WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH066 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active tablet contains 0.15mg desogestrel and 0.03mg ethinylestradiol film-coated tablets

Excipients with known effects:

Each active (white) tablet contains about 54.90 mg lactose monohydrate.
Each placebo (green) tablet contains about 55.50 mg lactose monohydrate.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Active tablet: White, round, biconvex film- coated tablet with C and 7 debossed on opposite sides.
Placebo tablet: Green, round, film- coated tablet with a diameter of approximately 5mm

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH066 trade name] is an oral combined hormonal contraceptive (CHC) agent for women.

4.2 Posology and method of administration

[RH066 trade name] should be taken every day at around the same time, in the sequence indicated on the package. Each pack contains 28 tablets, of which the first 21 contain the active contraceptive and the last 7 contain a placebo. When taking [RH066 trade name] in this formulation, there are no "pill-free" days. There is generally a withdrawal bleed during the last 7 days of the cycle when the placebo tablets are taken. This usually begins 2 or 3 days after finishing the active tablets and can persist until taking tablets from the next pack has begun.

Starting [RH066 trade name]:

When no hormonal contraceptives have been taken in the last month:

- The woman may start the course on any of the first five days of her cycle (day 1 to 5 of menstruation) without needing additional contraceptive protection. She may start the course after day 5 provided she is reasonably certain that she is not pregnant, but an additional non-hormonal (barrier) method of contraception should be used during the first 7 days of taking the tablets.
- If the woman is amenorrhoeic, [RH066 trade name] may be started at any time provided she is reasonably certain that she is not pregnant. Additional contraceptive protection should be used for the first seven days.

Postpartum (breastfeeding):

- Less than 6 weeks postpartum and primarily breastfeeding: The woman should not use COCs
- 6 weeks to 6 months postpartum and primarily breastfeeding: COCs are not recommended unless other more appropriate methods are not available or not acceptable.
- More than 6 months postpartum: COCs can be initiated as advised above for menstruating or non-menstruating women.

Postpartum (not breastfeeding):

- Less than 21 days postpartum: COCs are generally not recommended unless other more appropriate methods are not available or not acceptable. It is highly unlikely that a woman will ovulate and be at

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

risk of pregnancy during the first 21 days postpartum. However, depending on national, regional and/or local programme protocols, some contraceptive methods may be provided during this period.

- 21 days of more postpartum: COCs can generally be initiated if there are no other risk factors for venous thromboembolism.
    - If menstrual cycles have not returned, COCs can be started immediately if it is reasonably certain that she is not pregnant. She will need to abstain from sex or use additional contraceptive protection for the next seven days.
    - If menstrual cycles have returned, COCs can be started as advised for other women having menstrual cycles.

Post-abortion or miscarriage:

- [RH066 trade name] can be initiated immediately. No additional contraceptive protection is needed.

Switching from another hormonal contraceptive:

- If the woman has been using her hormonal method consistently and correctly or if it is reasonably certain that she is not pregnant, [RH066 trade name] can be started immediately; there is no need to wait for her next menstrual period.
- If the woman's previous method was an injectable contraceptive, [RH066 trade name] should be started when the next injection would be given. No additional contraceptive protection is needed.

Switching from an IUD (including the levonorgestrel-releasing IUD):

- [RH066 trade name] can be initiated within five days after the start of menstrual bleeding. No additional contraceptive protection is required, and the IUD can be removed at this time.
- [RH066 trade name] can be initiated more than five days after the start of menstrual bleeding provided the woman is reasonably certain that she is not pregnant.
    - If the woman is sexually active in this menstrual cycle, it is recommended that the IUD be removed at the time of the next menstrual period.
    - If the woman is not sexually active in this menstrual cycle, she will need to abstain from sex or use additional contraceptive protection for the next seven days. If that additional protection is to be provided by the IUD she is using, it is recommended that the IUD be removed at the time of the next menstrual period.
- If the woman is amenorrhoeic or has irregular periods, [RH066 trade name] can be started as advised for other amenorrhoeic women.

Duration of administration:

[RH066 trade name] can be used as long as a hormonal contraceptive method is desired and there are no health risks contraindicating it (see section 4-4 regarding regular checkups).

