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/prequal/sites/default/files/documents/75%20SRA%20clarification_February2017_0.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH071 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active tablet contains 0.03 mg of ethinylestradiol and 0.15 mg of levonorgestrel.

Excipients with known effects:

Each active (yellow) tablet contains about 84.32 mg lactose monohydrate.

Each placebo (white) tablet contains about 89.50 mg lactose anhydrous.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Active tablet: Yellow, round, biconvex film-coated tablet and plain on both sides with a diameter of 6 mm and thickness less than 4 mm.

Placebo tablet: White, round, film-coated tablet and plain on both sides with a diameter of 6 mm and thickness of 3-4 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH071 trade name] is an oral combined hormonal contraceptive (CHC) agent for women.

4.2 Posology and method of administration

[RH071 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 [RH071 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 [RH071 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, [RH071 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.

When switching from another combination product (combined oral contraceptive, vaginal ring, transdermal patch) to [RH071 trade name]:

- [RH071 trade name] may be started on the first day immediately after the last tablet of the previous oral contraceptive course, whether it was a 21-day or and every-day (28-day) regimen. Additional contraceptive precautions are not required.
- If a vaginal ring or a transdermal patch was previously used, [RH071 trade name] should be started on the day after the usual interval, during which neither ring nor patch was used.

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

When switching from a progesterone-only product (mini pill, depot injection, implant)

- [RH071 trade name] should be started on the first day of bleeding, even if a progestogen-only pill has already been taken on that day. No additional contraceptive protection is required. [RH071 trade name] may be started after menstrual bleeding has stopped provided the woman is reasonably certain that she is not pregnant. An additional non-hormonal (barrier) method of contraception should be used during the first 7 days of taking [RH071 trade name].
- When changing from an implant or an intrauterine system, it should be on the day of its removal, or on the day the next injection is due, when switching from an injectable. The woman should use an additional non-hormonal contraceptive method (barrier method) for the first seven days of taking [RH071 trade name].

When switching from an IUD (including the levonorgestrel-releasing IUD):

- [RH071 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.
- [RH071 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. The IUD can be removed at the time of the next menstrual period.
- If the woman is amenorrhoeic or has irregular periods, [RH071 trade name] can be started at any time provided she is reasonably certain that she is not pregnant. The IUD can be removed at the time of the next menstrual period.

Following a first or second trimester abortion:

[RH071 trade name] can be started immediately. No additional contraceptive precautions are required.

Following childbirth:

If breastfeeding:

- [RH071 trade name] should not be initiated within 6 weeks of delivery as milk production may be reduced and small amounts of the active substances may pass into milk.
- Between 6 weeks and 6 months post partum, combined oral contraceptives are not recommended unless other more appropriate methods are not available or not acceptable.
- [RH071 trade name] may be started after 6 months post partum.

If not breastfeeding:

- Combined oral contraceptives are not recommended within the first 21 days post partum due to the increased risk of venous thromboembolism. Ovulation is very unlikely to occur during the first 21 days, and the risk of pregnancy is low. However, if national, regional, or local programme protocols require it, other contraceptive methods may be used during this time.
- After 21 days post partum, [RH071 trade name] can be started if there are no other risk factors for venous thromboembolism.
    - If menstruation has not restarted, [RH071 trade name] can be started immediately if the woman is reasonably certain that she is not pregnant. She will need to abstain from sex or use additional contraceptive protection for the first seven days.
    - If menstruation has restarted, [RH071 trade name] can be started as advised for menstruating women who have not been on the combined oral contraceptive pill or have taken a break (see above).

Duration of administration:

[RH071 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 [RH071 trade name] may be decreased if it is not taken regularly.

If one or two active 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.
    - 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 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 [RH071 trade name] 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 [RH071 trade name].

Diarrhoea or vomiting:

- If the woman vomits or has significant diarrhoea within two hours of taking [RH071 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 [RH071 trade name].

