflammation of the pancreas (Pancreatitis)</p>	<p>Women with elevated levels of fat in the blood (hypertriglyceridemia), or a positive family history for this condition, may be at an increased risk of inflammation of the pancreas (pancreatitis) when using COCs.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>
<p>-Increased blood pressure (Hypertension)</p>	<p>Although small increases in blood pressure have been observed in many women taking COCs, clinically</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> </ul>

Risk	What is known	Preventability
	<p>relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in pre-existing high blood pressure, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to treatment with blood pressure medicine, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normal values can be achieved with blood pressure medicine.</p>	<ul style="list-style-type: none"> <li>•Prior to the initiation or reinstatement of Levonorgestrel / Ethinylestradiol blood pressure should be measured.</li> <li>•Early detection and monitoring.</li> </ul>
<p>-Effect on hereditary angioedema</p>	<p>In women with hereditary angioedema, exogenous estrogens may cause or worsen symptoms.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>
<p>-Allergy (Hypersensitivity)</p>	<p>Cases of hypersensitivity included discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma) have been reported, especially in women with a history of chloasma gravidarum.</p>	<ul style="list-style-type: none"> <li>•Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.</li> <li>•Early detection and monitoring.</li> </ul>
<p>-Levonorgestrel / Ethinylestradiol and other medicines (Drug-drug interactions)</p>	<p>Interactions between oral contraceptives and other medicinal products may decrease the contraceptive efficacy and/or lead to breakthrough bleeding and/or contraceptive failure.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>

Risk	What is known	Preventability
-Migraine (Migraine with aura)	<p>COCs should not be used in case of history of migraine, especially migranes with aura.</p> <p>Cases of hypersensitivity included headache and migraine have been reported.</p>	<ul style="list-style-type: none"> <li>•Levonorgestrel / Ethinylestradiol should be prescribed with caution in patients with predisposing factors.</li> <li>•Early detection and monitoring.</li> </ul>

**Potential Risk**

Risk	What is known
-Depression (Endogenous depression)	<p>Worsening of depression (endogenous depression) has been reported during COC use. Depressed mood and mood altered have been observed with the use of combined oral contraceptives containing levonorgestrel / ethinylestradiol.</p>
-Inflammatory bowel disease (Crohn ´s disease and ulcerative colitis)	<p>Worsening of inflammatory bowel disease (Crohn’s disease and of ulcerative colitis) has been reported during COC use.</p> <p>Inflammatory bowel diseases (Crohn’s disease and ulcerative colitis) have been reported in women using COC.</p>
-Cholelithiasis	<p>Jaundice and/or itching related to cholestasis have been reported to occur or deteriorate during pregnancy and COC use but the evidence of an association with COC use is inconclusive.</p> <p>Cholelithiasis has been uncommonly observed with COC use.</p> <p>Cholestatic jaundice has been reported in women using COCs</p>
-Diabetes (Insulin resistance)	<p>Although COCs may have an effect on peripheral insulin resistance and glucose tolerance there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing &lt; 0.05 mg ethinylestradiol). However, diabetic women should be carefully monitored, particularly in the early stage of COC use.</p>



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Risk	What is known
-Epilepsy	Worsening of epilepsy has been reported during COC use. Epilepsy has been reported during COC use.

**Missing information**

N/A

### **VI.2.5 Summary of risk minimisation measures by safety concern**

The MAH believes that the current contraindications, warnings and precautions within the SmPC for Diginova 0.15 mg / 0.03 mg film-coated tablets, adequately inform prescribers and patients about the benefit-risk of Levonorgestrel / Ethinylestradiol.

For each safety concern, a reference has been made to the part of the SmPC to address the specific safety concerns.

Routine risk minimisation measures have been proposed to offer further information health care practitioners about the possible risks of use of Diginova 0.15 mg / 0.03 mg film-coated tablets:

- Venous thromboembolism
- Arterial thromboembolism
- Benign and malignant tumors
- Breast cancer
- Cervical cancer
- Liver tumours (benign or malignant)
- Pancreatitis
- Increased blood pressure
- Effect on hereditary angioedema
- Hypersensitivity
- Drug-drug interactions
- Migraine
- Worsening of endogenous depression
- Worsening of Crohn's disease and ulcerative colitis
- Cholelithiasis
- Insulin resistance
- Worsening of epilepsy

The MAH will be updated the Core SmPC/PIL to reflect this risk minimization measures if applicable.

No additional risk minimisation measures are proposed.

The applicant will follow any actions taken based on the additional pharmacovigilance activities undertaken by the MAH of the reference product, Microgynon 30 ® once required.

### **VI.2.6 Planned post authorisation development plan**

N/A

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

N/A