If a tablet is missed:

The contraceptive efficacy of [RH066 trade name] may be decreased if it is not taken regularly.

If one or two active (hormonal) pills in a row are missed, or if the pack is started one or two days late:

- The woman should take a pill as soon as possible and then continue taking the pills daily at her usual time.
    - If the woman misses two or more active pills in a row, she can take the first missed pill and then either continue taking the rest of the missed pills (one each day) or discard them to stay on schedule.
    - Depending on when the woman remembers when she missed the pill(s), she may take two pills on the same day (one as soon as she remembers, and the other at her usual time) or even at the same time.
- No additional contraceptive protection is required.

If three or more active pills in a row are missed or if the pack is started three or more days late:

- The woman should take a pill as soon as possible and then continue taking the pills daily at her usual time.

- If the woman misses three or more active pills in a row, she can take the first missed pill and then either continue taking the rest of the missed pills (1 each day) or discard them to stay on schedule.
- Depending on when the woman remembers when she missed the pills, she may take two pills on the same day (one as soon as she remembers, and the other at her usual time) or even at the same time.

- The woman should abstain from sex or use additional contraceptive protection until she has taken active pills for seven consecutive days.
- If the woman missed the active pills in the third week, she should finish the active pills in her current pack and start a new pack the next day. She should not take the usual seven days of placebo pills.
- If the woman missed the pills in the first week and had unprotected sex, she may wish to consider the use of emergency contraception.

If after missing a pill or pills, the woman does not have the usual withdrawal bleed during her first placebo-pill week, pregnancy should be ruled out before restarting [RH066 trade name].

Diarrhoea or vomiting:

- If the woman vomits or has significant diarrhoea within two hours of taking [RH066 trade name] she should take another pill as soon as she can.
- If the woman continues to vomit or has severe diarrhoea for more than 24 hours, she should try to continue taking the pills despite her discomfort.
- If the vomiting or diarrhoea continues for two or more days, the woman should follow the guidance for missed pills. A barrier form of protection may be required until the woman has recovered and completed seven consecutive days of [RH066 trade name].

Delaying the withdrawal bleed:

To postpone the withdrawal bleed, the woman should continue taking the active tablets from the next pack of [RH066 trade name] immediately, without taking any placebo pills. The withdrawal bleed can be delayed for as long as desired by taking the active tablets continuously, though evidence for this is limited beyond 2 years. Increased breakthrough bleeding and spotting can occur during this time. Following a subsequent regular seven-day break in taking the active tablets, the user may continue to take [RH066 trade name] as usual.

4.3 Contraindications

Combined oral contraceptives are contraindicated in the following situations:

- Existing or prior history of venous thromboembolism (deep-vein thrombosis, pulmonary embolism), whether on anticoagulation therapy or not
- Current or prior history of arterial thrombosis (e.g. myocardial infarction) or its prodromal stages (e.g. angina pectoris)
- Current or prior history of cerebrovascular disease (e.g. stroke) or prodromal condition (e.g. transient ischemic attack (TIA))
- Multiple co-existing risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension)
- Known predisposition to venous or arterial thromboses such as APC (activated protein C) resistance, antithrombin-III deficiency, factor V Leiden, hyperhomocysteinaemia, protein-C deficiency, protein-S deficiency or to another thrombogenic coagulopathy, thrombogenic valvular heart disease or thrombogenic heart-rhythm disturbances
- Major surgery with prolonged immobilisation (see section 4-4)
- Smoking (see section 4-4)
- Hypertension above 160/100
- Diabetes mellitus with vascular changes
- History of migraines with aura or focal neurological symptoms,

- Existing or prior history of pancreatitis, when accompanied by severe hypertriglyceridemia
- Existing or prior history of severe liver disease/uncompensated cirrhosis (also Dubin-Johnson and Rotor syndromes)
- Systemic lupus erythematosis with positive (or unknown) antiphospholipid antibodies
- Acute hepatitis or flare (combined oral contraceptives should not be started during these; continuing use for those already taking combined oral contraceptives is usually possible)
- Existing or prior history of benign or malignant hepatic tumours
- Known or suspected sex-hormone dependent, malignant tumours (e.g. of the breast or the endometrium)
- Known or suspected pregnancy
- Undiagnosed vaginal bleeding
- Undiagnosed amenorrhoea
- Hypersensitivity to the active substances or one of the other components of [RH066 trade name]
- [RH066 trade name] is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections 4.4 and 4.5)

If one of these disorders occurs for the first time while using [RH066 trade name], it must be discontinued immediately.

