WHO-PQ RECOMMENDED PATIENT INFORMATION LEAFLET

This patient information leaflet 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

Information for the patient

[RH087 trade name] †

estradiol valerate/norethisterone enantate

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have questions about the medicine, ask your health care provider.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness seem to be the same as yours.
- If you get any side effects, talk to your health care provider.This includes unwanted effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [RH087 trade name] is and what it is used for

[RH087 trade name] is a hormonal contraceptive used to prevent pregnancy.

[RH087 trade name] contains the female hormones estradiol valerate and norethisterone enantate.

Because [RH087 trade name] contains a combination of two hormones it is a so-called “combined hormonal contraceptive”.

2. What you need to know before you are given [RH087 trade name]

General notes:

Before you can begin using [RH087 trade name], your healthcare provider will ask you some questions about your personal health history and that of your close relatives. Your healthcare provider will also measure your blood pressure and, depending upon your personal situation, may also carry out some other tests.

Because [RH087 trade name] contains a combination of two female hormones, the precautions related to its use are similar to those of the so-called ‘Pill’ (or combined oral contraceptives).

[RH087 trade name], like other hormonal contraceptives, does not protect against HIV infection (AIDS) or any other sexually transmitted disease.

Do not use [RH087 trade name]:

[RH087 trade name] should not be used if you have any of the conditions listed below. If any of these apply to you, tell your healthcare provider before [RH087 trade name] is started. Your healthcare provider may advise you to use a different type of hormonal contraceptive or an entirely different (non-hormonal) method of birth control.

- if you have (or have ever had) a **blood clot** in a blood vessel of the leg (thrombosis), of the lung (pulmonary embolism) or other parts of the body
- if you have (or have ever had) a **heart attack** or **stroke** (caused by a blood clot or a rupture of a blood vessel in the brain)

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

- if you have (or have ever had) a **disease that can be an indicator of**
    - **a future heart attack** (for example, angina pectoris which causes severe chest pain which may spread to the left arm) **or**
    - **of a stroke** (for example, a minor stroke with no residual effects, a so-called transient ischaemic attack)
- if you have a high risk of venous or arterial blood clots (see 'Combined hormonal contraceptives and blood clots', and consult your healthcare provider who will decide whether you may use [RH087 trade name])
- if you have (or have ever had) a certain kind of **migraine** (with so-called focal neurological symptoms such as visual symptoms, speech disability, or weakness or numbness in any part of your body)
- if you have diabetes mellitus with damaged blood vessels.
- if you have (or have ever had) **liver disease** (symptoms of which may be yellowing of the skin or itching over the whole body) and your liver is still not working normally
- if you have (or have ever had) a **cancer** that may grow under the influence of sex hormones (e.g. **of the breast or the genital organs**)
- if you have (or have ever had) a benign or malignant **tumor of the liver**
- if you have any **unexplained bleeding from the vagina**
- if you are pregnant or think you might be pregnant
- if you are **allergic** (hypersensitive) to estradiol valerate, norethisterone enantate or any of the other ingredients in [RH087 trade name]. This may cause, for example, itching, rash or swelling

If any of these conditions appear for the first time while using [RH087 trade name], consult your healthcare provider because it may be necessary to discontinue [RH087 trade name]. In the meantime, use non-hormonal contraceptive measures.

Special populations:

Use in children
[RH087 trade name] is not intended for use in females whose periods have not yet started.

Use in older women
[RH087 trade name] is not intended for use after the menopause.

Women with liver impairment
Do not use [RH087 trade name] if you suffer from liver disease. See also sections 'Do not to use [RH087 trade name]', (above) and 'Warnings and precautions', (below).

Women with kidney impairment
Ask your healthcare provider. Available data do not suggest a need to change the use of [RH087 trade name].