Delaying the withdrawal bleed:

To postpone the withdrawal bleed, the user should continue taking the active tablets from the next pack of [RH071 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 tablets, the user may continue to take [RH071 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)
- Undiagnosed vaginal bleeding
- Undiagnosed amenorrhoea
- Hypersensitivity to the active substances or one of the other components of [RH071 trade name]

If one of these disorders occurs for the first time while using [RH071 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 (see section 4-3).

Venous thrombosis and thromboembolism (VTE):

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE. Products that contain levonorgestrel, such as [RH071 trade name] are associated with the lowest risk of VTE. The decision to use [RH071 trade name] should be taken after a discussion with the woman to ensure she understands the risk of VTE with [RH071 trade name], how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use.

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 levonorgestrel, about 6 will develop a VTE in a year. 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:

There is an approximately 2-to-4-fold increase in the relative risk of post-operative thromboembolic complications when using oral contraceptives. The relative risk of venous thromboses is twice as high in obese women. If possible, oral contraceptives should be discontinued at least four weeks before elective surgery, as well as in the event of prolonged immobilisation.

[RH071 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 [RH071 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 [RH071 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). [RH071 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.

This increased risk gradually returns to a baseline age-appropriate risk within 10 years following the discontinuation of combined oral contraceptives. 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 frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). ALT elevations have also been observed with HCV anti-viral medicinal products containing glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir (see sections 4.3 and 4.5).

Angioedema:

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

Diabetes:

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. The type and dose of the progestogen may be of importance. 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 [RH071 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 period off tablets. If [RH071 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 [RH071 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 [RH071 trade name], a complete personal (and family) medical history should be taken along with a complete medical examination. 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 [RH071 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 [RH071 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 [RH071 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 [RH071 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 ethinylestradiol and levonorgestrol, the two active substances in [RH071 trade name], and other medications may increase or decrease their serum concentrations. Decreased concentrations of ethinylestradiol/levonorgestrol can result in an increase in breakthrough bleeding and menstrual cycle disturbances and lower the contraceptive efficacy of [RH071 trade name]. Increased levels of ethinylestradiol/levonorgestrel may cause more frequent occurrence and increased severity of adverse effects.

The metabolism of EE and LNG 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 [RH071 trade name].

CYP3A Inducers

Effect of CYP3A inducers on the exposure to EE and progestins:

Strong CYP3A inducers, including rifampin, carbamazepine, and phenytoin, reduced the exposure of EE by 38–66%. Bosentan and eslicarbazepine, moderate CYP3A inducers, decreased the AUC of EE by 31% and 42%, respectively. Efavirenz, also a moderate CYP3A inducer, produced only a 10% reduction in EE exposure, but reduced LNG exposure by approximately 58%. Oxcarbazepine, nevirapine, both weak inducers of CYP3A, decreased EE exposure by 47% and 27% respectively, while perampanel, also a weak inducer, did not significantly affect the AUC of EE. St John's wort extract, a moderate to strong inducer of CYP3A4, decreased EE exposure by 14–32%.

Table: Effect of coadministration of CYP3A inducers on the exposure to EE and progestins

Strong inducers of CYP3A	**Effect on EE AUC**	**Effect on LNG AUC**
Rifampin	↓ 66%	↓ 51% - 60% (NET)
Carbamazepine	↓ 45%	↓ 44%
Phenytoin	↓ 49%	↓ 42%
Moderate inducers of CYP3A		
Bosentan	↓ 31%	↓ 14% (NET)

Eslicarbazepine	↓ 42%	↓ 34%
Efavirenz	↓ 10%	↓ 58%
St. John's wort	↓ 14% - 32%	↓ 12% (NET)
Weak inducers of CYP3A		
Oxcarbazepine	↓ 47%	↓ 36%
Nevirapine	↓ 27%	↓ 21% (NET)
Perampanel 4mg or 8 mg daily	NS	NS
Perampanel 12 mg daily	NS	↓ 40%

NET: Norethindrone; NS: No significant change

Other drugs that may reduce the exposure to EE and LNG:

Antibiotics:

Antibiotics can interrupt the enterohepatic cycling of estrogens by reducing the bacterial population of the small intestine, which is responsible for hydrolysis of the conjugated hormone excreted in bile, back to free drug. Although the conjugated hormone is excreted in faeces, the effect on circulating EE is small and inconsistent. Nevertheless, there have been reports of contraceptive failure associated with a wide range of antibiotics, and particularly with tetracyclines and ampicillin.