The presence of one or more risk factors related to venous or arterial diseases may constitute a contraindication, depending on the type and severity, (see section 4-4).

4.4 Special warnings and precautions for use

Warnings:

The use of combined oral contraceptives (COCs) is associated with an increased risk of various serious diseases, such as myocardial infarction, thromboembolism, stroke, and hepatic neoplasia. The presence of other risk factors, such as hypertension, hyperlipidaemia, obesity, and diabetes increase the morbidity and mortality risk.

Smoking while taking COCs increases the risk of serious cardiovascular events. The risk increases with increasing age and cigarette consumption. Women, particularly over age 30, should not smoke while using hormonal contraceptives. If smoking cessation cannot be achieved, other contraceptive methods should be used.

Venous thrombosis and thromboembolism (VTE):

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as [RH066 trade name] may have up to twice this level of risk. The decision to use [RH066 trade name] should be taken only after a discussion with the woman to ensure she understands the risk of VTE with [RH066 trade 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.

- In women who do not use a CHC and are not pregnant, about 2 out of 10,000 will develop a VTE over a period of one year.
- It is estimated that out of 10,000 women who use a CHC that contains desogestrel, between 9 and 12 will develop a VTE in a year; this compares with about 6 in women who use a levonorgestrel-containing CHC.
- This number of VTEs per year is fewer than the number expected in women during pregnancy or in the postpartum period (see section 4-6). However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).
- VTE may be fatal in 1-2% of cases.

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).

[RH066 trade 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 negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment
Increasing age	Particularly above 35 years
Obesity (Body Mass Index ≥30 kg/m^2)	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 pill (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 [RH066 trade name] has not been discontinued in advance.
Positive family history (VTE 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, SLE, haemolytic uraemic syndrome, inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

There is no consensus on the significance of varices and superficial phlebitis as related to the initial occurrence or progression of venous thrombosis.

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 provider that she is taking [RH066 trade name].

Symptoms of deep vein thrombosis (DVT) may 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) may 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).

Very rarely a venous occlusion may affect the retinal vessels which can cause symptoms ranging from painless blurring of vision to sudden loss of vision without previous signs or symptoms.

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 (CVA) in CHC users increases in women with risk factors (see below). [RH066 trade 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 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 (BMI > 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (ATE ever in a sibling or parent, especially at a 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 SLE

Symptoms of ATE:

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare provider that she is taking a CHC.

Symptoms of a cerebrovascular accident may 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) may 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.

Tumours:

Numerous epidemiological studies have been reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives (COCs). The evidence is clear that high dose combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low dose COCs confer protective effects to the same level.

Breast cancer:

A meta-analysis of 54 epidemiological studies showed a slightly increased risk of breast cancer (RR 1.24) for women who are currently using combined oral contraceptives. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The additional breast cancers diagnosed in current users of COCs or in women who have used COCs in the last ten years are more likely to be localised to the breast than those in women who never used COCs.

The most important risk factor for breast cancer in COC users is the age women discontinue the COC; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important, and the excess risk gradually disappears during the course of the 10 years after stopping COC use such that by 10 years there appears to be no excess.

Since breast cancer is rare in women under 40 years of age, the additional number of cases in current and recent users of combined oral contraceptives is small compared with the overall risk of breast cancer.

Cervical cancer:

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

Liver cancer:

Benign liver adenomata have very rarely been reported in connection with the use of combined oral contraceptives. In isolated cases, rupture with life-threatening intra-abdominal bleeding has been reported. Should severe epigastric pain occur, a liver tumour, liver enlargement or intra-abdominal bleeding should be considered.

Studies have shown an increased risk of hepatocellular carcinoma (HCC) in long-term users of combined oral contraceptives; however, this tumour is extremely rare in the absence of other pre-existing liver disease.

Other conditions:

Some chronic diseases or conditions may become worse during the use of COCs.