Warnings and precautions:

Before you start to use [RH087 trade name]

In some situations, you need to take special care while using [RH087 trade name] or any other combined hormonal contraceptive, and your healthcare provider may need to examine you regularly. Consult your healthcare provider before starting to use [RH087 trade name] if any of the following conditions apply to you or if any of them develop or worsen while you are using [RH087 trade name]:

- if you smoke
- if you have diabetes
- if you are overweight
- if you have high blood pressure
- if you have a heart valve disorder or a certain heart rhythm disorder
- if you have an inflammation of your veins (superficial phlebitis)

- if you have varicose veins
- if anyone in your immediate family has ever had a blood clot (thrombosis in the leg, lung 'pulmonary embolism', or elsewhere), a heart attack or a stroke at a young age
- if you suffer from migraine
- if you have epilepsy (see 'Other medicines and [RH087 trade name]')
- if you or someone in your immediate family has ever had high blood levels of cholesterol or triglycerides (fatty substances)
- if a close relative has or has ever had breast cancer
- if you have a disease of the liver or gall bladder
- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease)
- if you have systemic lupus erythematosus (or SLE, a disease of the immune system)
- if you have hemolytic uremic syndrome (or 'HUS', a disorder of blood coagulation causing failure of the kidneys)
- if you have sickle cell disease (especially if you suffer from the more pronounced homozygous form of sickle cell disease, you may be at an increased risk of thrombosis)
- if you have a condition that occurred for the first time or worsened during pregnancy or previous use of sex hormones (e.g. hearing loss, a metabolic disease called porphyria, a skin disease called herpes gestationis, or a neurological disease called Sydenham's chorea)
- if you have (or have ever had) golden brown pigment patches so-called 'pregnancy patches' especially on the face (chloasma). If this is the case, avoid direct exposure to sunlight or ultraviolet light
- if you have hereditary angioedema. Consult your healthcare provider immediately if you experience symptoms of angioedema such as swollen face, tongue or throat, and/or difficulty swallowing, or hives, together with difficulty breathing. Products containing estrogens may induce or worsen symptoms of angioedema

If any of the above conditions appear for the first time, recur, or worsen while using [RH087 trade name], contact your healthcare provider.

Combined hormonal contraceptives and blood clots

A thrombosis is the formation of a blood clot which may block a blood vessel. Blood clots can develop:

- In veins (referred to as a "venous thrombosis", "venous thromboembolism" or VTE)
- In an artery (referred to as an "arterial thrombosis", "arterial thromboembolism" or ATE)

A thrombosis sometimes occurs in the deep veins of the legs (deep venous thrombosis). Venous thromboembolism (VTE) can develop whether or not you are using [RH087 trade name] and may also happen if you become pregnant. If a blood clot breaks away from the vein where it has formed, it may reach and block the arteries of the lungs, causing a so-called 'pulmonary embolism'. Blood clots can also occur very rarely in the blood vessels of the heart (causing a heart attack). Blood clots or a ruptured blood vessel in the brain may cause a stroke.

[RH087 trade name] is an injectable for preventing pregnancy that has a composition similar to combined contraceptive pills. Therefore, general experience with the pill may also apply for users of [RH087 trade name].

Long-term studies have suggested that there may be a link between the use of the pill (also called 'combined oral contraceptive' or 'combined pill' because it combines two different female hormones, so-called estrogens and progestogens) and an increased risk of venous and arterial blood clots, embolism, heart attack or stroke. The occurrence of these events is rare.

The risk of venous thromboembolism is highest during the first year of use. This increased risk is present after initially starting the combined pill or restarting (following a 4 week or greater pill free interval) the same or a different combined pill. Data from a large study suggests that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (less than 50 µg ethinylestradiol) pills 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 combined injectable contraceptives cannot be excluded.

Very occasionally venous or arterial thromboembolic events may cause serious permanent disabilities, may be life-threatening, or may even be fatal.

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined hormonal contraceptives.

Extremely rarely blood clots can occur in other parts of the body including the liver, gut, kidney, brain, or eye.

<u>If any of the following events occur, [RH087 trade name] should be discontinued:</u>

Contact your healthcare provider immediately if you notice signs of:

Venous thrombosis or thromboembolism:

- **Deep venous thrombosis**, such as: swelling of one 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.
- **Pulmonary embolism**, such as: 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 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 infection).

Arterial thrombosis or thromboembolism:

- **Stroke,** such as: 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 or fainting with or without seizure.
- **Heart attack**, such as: 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, anxiety, or shortness of breath; rapid or irregular heartbeats.
- **Blood clots blocking other arterial blood vessels,** such as: sudden pain, and whitish or light blue discoloration of an extremity; severe abdominal pain.

Your healthcare provider will check whether you have a higher risk of getting a thrombosis due to a combination of risk factors or perhaps one very strong risk factor. In the case of a combination of factors the risk may be higher than simply adding two individual risks. If the risk is too high, your healthcare provider will not prescribe [RH087 trade name]; (see also ‘Do not use [RH087 trade name]’)

The risk of venous or arterial blood clots (e.g. deep venous thrombosis, pulmonary embolism, heart attack) or stroke increases:

- with age
- if you are overweight
- if anyone in your immediate family has ever had a blood clot (thrombosis in the leg, lung ‘pulmonary embolism’, or elsewhere), a heart attack or a stroke at a young age, or if you or any of your relatives are known or suspected of having a hereditary blood clotting disorder increasing your risk for developing blood clots. In this case you should see a specialist before deciding about using any combined hormonal contraceptive. Certain blood factors that may suggest you have tendency 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).

- with prolonged immobilization (for example, when you have your leg or legs in plaster or splints), major surgery, any surgery to the legs, or major trauma. In these situations, it is better to discontinue [RH087 trade name]. If the surgery is planned, inform your healthcare provider because [RH087 trade name] should be discontinued at least eight weeks beforehand, and not restarted until two weeks after you are fully on your feet again
- if you smoke (the risk increases the more you smoke and the older you get, especially in women over 35 years of age). When using [RH087 trade name] you should stop smoking, especially if you are older than about 35 years of age.
- if you or someone in your immediate family has or has ever had high blood levels of cholesterol or triglycerides (fatty substances)
- if you have high blood pressure. If you develop high blood pressure while using [RH087 trade name], your healthcare provider may inform you that [RH087 trade name] needs to be discontinued.
- if you suffer from migraine
- if you have a heart valve disorder or a certain heart rhythm disorder

Directly after giving birth, women are at an increased risk of blood clots so you should ask your healthcare provider how soon after delivery you can start using [RH087 trade name].

Combined hormonal contraceptives and cancer

The effect of the active ingredients contained in [RH087 trade name] on breast cancer/ovarian cancer risk has not been evaluated.

In women who use combined hormonal oral contraceptives (the 'Pill'), breast cancer has been observed slightly more often, but it is not known whether this is caused by the treatment itself. For example, it may be that more tumors are detected in women on combined pills because they are examined by their healthcare provider more often. The risk of breast tumors gradually goes down after stopping the combined hormonal contraceptive. It is important to regularly check your breasts and you should contact your healthcare provider if you feel any lump.

In rare cases, benign liver tumors, and in even fewer cases malignant liver tumors have been reported in contraceptive pill users. In isolated cases, these tumors have led to life-threatening internal bleeding. Contact your healthcare provider if you have unusually severe abdominal pain.

No association between a monthly injectable contraceptive and the risk of cervical cancer was observed in a study in Latin American women. No increased risk of developing pre-cancerous cervical lesions was found in users of injectable contraceptives in the USA.

The most important risk factor for cervical cancer is persistent Human Papilloma Virus (HPV) infection. Some studies suggest that long-term use of the pill increases a woman's risk of developing cervical cancer. However, it is not clear to what extent sexual behavior or other factors such as Human Papilloma Virus increases this risk.

Bleeding between periods

A vaginal bleeding episode will occur one to two weeks after the first injection of [RH087 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.

With all hormonal contraceptives, for the first few months, you may have irregular vaginal bleeding (spotting or breakthrough bleeding) between your periods. You may need to use sanitary protection but continue having [RH087 trade name] injections as normal. Irregular vaginal bleeding usually stops once your body has adjusted to [RH087 trade name] (usually after about 3 months). If it continues, becomes heavy or starts again, tell your healthcare provider.