Studies performed in humans to demonstrate decreased oral contraceptive efficacy with antibiotic use have been unable to show an interaction exists, with the exception of CYP3A4 induction by rifampin. Because many of the data are conflicting and inconclusive, it has only been possible to categorise antibiotic-associated contraceptive failure based on the number of case reports.

Table: Antibiotic Categories

Category	Drugs
A: Antibiotic known to reduce birth control pill effectiveness	Rifampicin
B: Antibiotics associated with oral contraceptive failure in three or more case reports	Ampicillin, Amoxicillin, Co-trimoxazole, Griseofulvin, Metronidazole, Tetracycline
C: Antibiotics associated with oral contraceptive failure in at least one case report	Cephalexin, Clindamycin, Dapsone, Erythromycin, Isoniazid,

Adapted from Zhanel et al, 1999

Rifampicin (category A) is the only antibiotic that has been shown to reduce plasma estrogen levels. [RH071 trade name] should not be relied upon for birth control while taking rifampicin. An alternative method of contraception is necessary, and it is important to inform the patient of the chance for an interaction.

Antibiotics in category B have infrequently been linked with reduced oral contraceptive effectiveness. Retrospective case studies have contributed a large portion of information regarding these antibiotics, and a definite interaction is unproven. The clinician should discuss the available data with the patient and offer a second form of birth control to patients who request it.

The antibiotics in category C have only rarely been associated with reduced oral contraceptive efficacy and are most likely safe to use concomitantly with oral contraceptives.

Coadministration of drugs that are known to increase the clearance of both active components of [RH071 trade name]:

Women who require short term use of a drug known to cause decreased concentrations of the active components of [RH071 trade name] are at risk of contraception failure. If the drug is for short term use, a barrier method of contraception should be used while continuing to take [RH071 trade name]. The barrier method should be used for the duration of treatment with the enzyme-inducing drug and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of a pack, the next pack should be started without a break. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack.

For women requiring long-term therapy with a drug or drugs that reduce the concentration of the active components of [RH071 trade name], another method of contraception should be used.

Antiretrovirals used for pre-exposure prophylaxis against HIV infection do not affect contraceptive effectiveness. With the exception of efavirenz, the use of antiretroviral drugs should not affect the choice of contraceptive.

CYP3A Inhibitors

Effect of CYP3A inhibitors on the exposure to EE and progestins:

The magnitude of increase in the exposure (AUC) to EE was variable in the presence of CYP3A inhibitors. Strong CYP3A inhibitors, such as voriconazole and ketoconazole, increased EE exposure by 60% and 40%, respectively. Moderate CYP3A inhibitors, including fluconazole, and atazanavir, resulted in a 38% to 48% increase in the AUC of EE. No significant effect on the exposure of EE was observed with other moderate or weak CYP3A inhibitors.

The effect of CYP3A inhibitors on the systemic exposure to progestins was somewhat more predictable but varied with different progestins. The moderate CYP3A inhibitors fluconazole, netupitant increased the AUC of LNG by 25% to 40% while weak inhibitors of CYP3A had a negligible effect on LNG exposure.

Table: Effect of coadministration of CYP3A inhibitors on the exposure to EE and progestins

Strong inhibitors of CYP3A	**Effect on EE AUC**	**Effect on LNG AUC**
Voriconazole	↑ 60%	↑ 53% (NET)
Ketoconazole	↑ 40%	↑ 268% (DRSP)
Moderate inhibitors of CYP3A		
Fluconazole	↑ 38%	↑ 25%
Atazanavir	↑ 48%	↑ 210% (NET)
Netupitant	NS	↑ 40%
Weak inhibitors of CYP3A		
Ivacaftor	NS	NS (NET)
Ticagrelor	NS	NS

NET: Norethindrone; DRSP: Drospirenone; NS: No significant change

Other drugs that may increase the exposure to EE and LNG:

- Drugs that inhibit the sulphation of EE in the gastrointestinal wall, e.g. ascorbic acid or acetaminophen
- Atorvastatin

Effect of [RH071 trade name] on laboratory tests:

The results of some laboratory tests may be altered in women using combined oral contraceptives, including those assessing hepatic, adrenal and thyroid functions, plasma levels of carrier proteins (e.g. SHBG, lipoproteins), parameters for carbohydrate metabolism, coagulation, and fibrinolysis.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy:

[RH071 trade name] should not be used during pregnancy.

Pregnancy must be ruled out before starting to use [RH071 trade name]. [RH071 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 early pregnancy.

Animal experimental studies have shown reproductive toxicity (see section 5.3) and undesirable hormonal effects on the development of the urogenital tract cannot completely be ruled out.

The increased risk of VTE during the postpartum period should be considered when re-starting [RH071 trade name] (see section 4.2 and 4.4).

Breastfeeding:

[RH071 trade name] should not be initiated within 6 weeks of delivery as milk production may be reduced and small amounts of the active substances may pass into milk.

Between 6 weeks and 6 months post partum, combined oral contraceptives are not recommended unless other more appropriate methods are not available or not acceptable.

[RH071 trade name] may be started after 6 months post partum.

4.7 Effects on ability to drive and use machines

[RH071 trade name] does not affect the ability to drive or operate machines.

4.8 Undesirable effects

The most frequent adverse drug reactions related to the use of [RH071 trade name] are headache, depressed mood, breast pain, spotting and intermenstrual bleeding.

The following adverse drug reactions have been reported following the use of combined oral contraceptives containing EE and LNG:

Body system	**Frequency of adverse reactions**		
	Common: ≥ 1% to < 10%	Uncommon: ≥ 0.1% to < 1%	Rare: ≥ 0.01% to < 0.1%
Eye disorders			Contact lens intolerance
Infections and infestations	Vaginitis, including candidiasis		
Immune system disorders		Urticaria	Hypersensitivity reactions
Metabolic disturbances		Change of appetite (increase or decrease)	Glucose intolerance
Psychiatric disorders	Mood swings including depression;	Reduced libido	Increased libido
Nervous system disorders	Headache	Migraine	
Gastrointestinal tract disorders	Nausea; abdominal pain	Vomiting; diarrhoea	

Liver and gall bladder disorders			Cholestatic jaundice
Skin and subcutaneous tissue disorders	Acne	Skin rash	Erythema nodosum; erythema multiforme
Genital and breast disorders	Breast tenderness; dysmenorrhea; changes in menstrual flow; amenorrhea	Breast enlargement	Vaginal discharge; breast discharge
General disorders	Fluid retention; oedema		
Physical and laboratory evaluations	Weight change (increase or decrease)	Increased blood pressure; elevated blood lipids	Decreased folic acid levels

See section 4.4 for information on further severe adverse reactions, such as thromboembolic disease, liver tumours, cervical and breast cancer.

The following adverse drug reactions have rarely been reported in connection with the use of combined oral contraceptives, but their frequency cannot be calculated from the reports:

- Severe anaphylactic reaction with cardiorespiratory involvement
- Optic neuritis (may cause partial or complete loss of vision)
- Worsening of varicose veins
- Pancreatitis with a currently existing severe lipid metabolic disturbance
- Gall bladder disease, including gall stones (combined oral contraceptives can cause gall bladder disease or worsen existing gall bladder disease)
- Haemolytic-uraemic syndrome
- Herpes gestationis
- Otosclerosis
- Worsening of systemic lupus erythematosus
- Worsening of porphyria
- Worsening of Chorea minor (Sydenham's chorea)
- Worsening of depression
- Worsening of chronic-inflammatory intestinal diseases (Crohn's disease and ulcerative colitis)

Conditions reported to deteriorate with pregnancy or previous COC use

Jaundice and/or pruritus related to cholestasis; gallstone formation; systemic lupus erythematosus; herpes gestationis; otosclerosis-related hearing loss; sickle cell anaemia; renal dysfunction; hereditary angioedema; porphyria

Changes in glucose tolerance or effect on peripheral insulin resistance have been reported in women using COCs (see section 4.4).

