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

[RH054 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains estradiol valerate 5mg and norethisterone enantate 50mg

Each mL also contains about 424 mg of benzyl benzoate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

A clear oily solution, free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[RH054 trade name] is indicated for hormonal contraception.

4.2 Posology and method of administration

Posology:

[RH054 trade name] must always be administered as a deep intramuscular injection, preferably intragluteal, alternatively into the upper arm.

Dosage regimen:

[RH054 trade name], when used correctly, has a failure rate of approximately 1% per year. The failure rate may increase when intervals between injections are prolonged.

The injection must be administered extremely slowly (see sections 'Special warnings and precautions for use' and 'Undesirable effects'). The oily solution is injected immediately after its drawing up into the syringe.

How to start [RH054 trade name]:

Women with menstrual cycles:

- If the first injection of [RH054 trade name] is given within seven days after the start of menstrual bleeding, no additional contraceptive protection is needed.
- If it is more than seven days after the start of menstrual bleeding, the first injection of [RH054 trade name] can be given if it is reasonably certain that the women is not pregnant. Additional contraceptive protection is required for the next seven days.

Women who are amenorrhoeic:

- The first injection of [RH054 trade name] can be given at any time if it is reasonably certain that the woman is not pregnant. She will need to abstain from sex or use additional contraceptive protection for the next 7 days.

Postpartum (breastfeeding):

- Less than 6 weeks postpartum and primarily breastfeeding: [RH054 trade name] should not be used unless other more appropriate methods are not available or not acceptable.
- 6 weeks to 6 months postpartum and primarily breastfeeding: Use of [RH054 trade name] is not recommended unless other more appropriate methods are not available or not acceptable.

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

- More than 6 months postpartum and amenorrhoeic: The first injection of [RH054 trade name] can be given as advised for other amenorrhoeic women.
- More than 6 months postpartum and menstrual cycles have returned: The first injection of [RH054 trade name] can be given as advised for other women having menstrual cycles (see above).

Postpartum (not breastfeeding):

- Less than 21 days postpartum: Use of [RH054 trade name] is 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 risk of pregnancy during the first 21 days postpartum. However, for programmatic reasons (i.e. depending on national, regional, and/or local programme protocols), some contraceptive methods may be provided during this period.
- 21 or more days postpartum and menstrual cycles have not returned: The first injection of [RH054 trade name] can be given immediately if it is reasonably certain that the woman is not pregnant. She will need to abstain from sex or use additional contraceptive protection for the next 7 days.
- 21 or more days postpartum and menstrual cycles have returned: The first CIC injection can be given as advised for other women having menstrual cycles (see above).

Post-abortion:

- The first injection of [RH054 trade name] can be given immediately post-abortion. 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, the first injection of [RH054 trade name] can be given immediately; there is no need to wait for her next menstrual period.
- If a woman's previous method was another injectable contraceptive, the [RH054 trade name] injection should be given when the repeat injection would have been given. No additional contraceptive protection is needed.

Switching from a non-hormonal method (other than the IUD):

- The first injection of [RH054 trade name] can be given immediately if it is reasonably certain that the woman is not pregnant; there is no need to wait for her next menstrual period.
    - Within 7 days of the start of menstrual bleeding: No additional contraceptive protection is needed.
    - More than 7 days since the start of menstrual bleeding: She will need to abstain from sex or use additional contraceptive protection for the next 7 days.

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

- Within 7 days after the start of menstrual bleeding: The first injection of [RH054 trade name] can be given. No additional contraceptive protection is needed. The IUD can be removed at that time.
- More than 7 days since the start of menstrual bleeding: The first injection of [RH054 trade name] can be given if it is reasonably certain that the woman is not pregnant.
    - Sexually active in this menstrual cycle: It is recommended that the IUD be removed at the time of her next menstrual period.
    - Not sexually active in this menstrual cycle: She will need to abstain from sex or use additional contraceptive protection for the next 7 days. If that additional protection is to be provided by the IUD she is using, it is recommended that this IUD be removed at the time of her next menstrual period.
- If the woman is amenorrhoeic or has irregular bleeding, the injection can be given as advised for other amenorrhoeic women.