Known hyperlipidaemias:

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

Women with hyperlipidaemias are at an increased risk of arterial disease (see section 4.4 “Risk of arterial thromboembolism (ATE)”). However routine screening of women on COCs is not required.

Hypertension:

Hypertension is a risk factor for stroke and myocardial infarction (see section 4.4 “Risk of arterial thromboembolism (ATE)”). Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare and are generally associated with older age and long-term use.

Women with a history of hypertension or who develop sustained hypertension while taking a COC should use an alternative method of contraception.

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. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs).

Angioedema:

In women with acquired or hereditary angio-oedema, exogenously administered oestrogens may trigger or worsen symptoms.

Diabetes:

Although CHCs may affect peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using CHCs.

Insulin-dependent diabetics without vascular disease can use COCs. However, all diabetics are at an increased risk of vascular disease and this should be taken into consideration when prescribing COCs. Diabetics with existing vascular disease are contraindicated from using COCs (see section 4.3 Contraindications).

Psychiatric disorders:

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Chloasma:

Chloasma may occur, especially in women with a history of chloasma gravidarum. Women predisposed to chloasma should avoid exposure to the sun and ultraviolet radiation while taking combined oral contraceptives.

Menstrual changes:

Breakthrough bleeding or spotting has been observed in users of combined oral contraceptives, especially in the first months of use. An accurate assessment of irregular bleeding is thus likely to be possible only after about three months of use.

If bleeding irregularities persist or recur after previously regular cycles, then non-hormonal causes should be considered and, as is the case with any abnormal vaginal bleeding, adequate diagnostic measures are indicated to rule out malignancy or pregnancy. When both possibilities have been ruled out, the user may continue to take [RH066 trade name] or change to another product. Intermenstrual bleeding may be an indication of reduced contraceptive efficacy (see section 4.2 and 4.5).

The withdrawal bleed may not occur in some users during the seven-day placebo pill period. If [RH066 trade name] was not taken correctly prior to the first missed withdrawal bleed, or if the withdrawal bleed has been missed for two subsequent cycles, pregnancy must be ruled out before continuing use.

After discontinuing hormonal contraceptives, it may take some time to return to a normal cycle.

Reduced efficacy:

The contraceptive efficacy of [RH066 trade name] may be reduced:

- If tablets are missed (see section 4-2)
- If there is vomiting or diarrhoea (see section 4-2)
- If certain other medicinal products are taken at the same time (see section 4-5)

Medical examination / consultation:

Prior to the initiation or reinstitution of [RH066 trade name], a complete personal medical history (including family history) and a physical examination should be performed, and pregnancy must be ruled out.

The history and physical examination should address the contraindications (section 4-3) and warnings (section 4-4) and should be repeated at intervals while the woman remains on [RH066 trade name]. The frequency of these checkups should be individually specified. The following items should be explicitly performed: measurement of blood pressure and examination of the breasts, abdomen and pelvic organs including cervical cytology.

Women should be informed that [RH066 trade name] does not protect against HIV or other sexually transmitted infections. Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission.

Women who stop taking [RH066 trade name] because they desire to have a child should be informed about the fact that folic acid deficiency can lead to neural tube defects in the unborn child and that periconceptional supplementation with folic acid is recommended. In addition to food rich in folic acid (vegetable, fruits, whole-grain products), 0.4 mg of folic acid should be taken daily. Ideally it should be taken four weeks prior to conception and continued up to week 12 of pregnancy. Any woman who has already been pregnant with a child having a neural tube defect should take 4 mg or 5 mg of folic acid daily for the same period. Consult the contraindications and warnings in the labelling of folic acid preparations.

Excipients

The active tablets in [RH066 trade name] contain lactose monohydrate, whereas the placebo tablets contain lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature:

Hepatic metabolism:

Interactions can occur with medicinal or herbal products that induce microsomal enzymes, and result in increased clearance reducing plasma concentrations of sex hormones which may decrease the effectiveness of combined oral contraceptives, including [RH066 trade name]. These products include phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, rifabutin and possibly also oxcarbazepine, modafinil, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g., ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz) and products containing the herbal remedy St. John's wort.

Enzyme induction can occur after a few days of treatment. Maximal enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days.