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 [RH071 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 estrogens, fixed combinations

ATC Code: G03AA07

[RH071 trade name] is an oral combined hormonal contraceptive product containing ethinylestradiol (EE) and levonorgestrel (LNG).

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 [RH071 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	**Levonorgestrel**
Maximum concentration (C_{max})	67.9 (±21.9) pg/ml	4.22 (±1.73) ng/ml
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	787 (±236) pg·h/ml	47.5 (±19.4) ng·h/ml
Time to attain maximum concentration (t_{max})	1.5 (± 0.3) h	1.2 (± 0.3) h

* Arithmetic mean

	Ethinylestradiol	**Levonorgestrol**
Absorption		
T_{max}	Approximately 1 to 2 hours	Approximately 1 hour
Oral Bioavailability	Mean approximately 45% Inter-individual range approximately 20% to 65%	Almost 100%
Food effect	NA	NA
Distribution		
General note	Approximately 1% of the total serum concentration is free steroid	Approximately 1.1% of the total serum concentration is free steroid
Volume of distribution (mean)	2.8 to 8.6 L/kg	129 L
Plasma protein binding *in vitro*	98% bound to albumin Induces SHBG but no significant binding to SHBG	35% bound to albumin 65% bound to SHBG
Tissue distribution	NA	NA
Metabolism		
	Pre-systemic conjugation in the small intestine mucosa with enterohepatic cycling and first pass effect Mainly metabolised by aromatic hydroxylation	Mainly through reduction and hydroxylation, with subsequent conjugation Metabolic clearance is highly variable between individuals
Elimination		

	Ethinylestradiol	Levonorgestrol
Elimination half-life	10-20 hours	25 hours
Mean systemic clearance (Cl/F)	5 mL/min/kg	1.5 mL/min/kg
% of dose excreted in urine	6% unchanged drug; 40% of the dose as metabolites	40% to 68%
% of dose excreted in faeces	9% unchanged drug; 60% of the dose as metabolites	16% to 48%
Pharmacokinetic linearity	Dose proportionality between 20 to 100 mcg	Non-linear due to an increase in SHBG production when given with ethinyl estradiol
Drug interactions *(in vitro)*		
Transporters	NA	NA
Metabolising enzymes	Multiple P450 isoforms: mainly CYP3A4 and CYP2C9 Other pathways also likely to be involved	Multiple P450 isoforms: CYP3A4 is the main enzyme involved in oxidative metabolism
Special populations		
Renal impairment	NA	NA
Hepatic impairment	NA	NA
Elderly patients	NA	NA
Paediatric patients	Not studied in premenarchal female	Not studied in premenarchal females

SHBG: Sex hormone binding globulin, NA: Not available

5.3 Preclinical safety data

The toxicity profiles of ethinylestradiol and levonorgestrel are well established.

Because of the pronounced differences in species, results from animal experimental testing with oestrogens possess limited predictive value for administration to humans.

In experimental animals, ethinylestradiol exhibits an embryo-lethal effect in relatively small dosage; malformations of the urogenital system and feminization of male foetuses have been observed. Levonorgestrel showed an embryo-lethal effect in animal experiments and, in high doses, a virilizing effect on female foetuses. Reproduction-toxicological studies in rats, mice and rabbits showed no indication of a teratogenic effect.

Preclinical data for ethinylestradiol and levonorgestrel 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 tablets (yellow):

Core tablet:

Lactose monohydrate
Povidone
Crospovidone
Magnesium stearate

Film coat:

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc
Iron oxide yellow

Placebo tablets (white):

Core tablet:

Lactose monohydrate
Povidone
Magnesium stearate

Film coat:

Polyvinyl alcohol
Titanium dioxide
Macrogol
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister containing 21 active (yellow) tablets plus 7 placebo (white) tablets. One such blister card is 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
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Villaquilambre
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Spain

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH071

9. DATE OF PREQUALIFICATION

21 April 2020

10. DATE OF REVISION OF THE TEXT

September 2020

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