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/document_files/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH066 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active tablet contains 150 micrograms desogestrel and 30 micrograms ethinylestradiol film-coated tablets.

Excipients with potential clinical effect

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, film-coated tablets. They are biconvex (rounded on top and bottom) with a flat edge. The tablets have 'C' debossed (stamped into) one side and '7' on the other side.

Placebo tablet:

Green, round, film-coated tablet. They are biconvex (rounded on top and bottom) with a flat edge. The tablets are plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH066 trade name] is indicated in women for contraception.

4.2 Posology and method of administration

Posology

The dose of [RH066 trade name] is 1 tablet every day starting with active tablets for 21 days followed by inactive (placebo) tablets for 7 days. The tablets should be taken at around the same time each day and follow the sequence shown on the pack. The pack of [RH066 trade name] should be started without a break.

A withdrawal bleed generally occurs during the 7-day interval when the woman is taking the inactive tablets. The bleed usually starts 2 to 3 days after taking the active tablet of the pack.

[RH066 trade name] can continue to be used for as long as contraception is needed, and no health risks arise that contraindicate its use.

Starting [RH066 trade name]

A woman can start taking [RH066 trade name] at any time she wants to if it is reasonably certain she is **not pregnant**; robust methods should be used to rile out pregnancy.

Starting contraception or switching from a non-hormonal method

- The woman may start the course on any of the first 5 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

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

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 7 days.

Switching from an IUD (including levonorgestrel-releasing IUD)

- If the woman starts taking [RH066 trade name] within 5 days after the start of her monthly bleeding, there is no need for additional contraceptive protection. The IUD can be removed at this time.
- If it is more than 5 days since the start of monthly bleeding, the woman can start taking [RH066 trade name] if it is reasonably certain that the woman is not pregnant. The IUD can be removed at the next monthly bleeding.
- If the woman is amenorrhoeic or has irregular periods, [RH066 trade name] can be started at any time if it is reasonably certain that the woman is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days.

Switching from another hormonal contraception method

- If the woman has been using the hormonal method correctly, she can start taking [RH066 trade name] immediately. Additional contraceptive protection is not required.
- If the woman has been receiving injectable hormonal contraception, she can start taking [RH066 trade name] on the day she would have received the injection. Additional contraceptive protection is not required.

After progesterone-containing emergency contraceptive pill

[RH066 trade name] can be started immediately after taking the emergency contraceptive pill, or at any time afterwards if it is reasonably certain that the woman is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days.

After ulipristal acetate emergency contraceptive pill

[RH066 trade name] can be started on the sixth day after taking the emergency contraceptive pill (see section 4.5), or at any time afterwards if it is reasonably certain that the woman is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days of taking [RH066 trade name].

After miscarriage or abortion

- [RH066 trade name] can be started within 7 days of a first- or second-trimester abortion or miscarriage. Additional contraceptive precaution is not required.
- If it is longer than 7 days after a first- or second-trimester abortion, the woman can start [RH066 trade name] at any time if it is reasonably certain that she is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days of taking [RH066 trade name].

After birth and fully or nearly fully breast-feeding

- [RH066 trade name] can be started either 6 months after delivery or when the baby's main food is no longer breast milk if that occurs earlier.
- If it is longer than 6 months after delivery and monthly bleeding has not started, [RH066 trade name] can be started at any time if it is reasonably certain that the woman is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days.
- If monthly bleeding has returned, [RH066 trade name] can be started as described under 'Starting contraception or switching from a non-hormonal method'.

After birth and partially breast-feeding

- [RH066 trade name] can be started 6 weeks after delivery. If monthly bleeding has returned during these 6 weeks, an additional non-hormonal (barrier) contraception should be used until [RH066 trade name] is started.
- If it is longer than 6 weeks after delivery and monthly bleeding has not returned, the woman can start taking [RH066 trade name] immediately. An additional non-hormonal (barrier) contraception should be used for the first 7 days.
- If it is longer than 6 weeks after delivery and monthly bleeding has returned, [RH066 trade name] can be started as described under 'Starting contraception or switching from a non-hormonal method'.

After birth and not breast-feeding

- [RH066 trade name] can be started between 21 to 28 days after delivery.
- If it is longer than 28 days after delivery and monthly bleeding has not returned, [RH066 trade name] can be started at any time if it is reasonably certain that the woman is not pregnant. An additional non-hormonal (barrier) contraception should be used for the first 7 days.
- If it is longer than 28 days after delivery and monthly bleeding has returned, [RH066 trade name] can be started as described under 'Starting contraception or switching from a non-hormonal method'.

Missed doses

DotWP-ProductName} should be taken regularly at around the same time each day to maintain its contraceptive efficacy.

If one or two active tablets are missed, or if a new pack is started one or two days late

- The woman should take the active tablet as soon as possible and then continue taking the tablets daily at her usual time.
- Additional contraceptive protection is not required.

If at least 3 active tablets in a row are missed or if the pack is started at least 3 days late

- The woman should take an active tablet as soon as possible and then continue taking the tablets daily at her usual time.
- An additional non-hormonal (barrier) contraception should be used for the next 7 days.
- An emergency contraceptive pill should be used if the woman has had sex in the previous 5 days.
- If the tablets are missed in the last 3 weeks of the pack, the woman should continue using the pack until all the active tablets are used up. She should discard the inactive tablets and start a new pack the next day.

Diarrhoea or vomiting

- If the woman vomits within 2 hours of taking [RH066 trade name] she should take another active tablet as soon as she can and then continue the taking the tablets as usual.
- If vomiting or diarrhoea continue for longer than 2 days, the woman should follow the instructions for missing at least 3 tablets in a row, above.

Extended and continuous use

Extended or continuous use of active tablets of [RH066 trade name] can reduce the frequency of bleeding and of headaches, premenstrual syndrome, mood changes and heavy or painful bleeding.

Extended use involves taking active tablets of [RH066 trade name] every day for 12 weeks (4 packs) followed by 7 inactive tablets (from the fourth pack) when bleeding may occur. [RH066 trade name] is started again after this interval.

Continuous use involves taking active tablets of [RH066 trade name] every day for as long as the woman wishes. If troublesome irregular bleeding occurs, the woman can interrupt [RH066 trade name] for 3 or 4 days and then start taking the tablets again.

4.3 Contraindications

[RH066 trade name] should not be used in the following situations:

- Risk of venous thromboembolism
  - Current or prior history of venous thromboembolism (e.g. deep-vein thrombosis, pulmonary embolism), whether on anticoagulant therapy or not
  - Hereditary or acquired predisposition for venous thromboembolism, such as activated protein C (APC) resistance, (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency
  - Major surgery with prolonged immobilisation (see section 4.4)
  - High risk of venous thromboembolism because of multiple risk factors (see section 4.4), including:
    - obesity
    - family history of thromboembolism
    - higher age (particularly above 35 years)
- Risk of arterial thromboembolism
  - Current or prior history of arterial thrombosis (e.g. myocardial infarction) or its prodromal stages (e.g. angina pectoris)
  - High risk of arterial thromboembolism due to multiple risk factors or a serious risk factor (see section 4.4), including:
    - diabetes with vascular symptoms
    - severe hypertension (above 160/100 mm Hg)
    - severe dyslipoproteinaemia
  - Current or prior history of cerebrovascular disease (e.g. stroke) or prodromal condition (e.g. transient ischemic attack
  - Hereditary or acquired predisposition for arterial thromboembolism such as, hyperhomocysteinaemia and anti-phospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant)
  - History of migraines with aura or focal neurological symptoms
- Existing or prior history of severe liver disease e.g. active viral hepatitis, severe cirrhosis while liver function values remain abnormal
  - Concomitant use with certain medicines used for treating hepatitis C (see section 4.5)
- Existing or prior history of benign or malignant hepatic tumours
- Existing or prior history of breast cancer
- Hypersensitivity to the active substances or one of the other components of [RH066 trade name]

Relevant national and other authoritative guidelines should also be consulted.

4.4 Special warnings and precautions for use

If there is a concern about any condition listed below, the health care provider and the woman should discuss if [RH066 trade name] should be stopped. The woman should be advised to be alert about these conditions and to contact her health care provider if a listed condition appears or worsens.

Medical examination and consultation

Before starting or restarting [RH066 trade name], a complete personal and family medical history should be taken along with a full medical examination. The history and physical examination should address the contraindications (section 4.3) and warnings (see below) and should be repeated at intervals while the woman remains on [RH066 trade name]. The frequency of check-ups depends on the woman's individual circumstances.

Medical assessment should include 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.

Conditions which require close supervision

Exacerbation or first appearance of any of the conditions or risk factors listed may necessitate discontinuing [RH066 trade name]:

- diabetes with mild vascular disease or mild nephropathy, retinopathy or neuropathy
- hypertension that is adequately controlled, i.e. systolic pressured exceeding 140–159 mm Hg or diastolic pressured exceeding 90–94 mm Hg (see also Section 4.4 'Reasons for stopping [RH066 trade name] immediately')
- porphyria
- obesity
- migraine
- cardiovascular diseases

Reasons for stopping [RH066 trade name] immediately

When stopping [RH066 trade name], non-hormonal contraception should be used to maintain contraceptive protection.

- Occurrence for the first time, or exacerbation, of migraine headaches or unusually frequent or unusually severe headaches
- Sudden disturbances of vision, of hearing or other perceptual disorders
- First signs of thrombosis or blood clots (e.g. unusual pain or swelling in a leg, stabbing pains on breathing, or coughing for no apparent reason). Pain and tightness in the chest
- At least 4 weeks before an elective major operation (e.g. abdominal, orthopaedic), any surgery to the legs, medical treatment for varicose veins or prolonged immobilisation, e.g. after accidents or surgery. [RH066 trade name] must not be restarted until 2 weeks after full ambulation. In case of emergency surgery, thrombotic prophylaxis is usually indicated e.g. subcutaneous heparin
- Onset of jaundice, hepatitis, itching of the whole body
- Significant rise in blood pressure
- Severe upper abdominal pain or liver enlargement
- Exacerbation of following conditions:
  - gallstone formation
  - systemic lupus erythematosus
  - pemphigoid gestationis
  - otosclerosis-related hearing loss
  - sickle cell anaemia
  - renal dysfunction
  - hereditary angioedema
  - any other condition that worsened during the woman's pregnancy or previous use of a combined oral contraceptive.

Venous thrombosis and thromboembolism

The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE). Products that contain levonorgestrel, such as [RH066 trade name] are associated with the lowest risk of VTE. The decision to use [RH066 trade name] should be taken 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 year of use. The risk may be increased when a combined hormonal contraceptive is re-started after a break in use of 4 weeks or longer.

In women who do not use a combined hormonal contraceptive and are not pregnant, about 2 out of 10 000 will develop VTE over one year. It is estimated that out of 10 000 women who use a combined hormonal contraceptive 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 combination hormonal contraceptive. 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.

Extremely rarely, in women who use a combined hormonal contraceptive, thrombosis can occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

Risk factors for venous thromboembolism

The risk for venous thromboembolic complications may increase substantially in a woman using combined hormonal contraceptive who has additional risk factors, particularly if there are multiple risk factors (see list, below).

[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, the increase in risk may be greater than the sum of the individual factors; in this case her total risk of VTE should be considered.

List of risk factors for venous thromboembolism

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. 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 longer than 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 [RH066 trade name] (for elective surgery, at least 4 weeks in advance) and not resume until 2 weeks after complete remobilisation. Another method of contraception should be used. Antithrombotic treatment should be considered if [RH066 trade name] has not been discontinued in advance.
Family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period after delivery, should be considered.

There is no consensus on the significance of varicose veins and superficial phlebitis on the occurrence or progression of venous thrombosis.

Symptoms of venous thromboembolism

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) include:

- unilateral swelling of the leg, 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 lightheadedness 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)

The use of combined oral contraceptives is associated with an increased risk for arterial thromboembolism (myocardial infarction) or cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk factors for arterial thromboembolism

The risk of arterial thromboembolic complications or of a cerebrovascular accident (CVA) in combined oral contraceptive users increases in women with risk factors (see list, below).

[RH066 trade name] is contraindicated if a woman has multiple risk factors that put her at high risk of arterial thromboembolism (see section 4.3). If a woman has more than one risk factor, the increase in risk may be greater than the sum of the individual factors; in this case her total risk should be considered.

List of risk factors for arterial thromboembolism

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 years who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Family history (arterial thromboembolism in a sibling or parent, especially at a relatively early age e.g. below 50 years)	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about 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, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus

Symptoms of arterial thromboembolism

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 combined oral contraceptive.

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.

Cancers

Numerous epidemiological studies have reported on the risks of ovarian, endometrial, cervical and breast cancer in women using combined oral contraceptives. High-dose combined oral contraceptives offer substantial protection against both ovarian and endometrial cancer. However, it is not clear whether low-dose combined oral contraceptives such as [RH066 trade name] confer protection to the same level.

Breast cancer

A meta-analysis of 54 epidemiological studies showed a slightly increased relative risk (RR 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives. The pattern of increased risk may be due to an earlier diagnosis of breast cancer in combined oral contraceptive 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 after discontinuing combined oral contraceptives. Since breast cancer is rare in women under 40 years of age, the additional cases in current and recent users of combined oral contraceptives is small compared with the overall risk of breast cancer.

The additional breast cancers diagnosed in current or past users of combined oral contraceptives are more likely to be localised to the breast than those in women who never used combined oral contraceptives.

The most important risk factor for breast cancer in women using a combined hormonal contraceptive is the age when the woman discontinues it; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important, and the excess risk gradually disappears such that by 10 years after stopping the combined hormonal contraceptive there appears to be no excess risk.

The possible increase in risk of breast cancer should be discussed with the woman and weighed against the benefits of using [RH066 trade name], taking into account evidence that they offer substantial protection against the risk of developing certain other cancers (e.g. ovarian and endometrial cancer).

Cervical cancer

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies indicate that long-term use of combined oral contraceptives may further increase the risk but there is uncertainty whether this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

Liver cancer

In rare cases benign and, in even rarer cases, malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have occurred after the use of hormonal substances such as [RH066 trade name].

If severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be considered.

Other conditions

Some chronic diseases or conditions may become worse during the use of combined oral contraceptives.

Hyperlipidaemias

Women with hypertriglyceridemia, or a family history of it, may be at an increased risk of pancreatitis when using combined oral contraceptives.

Women with hyperlipidaemias are at an increased risk of arterial disease (see 'Arterial thromboembolism (ATE)', above). However routine screening of women on COCs is not required.

Hypertension

Hypertension is a risk factor for stroke and myocardial infarction (see 'Arterial thromboembolism (ATE)', above). Although small increases in blood pressure have been reported in many women taking combined oral contraceptives, clinically relevant increases are rare.

Women with a history of hypertension or who develop sustained hypertension (usually above 140/90 mm Hg) while taking a combined oral contraceptive should use an alternative method of contraception.

Disturbances of liver function

Acute or chronic disturbances of liver function may necessitate the discontinuation of [RH066 trade name] until markers of liver function return to normal. Recurrence of cholestatic jaundice or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of combination oral contraceptives.

Angioedema

In women with acquired or hereditary angioedema, use of oestrogens may trigger or worsen symptoms.

Diabetes

Women with insulin-dependent diabetes without vascular disease can use [RH066 trade name]. However, diabetes increases the risk of vascular disease and this should be considered when prescribing [RH066 trade name]. [RH066 trade name]is contraindicated in women with diabetes as well as vascular disease.

Psychiatric disorders

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. 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 starting [RH066 trade name].

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 light while taking [RH066 trade name].

Menstrual changes

Breakthrough bleeding or spotting can occur in users of combined oral contraceptives, especially in the first months of use. An assessment of irregular bleeding is thus likely to be meaningful only after about 3 months of use.

If bleeding irregularities persist or recur after previously regular cycles, then non-hormonal causes should be considered and, as for any abnormal vaginal bleeding, adequate diagnostic measures are indicated to rule out malignancy or pregnancy.

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 the woman:

- misses (see section 4.2)
- is vomiting or has diarrhoea (see section 4.2)
  takes certain other medicines at the same time (see section 4.5)

Excipients

The active tablets in [RH066 trade name] contain lactose monohydrate, whereas the placebo tablets contain lactose anhydrous. Patients with congenital lactase deficiency, galactosaemia or glucose-galactose intolerance must not be given this medicine unless strictly necessary. The small amount of lactose in each dose is unlikely to cause symptoms of lactose intolerance in other patients.

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 [RH066 trade name] (which contains desogestrel/ethinylestradiol) and other medicines may increase or decrease their serum concentrations. Decreased concentrations of desogestrel/ethinylestradiol can result in breakthrough bleeding and menstrual cycle disturbances, and lower contraceptive efficacy. Raised concentrations of desogestrel/ethinylestradiol may increase the frequency and severity of adverse effects.

Multiple enzyme pathways are involved in the metabolism of desogestrel/ethinylestradiol. Although CYP3A4 is the major enzyme involved in the metabolism of both compounds, drug interactions based on enzyme induction or inhibition of CYP3A4 are not predictable due to the presence of alternative metabolic pathways. For this reason, published drug-drug interaction studies are more reliable on the potential effects of commonly used drugs on combined oral contraceptives including [RH066 trade name].

Enzyme inducers

Interactions with drugs that induce microsomal enzymes (especially CYP3A4) can increase clearance of desogestrel and ethinylestradiol; this may lead to breakthrough bleeding and reduce the contraceptive effect.

Enzyme induction can occur within a few days of treatment. Maximal enzyme induction generally occurs within a few weeks. An enzyme inducing effect may persist for about 4 weeks after stopping the enzyme inducer.

The following enzyme inducing drugs can have clinically important interactions with combined oral contraceptives:

- Anticonvulsants: barbiturates (including phenobarbital), carbamazepine, oxcarbazepine, phenytoin, primidone, topiramate.
- Antifungal: griseofulvin
- Antibiotics: rifabutin, rifampicin.
- Herbal remedy: St John’s wort (*Hypericum perforatum*)
- Antiretrovirals: nelfinavir, nevirapine, ritonavir.

Women on short-term treatment with an enzyme inducer should temporarily use a barrier method in addition to the combined oral contraceptive or choose another method of contraception. The barrier method should be used during concomitant use of an enzyme inducer and for 28 days after discontinuing it. 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 is unlikely until the end of the second pack. If the patient does not have a withdrawal bleed after finishing the active tablets in the second pack, pregnancy must be ruled out before resuming with the next pack.

For women on long-term therapy with enzyme inducers, another method of contraception should be used.

Enzyme inhibitors

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. fluconazole, itraconazole, and voriconazole) and macrolides (e.g. erythromycin and clarithromycin) can increase plasma concentrations of the oestrogen or the progestogen or both.

Etoricoxib doses of 60 to 120 mg daily can increase plasma concentrations of ethinylestradiol 1.4- to 1.6-fold, respectively, when taken concomitantly with a combined hormonal contraceptive containing 35 micrograms ethinylestradiol.

Pharmacodynamic interactions

Concomitant use with hepatitis C medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of transaminase (ALT) elevations. Also, in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT was raised in women using ethinylestradiol-containing medicines such as combined hormonal contraceptives. Therefore, [RH066 trade name] users must switch to an alternative method of contraception (e.g. progestogen-only contraception or non-hormonal methods) before starting these hepatitis C medicines. [RH066 trade name] can be restarted 2 weeks after completing treatment with these medicines.

Ulipristal acetate (used as an emergency contraceptive) may reduce the contraceptive effectiveness of [RH066 trade name]. This is because ulipristal acetate binds to the progesterone receptor with high affinity and interfere with the action of progestogens (such as levonorgestrel)

Effects on other drugs

Oral contraceptives may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine). Because [RH066 trade name] may reduce the effectiveness of lamotrigine, concomitant use is not recommended.

Effect of [RH066 trade name] on laboratory tests

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

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[RH066 trade name] should not be used during pregnancy. Pregnancy must be ruled out before starting [RH066 trade name].

[RH066 trade name] should be discontinued immediately 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 combined oral contraceptives before pregnancy, nor a teratogenic effect when taken inadvertently during early pregnancy.

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

Breastfeeding

[RH066 trade name] should not be started within 6 weeks of delivery as milk production may be reduced and its composition may change. Very small amounts of the active substances may pass into milk, which may affect the baby particularly in the first 6 months.

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

Summary of the safety profile

The most frequent adverse reactions related to the use of [RH066 trade name] are changes in menstrual bleeding patterns, nausea, headache, dizziness, breast tenderness, weight change, mood change, acne (can worsen but usually improves).

Serious adverse reactions are arterial and venous thromboembolism.

Tabulated list of adverse reactions

Adverse reactions to [RH066 trade name] are listed below by body system or organ. Frequencies are defined as follows: common (1 in 100 to 1 in 10) uncommon (1 in 1000 to 1 in 100), rare (1 in 10 000 to 1 in 1000) or not known (frequency cannot be estimated from available data).

Immune system disorders

Rare	hypersensitivity
Not known	exacerbation of symptoms of hereditary and acquired angioedema

Metabolism and nutrition disorders

Uncommon	fluid retention
Not known	hypertriglyceridemia

Psychiatric disorders

Common	depressed mood, mood altered
Uncommon	libido decreased
Rare	libido increased

Nervous system disorders

Common	Headache
Uncommon	Migraine
Not known	exacerbation of chorea

Eye disorders

Rare	contact lens intolerance

Vascular disorders

Rare	venous thromboembolism (VTE), arterial thromboembolism (ATE)

Gastrointestinal disorders

Common	nausea, abdominal pain
Uncommon	vomiting, diarrhoea
Not known	Crohn’s disease, ulcerative colitis

Hepatobiliary disorders

Not known	liver function disturbances

Skin and subcutaneous tissue disorders

Uncommon	rash, urticaria
Rare	erythema nodosum, erythema multiforme
Not known	Chloasma

Reproductive system and breast disorders

Common	breast pain, breast tenderness
Uncommon	breast hypertrophy
Rare	vaginal discharge, breast discharge
Not known	reduced menstrual flow, spotting, breakthrough bleeding and missed withdrawal bleeding, post-pill amenorrhoea

Investigations

Common	weight increased
Rare	weight decreased

Description of selected adverse reactions

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

Conditions reported to deteriorate with pregnancy or previous combined oral contraceptive use

Jaundice or pruritus or both related to cholestasis; gallstone formation; systemic lupus erythematosus; pemphigoid gestationis (herpes gestationis); otosclerosis-related hearing loss; sickle cell anaemia; renal dysfunction; hereditary angioedema; porphyria; cervical cancer.

Changes in glucose tolerance or effect on peripheral insulin resistance have been reported in women using combined oral contraceptives.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

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 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 (an oestrogen) and desogestrel (a progestogen).

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 that form a barrier to sperm entry beyond the cervix and render the endometrium unreceptive to implantation.

5.2 Pharmacokinetic properties

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

Characteristic	Arithmetic mean ± standard deviation	
	Ethinylestradiol	**Desogestrel**
Maximum concentration (C_{max})	69 ± 21 pg/mL	1340 ± 391 pg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	772 ± 356 pg·h/mL	9764 ± 3848 pg·h/mL
Time to attain maximum concentration (T_{max})	1.48 ± 0.31hours	1.37 ± 0.40 hours

Pharmacokinetics of ethinylestradiol and desogestrel

	Ethinylestradiol	Desogestrel
Absorption		
T_{max}	Approximately 1 to 2 hours	1.5 hours
Oral bioavailability	Mean approximately 45%; range approximately 20 to 65%	62 to 81% as etonogestrel After oral dosing, desogestrel is rapidly and completely absorbed and converted into etonogestrel.
Food effect	Not available	Not available
Distribution		
General note	Approximately 1% of the total serum concentration is free steroid	2 to 4% of the total serum concentration is free steroid
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	95 to 99% of etonogestrel is bound to serum proteins, mainly SHBG (40 to 70%) and albumin. Over time, the ethinylestradiol-induced induction of SHBG increases the SHBG-bound fraction with a corresponding decrease in the albumin-bound fraction.
Tissue distribution	Not available	Etonogestrel is present 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	Desogrestrel is metabolised via hydroxylation and dehydrogenation to the active metabolite etonogestrel. Etonogestrel is metabolised via sulphate and glucuronide conjugation.
Elimination		
Elimination half-life	10–20 hours	Approximately 30 hours for etonogesterel
Mean systemic clearance (Cl/F)	5 mL/minute/kg	2 mL/minute/kg
% of dose excreted in urine	6% unchanged drug; 40% of the dose as metabolites	Approximately 45 to 48% as metabolites
% of dose excreted in faeces	9% unchanged drug; 60% of the dose as metabolites	Approximately 31 to 35% as metabolites

	Ethinylestradiol	Desogestrel
Pharmacokinetic linearity	Dose proportionality between 20 to 100 microgram	Not available
Drug interactions *(in vitro)*		
Transporters	Not available	Not available
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	Not available	Not available
Hepatic impairment	Not available	Not available
Elderly patients	Not available	Not available
Paediatric patients	Not studied in premenarchal females	Not studied in premenarchal females

SHBG: Sex hormone binding globulin

5.3 Preclinical safety data

The toxicity profiles of ethinylestradiol and desogestrel are well established.

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

In experimental 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 fetuses 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

Clear colorless plastic (PVC/PVDC) on aluminium foil blisters cards, each containing 21 active (white) tablets plus 7 placebo (green) tablets. Available in carton boxes of 1 × 28, 3 × 28 or 6 × 28 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH066

9. DATE OF PREQUALIFICATION

27 October 2020

10. DATE OF REVISION OF THE TEXT

June 2024

References

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Marvelon tablets: package leaflet. MHRA; November 2022 (https://mhraproducts4853.blob.core.windows.net/docs/b75fe2a6f91863c4796784d8ea177f899e1c0db5, accessed 10 May 2024).

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/prequal/medicines/prequalified/finished-pharmaceutical-products