Women receiving any of the above-mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of [RH066 trade name] may be reduced. A barrier contraceptive method should be used in addition to [RH066 trade name] during administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product. If concomitant drug administration runs beyond the end of the tablets in the current COC pack, the next COC pack should be started right away without taking the placebo pills.

For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

The metabolism of EE and DSG is incompletely understood, and multiple enzyme pathways are involved in the breakdown of both sex steroids. Although CYP3A is the major enzyme involved in the metabolism of both compounds, drug interactions based on enzyme induction or inhibition of CYP3A are not entirely

predictable due to the presence of alternative metabolic pathways. For this reason, published drug-drug interaction (DDI) studies provide better data on the potential effects of commonly used drugs on combined oral contraceptives including [RH066 trade name].

Pharmacodynamic interactions:

Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, [RH066 trade name] users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. [RH066 trade name] can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Effect of [RH066 trade name] on laboratory tests:

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range**.**

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[RH066 trade name] should not be used during pregnancy.

Pregnancy must be ruled out before starting to use [RH066 trade name]. [RH066 trade name] should be immediately discontinued if a woman becomes pregnant while taking it. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting [RH066 trade name] (see section 4.2 and 4.4).

Breastfeeding

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during COC use. These amounts may affect the child.

Fertility

[RH066 trade name] is indicated for the prevention of pregnancy. For information on return to fertility, see section 5.1.

4.7 Effects on ability to drive and use machines

[RH066 trade name] does not affect the ability to drive or operate machines.

4.8 Undesirable effects

As with all COCs, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent, or continuous), intensity (reduced or increased) or duration.

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis, and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Possibly related undesirable effects that have been reported in users of desogestrel/ethinylestradiol or CHC users in general are listed in the table below. All ADRs are listed by system organ class and frequency;

common (≥1/100), uncommon (≥1/1,000 to <1/100) and rare (<1/1,000).

System Organ Class	Common	Uncommon	Rare
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders	Weight increased	Fluid retention	Weight decreased
Psychiatric disorders	Depressed mood, mood altered	Libido decreased	Libido increased
Nervous system disorders	Headache	Migraine	
Vascular disorders			Venous thromboembolism[1] Arterial thromboembolism[1]
Gastrointestinal disorders	Nausea, abdominal pain	Vomiting, diarrhoea	
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, Erythema multiforme
Reproductive system and breast disorders	Breast pain, breast tenderness	Breast enlargement	Vaginal discharge, breast discharge

[1] Incidence in observational cohort studies of ≥1/10,000 to 1/1,000 women-years

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

There have been no reports of serious effects from overdose of [RH066 trade name].

Symptoms of an overdose with combined oral contraceptives in the case of adults and children may include nausea and vomiting. Vaginal bleeding can occur in women and girls.

There is no specific antidote and treatment is symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combinations

ATC Code: G03AA09

[RH066 trade name] is an oral combined hormonal contraceptive product containing ethinylestradiol 30 micrograms and desogestrel 150 micrograms.

The contraceptive effect of combination oral contraceptives is based on the interaction of various factors. The most important are the inhibition of ovulation and changes to cervical mucous.

5.2 Pharmacokinetic properties

The absorption characteristics of [RH066 trade name] have been determined after administration of single tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value* (± standard deviation)	
	Ethinylestradiol	Desogestrel
Maximum concentration (C_{max})	69 ± 21 (66) pg/ml	1340 ± 391 (1286) pg/ml
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	772 ± 356 (725) pg·h/ml	9764 ± 3848 (9222) pg·h/ml
Time to attain maximum concentration (t_{max})	1.48 ± 0.31 h	1.37 ± 0.40 h