Management of next injections:

Ideally, the second and all following injections are to be given - regardless of cycle pattern - at intervals of 30 ± 3 days, i.e. minimum of 27 days, maximum of 33 days.

Early for an injection:

- When the reinjection interval cannot be adhered to, the repeat injection can be given up to 7 days early, but this may disrupt bleeding patterns.

Late for an injection:

- When the reinjection interval cannot be adhered to, the repeat injection can be given up to 7 days late without requiring additional contraceptive protection.
- If the woman is more than 7 days late for an injection, she can have the injection 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 7 days. She may wish to consider the use of emergency contraception, if appropriate.

If no withdrawal bleeding occurs within 30 days after an injection, pregnancy must be ruled out by means of a suitable test.

Special populations:

Pediatric patients

[RH054 trade name] is only indicated after menarche.

Geriatric patients

Not applicable. [RH054 trade name] is not indicated after menopause.

Patients with hepatic impairment

[RH054 trade name] is contraindicated in women with severe hepatic diseases. See also section 'Contraindications'.

Patients with renal impairment

[RH054 trade name] has not been specifically studied in patients with renal impairment. Available data do not suggest a change in treatment in this patient population.

4.3 Contraindications

[RH054 trade name] should not be used if any of the following conditions are present. If any of these conditions develop during use, [RH054 trade name] should be stopped immediately.

- Presence or a history of venous or arterial thrombotic/ thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident
- Presence or history of prodrome of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- A high risk of venous or arterial thrombosis (see 'Special warnings and precautions for use').
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement
- Severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant)
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breast)
- Undiagnosed vaginal bleeding
- Known or suspected pregnancy
- Hypersensitivity to the active substances or to any of the excipients

4.4 Special warnings and precautions for use

No epidemiological studies investigating risk factors for combined injectable contraceptives (CICs) have been identified. The general experience with COCs regarding warnings and special precautions for use should be considered as a basis for CICs.

Warnings:

Circulatory disorders

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

Venous thromboembolism (VTE)

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

VTE manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined hormonal contraceptives. Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in COC users. VTE may be life-threatening or have a fatal outcome in 1-2% of cases.

The overall risk for VTE in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery. An additional increase in VTE risk in users of CICs cannot be excluded.

Symptoms of deep venous thrombosis (DVT) may include:

- unilateral swelling of the leg 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 discolored 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 bring up blood
- sharp chest pain which may increase with deep breathing
- sense of anxiety
- 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).

Arterial thromboembolism (ATE):

An arterial thromboembolic event can include cerebrovascular accident (“stroke”), myocardial infarction (MI) or other arterial occlusion. Arterial thromboembolic events may be life-threatening or have a fatal outcome.

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 confusion, trouble speaking or understanding
- sudden trouble seeing in one or both eyes
- sudden trouble walking
- dizziness, loss of balance or coordination
- sudden, severe, or prolonged headache with no known cause
- loss of consciousness with or without seizure.

Symptoms of a myocardial infarction 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

- fullness, indigestion or choking feeling
- sweating, nausea, vomiting or dizziness
- extreme weakness
- shortness of breath
- rapid or irregular heartbeats.

Symptoms of arterial vascular occlusion in other sites may include:

- sudden pain, swelling and pallor of an extremity with rapid and progressive loss of function
- sudden onset of severe pain in the abdomen, possibly presenting as an acute abdomen.

The potential for an increased risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A CIC should not be prescribed in case of a negative risk benefit assessment. (see 'Contraindications')

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age
- obesity (body mass index over 30 kg/m^2)
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any CIC use
- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations, it is advisable to discontinue CIC use (in case of elective surgery last injection at least eight weeks in advance) and not to resume until two weeks after complete remobilization.
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism in users of combined oral contraceptives.

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation see section 'Pregnancy and lactation').

Other medical conditions which have been associated with adverse circulatory events in users of combined oral contraceptives include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis). No data are available on the use of CICs by women suffering from sickle cell disease, however, women with a homozygous sickle cell disease may be at an increased risk of thrombosis.

An increase in frequency or severity of migraine during the use of CICs (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with the use of hormonal contraceptives.

Tumours

There are insufficient data to form an assessment regarding the likely effects of combined injectable contraceptives on their risk of neoplasia. Some general reassurance may be taken from experience with combined oral contraceptives.

Cervical cancer:

No association between a monthly injectable contraceptive (containing dihydroxyprogesterone acetophenid and an ester of estradiol) and the risk of cervical cancer was observed in an epidemiological assessment in Latin American women. No increased risk of developing cervical squamous intraepithelial lesions was found in users of injectable contraceptives in the USA.

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of combined oral contraceptives 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.

Breast cancer/ovarian cancer:

The effect of the oestrogen and progestogen contained in [RH054 trade name] on breast cancer/ovarian cancer risk has not been evaluated.

For women who are currently using combined oral contraceptives, a breast cancer warning is based on a meta-analysis from 54 epidemiological studies which reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed. The excess risk gradually disappears during the course of the 10 years after cessation of oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent users of oral contraceptive is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in users of combined oral contraceptives, the biological effects of combined oral contraceptives or a combination of both. The breast cancers diagnosed in users of combined oral contraceptives tend to be less advanced clinically than the cancers diagnosed in women who did not use combined oral contraceptives.

Liver tumours:

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of combined oral contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women using [RH054 trade name].

Other conditions

Although small increases in blood pressure have been reported in many women taking combined oral contraceptives, clinically relevant increases are rare. If sustained, clinically significant hypertension develops while using [RH054 trade name], it is recommended that an alternative form of contraception is used while the hypertension is treated. Reintroduction of [RH054 trade name] may be considered if normotension can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and oral contraceptive use and may be present for users of CICs, but the evidence of an association is inconclusive:

- jaundice and/or pruritus related to cholestasis
- gallstone formation
- porphyria
- systemic lupus erythematosus
- haemolytic uremic syndrome
- Sydenham's chorea
- herpes gestationis
- otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Because the steroid hormones contained in CICs are metabolized by the liver, they could in theory lead to adverse effects in women whose liver function is already compromised. Acute or chronic disturbances of liver function may necessitate the discontinuation of [RH054 trade name] until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of [RH054 trade name].

Although CICs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics. However, diabetic women should be carefully observed while using CICs.

The following conditions have been associated with the use of combined oral contraceptives and may be present for users of CICs:

- Crohn's disease and ulcerative colitis
- chloasma, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst using hormonal contraceptives.

As with all oily solutions, [RH054 trade name] must be injected strictly intramuscularly and very slowly. Pulmonary microembolism of oily solutions can lead to signs and symptoms such as cough, dyspnoea and chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhydrosis, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injection and are reversible. Treatment is usually supportive, e.g. by administration of oxygen.

Women should be advised that CICs do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy:

The efficacy of [RH054 trade name] may be reduced in the event of a prolonged injection interval (see section 'Dosage and method of administration') or concomitant medication (see section 'Interaction with other medicinal products and other forms of interaction').

Reduced cycle control:

With all hormonal contraceptives, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. A reduced cycle length (11-15 days) was observed after the first injection of [RH054 trade name].

A vaginal bleeding episode will occur one to two weeks after the first injection of [RH054 trade name]. This is normal and if the treatment is continued, bleeding episodes will usually occur at 30-day intervals. The time of the monthly injection will normally be during the bleeding-free interval.

In some women withdrawal bleeding may not occur within the 30 days after an injection. In this case, pregnancy must be ruled out by means of a suitable test. However, if [RH054 trade name] has been injected according to the instructions described in section 'Dosage and method of administration', it is unlikely that the woman is pregnant.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions have been reported for combined oral contraceptives in the literature and may be relevant for CICs as well.

Effects of other medicinal products on [RH054 trade name]:

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these drugs should temporarily use a barrier-method in addition to hormonal contraceptives or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Substances increasing the clearance of CICs through enzyme induction:

Anticonvulsants:

- phenytoin
- barbiturates
- primidone
- carbamazepine
- oxcarbazepine
- topiramate
- felbamate

Other agents:

- rifampicin
- griseofulvin
- products containing St. John's wort.

Substances with variable effects on the clearance of CICs:

When co-administered with combined hormonal contraceptives, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of CICs through enzyme inhibition:

Strong and moderate CYP3A4 inhibitors can increase plasma concentrations of the oestrogen or the progestin or both. Examples include:

Azole antifungals:

- fluconazole
- itraconazole
- ketoconazole
- voriconazole

Macrolide antibiotics:

- clarithromycin
- erythromycin

Other agents:

- diltiazem
- grapefruit juice

Effects of CICs on other medicinal products

Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin, tizanidine, theophylline) or decrease (e.g. lamotrigine).

Effects of CICs on laboratory tests

The use of contraceptives 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. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

[RH054 trade name] is not indicated during pregnancy.

If pregnancy occurs during use of [RH054 trade name], further administration must be stopped.

Norethisterone has some androgenic activity, and a virilising effect on the external genitalia of a female foetus exposed to norethisterone after the first month of pregnancy cannot be ruled out on theoretical grounds. However, no such virilisation has been observed after the few pregnancies that have been reported during the use of norethisterone.

Extensive epidemiological studies have not revealed an increased risk of birth defects in children born to women who used combined oral contraceptives prior to pregnancy, or a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting [RH054 trade name] (see section 4.2 and 4.4).

Breastfeeding

Lactation may be influenced by combined hormonal contraceptives as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk during combined hormonal contraceptive use. These amounts may affect the child. Combined hormonal contraceptives are usually not recommended while breastfeeding unless other more appropriate methods are not available or not acceptable.

Available data are not sufficient to exclude a negative effect of combined hormonal contraceptives in breastfed infants less than six weeks old. Current recommendations on contraception and breast-feeding should be consulted before advising patients on this matter. Preferred options may vary depending on the local circumstances.

Fertility

[RH054 trade name] is indicated for the prevention of pregnancy.

4.7 Effects on ability to drive and use machines

[RH054 trade name] does not affect the ability to drive or use machines.

4.8 Undesirable effects

The most commonly reported adverse reactions with [RH054 trade name], occurring in ≥ 1% of users, are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain and breast tenderness.

The following adverse drug reactions have been reported in users of hormonal contraceptives:

Body system	**Frequency of adverse reactions**		
	Common: ≥ 1% to < 10%	Uncommon: ≥ 0.1% to < 1%	Rare: ≥ 0.01% to < 0.1%
General disorders and administration site conditions			Injection site reaction
Eye disorders			Contact lens intolerance
Immune system disorders			Hypersensitivity reactions
Metabolic disturbances	Fluid retention; oedema	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	
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
Physical and laboratory evaluations	Weight change (increase or decrease)	Increased blood pressure; elevated blood lipids	
Vascular disorders			Venous and arterial thromboembolic events**

** 'Venous and arterial thromboembolic events' summarizes the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as hemorrhagic

Description of selected adverse reactions:

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives (COCs) are listed below (see also sections 'Contraindications', 'Special warnings and precautions for use'):

Tumours:

- The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumours (benign and malignant)

Other conditions:

- Increased risk of pancreatitis when using COCs (women with hypertriglyceridemia)
- Hypertension

- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss,
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis,
- Chloasma
- Cervical cancer
- Injections of oily solutions such as [RH054 trade name] have been associated with systemic reactions: cough, dyspnoea, chest pain. There may be other signs and symptoms including vasovagal reactions such as malaise, hyperhydrosis, dizziness, paraesthesia, or syncope.

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.

4.9 Overdose

Presentation of a single use injectable and administration by a physician minimize the risk of overdose. There have been no reports of serious deleterious effects from overdose of combined contraceptives.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[RH054 trade name] protects against pregnancy primarily by inhibiting ovulation and causing changes in the cervical mucus. The effect produced on the endometrium is similar to that of combined oral contraceptives. A normal menstrual-like bleeding pattern is achieved with the use of [RH054 trade name].

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7- 10 per 10,000 woman-years in low oestrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman-years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or postpartum. An additional increase in VTE risk in users of CICs cannot be excluded.

With respect to contraceptive reliability, monthly injections of [RH054 trade name] compare favorably with the efficacy of progestogen-only regimens and oral contraceptives.

Because [RH054 trade name] contains both an oestrogen and a progestogen, the precautions related to its use are similar to those of combined oral contraceptives. The oestrogen component contained in [RH054 trade name] is a natural oestrogen and the circulating oestrogen levels reach peaks that are in the range of the normal preovulatory phase of the menstrual cycle. The progestogen component, norethisterone enantate, exerts typical progestogenic effects on women, such as antigonadotrophic effects, secretory transformation of the endometrium and thickening of the cervical mucus.

[RH054 trade name] has favourable effects on lipid metabolism.

Combined injectable contraceptives like [RH054 trade name] have been shown to have a minimal effect on liver function in healthy woman and have no first-pass hepatic clearance. However, because the steroid hormones contained in combined injectable contraceptives are metabolized by the liver, they could, in theory, lead to adverse effects in a woman whose liver function is already compromised.

5.2 Pharmacokinetic properties

There was no bioequivalence study conducted with [RH054 trade name] as it is the comparator.

The pharmacokinetics properties of estradiol valerate and norethisterone enantate are as follows:

	Estradiol valerate (EV)	Norethisterone enantate (NET)
General		
	EV is a prodrug of oestradiol (E2)	NET is a prodrug of norethisterone (NE)
T_{max}	Approximately 2 days	Approximately 4 to 5 days
Absorption		
Absolute bioavailability	100%	100%
Food effect	N/A	N/A
Distribution		
Volume of distribution (mean)	2.8 to 8.6 L/kg (as E2)	Approximately 4 L/kg (as NE)
Plasma protein binding *in vitro*	Albumin 60% (as E2) SHBG 38% (as E2)	Albumin 61% (as NE) SHBG 35% (as NE) (2)
Tissue distribution	NA	NA
Metabolism		
	Hepatic esterases decompose EV into E2 and valeric acid. E2 is hydroxylated and finally conjugated with sulfate and glucuronate	NET is split mainly in the liver by enzymatic hydrolysis into NE and heptanoic acid (2)
Elimination		
General note	Approximately 85% of the dose of both components are excreted within the injection interval of 28 days	
Elimination half-life	4-5 days (1)	4-5 days and 15-20 days (biphasic release from depot) (2)
Means systemic clearance (Cl/F)		
% of dose excreted in urine	Approximately 54% as E2 and E2 metabolites	Approximately 40% as metabolites (2)
% of dose excreted in faeces	Approximately 6% as E2	Approximately 60% as metabolites (2)
Pharmacokinetic linearity	NA	NA
Drug interactions *(in vitro)*		
Transporters	NA	NA
Metabolising enzymes	E2 mainly metabolised by CYP3A4 and CYP1A2	NE is extensively metabolised in the liver through multiple pathways, including CYP3A4, before conjugation with sulfate and glucuronide.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies on repeated dose toxicity, genotoxicity and carcinogenic potential beyond those discussed in other sections of the SPC.

In experimental animals, estradiol or estradiol valerate displayed an embryolethal effect at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed.

Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. Embryolethal effects were observed at high doses of norethisterone.

Exogenous sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzyl benzoate
Castor oil for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

60 months
From a microbiological point of view, the product should be used immediately once opened.

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

1 mL of oily solution is filled in brown, OPC (one-point cut) colour-coded, type I glass ampoules.
100 ampoules are packed in a carton.

6.6 Instructions for use and handling and disposal

No special requirements.

7. SUPPLIER

Bayer AG
Müllerstraße 178
13353 Berlin
Germany
Tel. No.: +49 30 468 1111
Fax No.: +49 30 468 15305
Email: Use contact form on www.bayer.com

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References

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https://www.medicines.org.uk/emc/product/1134/smpc

WHO: Selected practice recommendations for contraceptive use. Third edition 2016
https://www.who.int/reproductivehealth/publications/family_planning/SPR-3/en/

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