With [RH087 trade name], only a low frequency of irregular bleeding was observed.

What to do if no bleeding occurs

In some women a withdrawal bleed may not occur within the 30 days after an injection. Tell your healthcare provider as soon as possible. In this case, pregnancy must be ruled out by means of a suitable test. The next injection should not be given until your healthcare provider has confirmed that you are not pregnant. In the meantime, use non-hormonal contraceptive measures. See also 'General notes'

It is unlikely that you will become pregnant if [RH087 trade name] has been injected at intervals mentioned in this leaflet and you are not using other medicines reducing the contraceptive efficacy (e.g. as mentioned in section 'Taking other medicines').

Other medicines and [RH087 trade name]:

Always tell your healthcare provider which medicines or herbal products you are already using. Also tell any other healthcare provider who prescribes another medicine (or the pharmacist from whom you got the medicine) that you use [RH087 trade name]. They can tell you if you need to take additional contraceptive precautions (for example condoms) and if so, for how long, or, whether the use of another medicine you need must be changed.

Some medicines can have an influence on the blood levels of [RH087 trade name] and can make it less effective in preventing pregnancy or more likely to cause unexpected bleeding.

These include:

- medicines used for the treatment of:
  - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate)
  - tuberculosis (e.g. rifampicin)
  - HIV and Hepatitis C Virus infections (so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors),
  - fungal infections (griseofulvin, azole antifungals, e.g. fluconazole, itraconazole, ketoconazole, voriconazole).
  - bacterial infections (macrolide antibiotics, e.g. clarithromycin, erythromycin)
  - certain heart diseases, high blood pressure (calcium channel blockers, e.g. verapamil, diltiazem),
  - arthritis, arthrosis (etoricoxib),
  - the herbal remedy St. John's wort (primarily used for the treatment of depressive moods),
- grapefruit juice

[RH087 trade name] may influence the effect of other medicines, e.g.

- cyclosporine
- melatonin,
- midazolam,
- theophylline,
- tizanidine.

Always tell your healthcare provider or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Laboratory tests

If you need a blood test or other laboratory tests tell your healthcare provider or the laboratory staff that you are using [RH087 trade name] because hormonal contraceptives can affect the results of some tests.

Pregnancy

Do not use [RH087 trade name] if you are pregnant. If you think you might be pregnant, stop taking [RH087 trade name] immediately and contact your health care provider.

Breastfeeding

Do not use [RH087 trade name] if you are breast-feeding.

3. How [RH087 trade name] is given

The injection will be administered very slowly (see section 'Possible side effects'). [RH087 trade name] is strictly for intramuscular injection (preferably into the buttocks, alternatively into the upper arm).

[RH087 trade name], when used correctly, has a failure rate of approximately 1% per year. The failure rate may be higher when intervals between injections are prolonged.

When should I start [RH087 trade name]?

If you have not used a contraceptive with hormones during the previous month:

If possible, [RH087 trade name] should be administered on the first day of your natural cycle, i.e. the first day of the menstrual bleeding.

Ask your healthcare provider what to do if you are not sure when to start.

Management of next injections

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

If an injection interval is extended beyond the maximum of 33 days, no adequate contraceptive protection will be available from that time onwards and you should use additional contraceptive measures and check with your healthcare provider as to how to proceed.

If you do not have a withdrawal bleeding within 30 days after an injection, pregnancy is a possibility that would have to be ruled out first by using a reliable pregnancy test. Consult your healthcare provider in any case when menstrual bleeding does not set in within 30 days after a [RH087 trade name] injection.

If you get more [RH087 trade name] injections than you should

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

If you forget to get your [RH087 trade name] injection

If you forgot to get your next injection, no adequate contraceptive protection will be available onwards from the time of your due date. You should use additional contraceptive measures and check with your healthcare provider how to proceed.

If you want to stop using [RH087 trade name]

After discontinuation of [RH087 trade name], no long-term effects on ability to get pregnant have been observed in women who used [RH087 trade name] for 2-3 years.

If you have any further questions on the use of this product, ask your healthcare provider.

4. Possible side effects

Like all medicines, [RH087 trade name] can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your healthcare provider.

The following side effects have been reported in users of combined hormonal contraceptives:

Common side effects (between 1 and 10 in every 100 users may be affected):

- nausea
- abdominal pain
- weight gain
- headache
- depressed or altered mood
- breast pain including breast tenderness

Uncommon side effects (between 1 and 10 in every 1,000 users may be affected):

- vomiting
- diarrhea
- fluid retention
- migraine
- reduced interest in sex
- breast enlargement
- rash
- urticaria (hives)

Rare side effects (between 1 and 10 in every 10,000 users may be affected):

- contact lens intolerance
- allergic reactions (hypersensitivity)
- weight loss
- increased interest in sex
- vaginal discharge
- breast discharge
- erythema nodosum or multiforme (skin disorders)
- injection site reaction

Unknown frequency of side effects:

- venous and arterial thromboembolic disorders*

*The term venous and arterial thromboembolic events covers the following: any blockage or clot in a deep peripheral vein, clots which travel through the venous blood system (e.g. to the lung known as pulmonary embolism or as pulmonary infarction), heart attack caused by blood clots, stroke caused by blockage of the blood supply to or in the brain.

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 are listed below (see also sections ‘Do not use [RH087 trade name]’, ‘Warnings and precautions’):

Tumours:

- The frequency of diagnosis of breast cancer is very slightly increased among combined oral contraceptive (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.
- Liver tumours (benign and malignant)

Other conditions:

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

Development 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
- liver function disturbances
- changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis
- chloasma
- cervical cancer

In women with hereditary angioedema, contraceptives containing oestrogen may induce or exacerbate symptoms of angioedema.

Injections of oily solutions such as [RH087 trade name] have been associated with reactions including cough, dyspnea (shortness of breath), chest pain. There may be other signs and symptoms including reactions such as malaise, hyperhydrosis (increased sweating), dizziness, paraesthesia ('pins and needles'), or syncope (fainting). These reactions may occur during or immediately after the injection and are reversible. Treatment by your healthcare provider is usually supportive, for example by administration of oxygen.

Your healthcare provider will inject [RH087 trade name] strictly into the muscle and very slowly.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your healthcare provider or pharmacist.

Reporting of side effects

If you get any side effects,talk to your health care provider.This includes unwanted effects not listed in this leaflet.If available, you can also report side effects directly through the national reporting system. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store [RH087 trade name]

Keep this medicine out of the sight and reach of children.

Do not store above 30°C. Keep the prefilled glass syringe in the carton to protect the product from light. Do not refrigerate or freeze.

This medicine must not be used after the expiry date stated on the syringe label or carton, after "EXP". The expiry date refers to the last day of that month.

This medicine must not be used if there are visible signs of deterioration.

Do not throw away any medicines in wastewater or household waste. Ask your health care provider how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [RH087 trade name] contains

- The active ingredients are estradiol valerate (5mg) and norethisterone enantate (50 mg).
- The other ingredients of [RH087 trade name] are benzyl benzoate(425 mg) and castor oil (545 mg)for injection.

What [RH087 trade name] looks like and contents of the pack

A clear oily solution, free of particles

1mL of [RH087 trade name] is contained in prefilled colourless glass syringes.

Each prefilled glass syringe consists of a glass barrel (1.5mL colourless glass type 1 with black colour code), grey tip cap with dark grey bromobutyl plunger stopper and a stainless-steel needle.

Supplier

Bayer S.A. Av.
Luxemburgo N34-359 y Av.
Portugal Quito
Pichincha 170505
Ecuador
Tel. No.: 1-800 229377
E-mail: Use contact form on www.andina.bayer.com

Manufacturer

Bayer de México S.A de C.V
Ixtaczoquitlán
Avenida Reforma No. 46 Col. Potrerillo
C.P. 94450 Ixtaczoquitlán, Veracruz Ignacio de la Llave, México

For any information about this medicine, contact the local representative of the supplier:

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Section 6 was updated in August 2023

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