***** Arithmetic mean

Pharmacokinetics of ethinylestradiol and desogestrel

	Ethinylestradiol	Desogestrel
Absorption		
T_{max}	Approximately 1 to 2 hours	1.5 hours
Oral Bioavailability	Mean approximately 45% Inter-individual range approximately 20% to 65%	62-81%
Food effect	NA	NA
Distribution		
General note	Approximately 1% of the total serum concentration is free steroid	After oral dosing, desogestrel (DSG) is rapidly absorbed and converted into etonogestrel (ENG).
Volume of distribution (mean)	2.8 to 8.6 L/kg	1.5 L/kg
Plasma protein binding *in vitro*	98% bound to albumin Induces SHBG but no significant binding to SHBG	ENG is 95-99% bound to serum proteins, mainly albumin and SHBG. Over time, the EE-induced induction of SHBG increases the SHBG-bound fraction with a corresponding decrease in the albumin-bound fraction.
Tissue distribution	NA	ENG is excreted in breast milk with a milk/serum ratio of 0.37-0.55.
Metabolism		
General note	Pre-systemic conjugation in the small intestine mucosa with enterohepatic cycling and first pass effect Mainly metabolised by aromatic hydroxylation	DSG is metabolised via hydroxylation and dehydrogenation to the active metabolite ENG. ENG is metabolised via sulphate and glucuronide conjugation.
Elimination		
Elimination half-life	10-20 hours	ENG: Approximately 30 hours
Mean systemic clearance (Cl/F)	5 mL/min/kg	2 mL/min/kg
% of dose excreted in urine	6% unchanged drug; 40% of the dose as metabolites	Approximately 45-48% as metabolites
% of dose excreted in faeces	9% unchanged drug; 60% of the dose as metabolites	Approximately 31-35% as metabolites
Pharmacokinetic linearity	Dose proportionality between 20 to 100 mcg	NA
Drug interactions *(in vitro)*		
Transporters	NA	NA

	Ethinylestradiol	Desogestrel
Metabolising enzymes	Multiple P450 isoforms: mainly CYP3A4 and CYP2C9 Other pathways also likely to be involved	Mainly CYP3A4. Other pathways also likely to be involved
Special populations		
Renal impairment	NA	NA
Hepatic impairment	NA	NA
Elderly patients	NA	NA
Paediatric patients	Not studied in premenarchal females	Not studied in premenarchal females

SHBG: Sex hormone binding globulin, NA: Information not available

5.3 Preclinical safety data

The toxicity profiles of ethinylestradiol and desogestrel are well established.

In laboratory animals, the effects of desogestrel and ethinylestradiol were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of [RH066 trade name], effects on sexual differentiation were observed in rat foetuses but not in monkeys.

Preclinical data for ethinylestradiol and desogestrel from conventional studies on chronic toxicity, genotoxicity and on carcinogenic potential do not show relevant risks for humans beyond those already described.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active film-coated tablet (white)

Core tablet:

- Lactose monohydrate
- Maize starch
- Povidone (E1201)
- D-alpha-tocopherol (E307)
- Soybean oil
- Silica colloidal hydrated (E551)
- Silica colloidal anhydrous (E551)
- Stearic acid (E570)

Film coat:

- Hypromellose (E464)
- Triacetin (E1518)
- Polysorbate
- Titanium dioxide (E171)

Placebo film-coated tablet (green)

Core tablet:

- Lactose monohydrate
- Maize starch
- Povidone (E1201)
- Silica colloidal anhydrous (E551)
- Magnesium stearate (E572)

Film coat:
Hypromellose (E464)
Triacetin (E1518)
Polysorbate
Titanium dioxide (E171)
FD&C blue #2 aluminium lake (E132)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC-aluminium blisters. Each blister card contains 21 active (white) tablets plus 7 placebo (green). Pack sizes: 1, 3 or 6 blister cards packed in a carton box.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Laboratorios Leon Farma SA
La Vallina s/n
Poligono Industrial Navatejera
Villaquilambre
Leon 24008
Spain

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH066

9. DATE OF PREQUALIFICATION

27 October 2020

10. DATE OF REVISION OF THE TEXT

January 2021

References

Marvelon PIL, Merck Sharp & Dohme Limited, Revised December 2018
https://www.medicines.org.uk/emc/product/1359/pil (accessed November 28, 2020)

Marvelon SmPC, Merck Sharp & Dohme Limited, Revised December 2018 https://www.medicines.org.uk/emc/product/1359/smpc (accessed November 28, 2020)

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Lammers P, Blumenthal PD, and Huggins GR; Developments in contraception: A comprehensive review of Desogen® (desogestrel and ethinyl estradiol) Contraception 1998;57 1S-27S

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines