For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

REGESTRONE

1. Generic Name

Norethindrone Acetate Tablets U.S.P.

2. Qualitative and quantitative composition

Each uncoated tablet contains:

Norethindrone Acetate U.S.P. ……5 mg

The excipients used are Lactose, Maize Starch, Vitamin E Acetate, Polyvinyl Pyrrolidone K-30 and Magnesium Stearate.

3. Dosage form and strength

Dosage form: Uncoated Tablets

Strength: 5 mg

4. Clinical particulars

4.1 Therapeutic indication

At low dose: Dysfunctional uterine bleeding, endometriosis, polymenorrhoea, menorrhagia, metropathia, haemorrhagia, postponement of menstruation and premenstrual syndrome.

At high dose: Disseminated carcinoma of the breast.

4.2 Posology and method of administration

Posology

Low dose

Dysfunctional uterine bleeding, polymenorrhoea, menorrhagia, dysmenorrhoea and metropathia haemorrhagia: 1 tablet three times daily for 10 days; bleeding usually stops within 48 hours. Withdrawal bleeding resembling true menstruation occurs a few days after the end of treatment. One tablet twice daily, from days 19 to 26 of the two subsequent cycles, should be given to prevent recurrence of the condition.

Endometriosis: 1 tablet three times daily for a minimum treatment period of six months. The dosage should be increased to 4 or 5 tablets a day if spotting occurs. The initial dosage should be resumed when bleeding or spotting stops.

Postponement of menstruation: 1 tablet three times daily, starting three days before the expected onset of menstruation. Menstruation usually follows within three days of finishing the treatment.

Pre-menstrual syndrome: 1 tablet daily from days 16 to 25 of the menstrual cycle.

High dose

For disseminated breast carcinoma the starting dose is 8 tablets (40mg) per day increasing to 12 tablets (60mg) if no regression is noted.

Method of administration

Oral Administration

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed.

Pregnancy

Previous idiopathic or current venous thromboembolism (deep vein thrombosis, pulmonary embolism)

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)

Disturbance of liver function

History during pregnancy of idiopathic jaundice

Severe pruritus or pemphigoid gestationis

Undiagnosed irregular vaginal bleeding

Porphyria

4.4 Special warnings and precautions for use

If menstrual bleeding should fail to follow a course of REGESTRONE, the possibility of pregnancy must be excluded before a further course is given.

Therapy should be discontinued if the following occur:

- Jaundice or deterioration in liver function

- Significant increase in blood pressure

- New onset of migraine-type headache

Progestogens may cause fluid retention. Special care should be taken when prescribing norethisterone in patients with conditions, which might be aggravated by this factor:

- Epilepsy

- Migraine

- Asthma

- Cardiac dysfunction

- Renal dysfunction

Risk of venous thromboembolism (VTE)

Long-term use of low dose progestogens as part of combined oral contraception or combined hormone replacement therapy has been associated with an increased risk of venous thromboembolism, although the role of progestogens in this aetiology is uncertain. A patient who develops symptoms suggestive of thromboembolic complications should have her status and need for treatment carefully assessed before continuing therapy.

Any patient who develops an acute impairment of vision, proptosis, and diplopia or migraine headache should be carefully evaluated ophthalmologically to exclude papilloedema or retinal vascular lesions before continuing medication.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI >30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Treatment with steroid hormones may add to these risk factors. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophillic predisposition. Until a thorough evaluation of thrombophillic factors has been made or anticoagulant treatment initiated, use of progestogens in these patients should be viewed as contraindicated. Where a patient is already taking anticoagulants, the risks and benefits of progestogen therapy should be carefully considered.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE. Where prolonged immobilisation is likely to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to stopping progestogen therapy 4-6 weeks pre-operatively. Treatment should not be restarted until the patient is fully remobilised.

If VTE develops after initiating therapy, the drug should be withdrawn. Patients should be advised to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g., painful swelling in the leg, sudden pain in the chest, dyspnoea).

Hepatic adenoma - In very rare cases, hepatic adenomas may be associated with progesterone-only pill (POP) use. In some cases, the hepatic adenoma may decrease in size or become undetectable after discontinuation of norethisterone. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage. In extremely rare cases, hepatocellular carcinoma may be associated with combined oral contraceptives use.

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

4.5 Drugs interactions

Interaction with other medicines

The metabolism of progestogens may be increased by concomitant administration of compounds known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes. These compounds include anticonvulsants (e.g., phenobarbital, phenytoin, and carbamazepine) and anti-infectives (e.g., rifampicin, rifabutin, nevirapine, efavirenz, tetracyclines, ampicillin, oxacillin and cotrimoxazole)

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of progestogens. Progestogen levels may therefore be reduced.

Aminoglutethimide has been reported to decrease plasma levels of some progestogens.

Concurrent administration of cyclosporin and norethisterone has been reported to lead to increased plasma cyclosporin levels and/or decreased plasma norethisterone levels.

When used in combination with cytotoxic drugs, it is possible that progestogens may reduce the haematological toxicity of chemotherapy.

Special care should be taken when progestogens are administered with other drugs which also cause fluid retention, such as NSAIDs and vasodilators.

Other forms of interaction

Progestogens can influence certain laboratory tests (e.g., tests for hepatic function, thyroid function and coagulation).

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Contraindicated in pregnancy

4.7 Effects on ability to drive and use machines

REGESTRONE has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Progestogens given alone at low doses have been associated with the following undesirable effects:

Genitourinary	breakthrough bleeding, spotting, amenorrhoea, abnormal uterine bleeding, (irregular, increase, decrease), alterations of cervical secretions, cervical erosions, prolonged anovulation
Reproductive system and breast disorders	Galactorrhea, mastodynia, tenderness
Central Nervous System	depression, headache, dizziness, fatigue, insomnia, nervousness, somnolence, confusion, euphoria, loss of concentration, vision disorders
Gastrointestinal/Hepatobiliary	nausea, vomiting, cholestatic icterus/jaundice, constipation, diarrhoea, dry mouth, disturbed liver function
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	hepatic adenoma
Metabolic & Nutritional	altered serum lipid and lipoprotein profiles, increased fasting glucose levels, increased fasting insulin levels, decreased glucose tolerance, adrenergic-like effects (e.g., fine hand tremors, sweating, cramps in calves at night), corticoid-like effects (e.g., Cushingoid syndrome), diabetic cataract, exacerbation of diabetes mellitus, glycosuria
Cardiovascular	Thrombo-embolic disorders, cerebral and myocardial infarction, congestive heart failure, increased blood pressure, palpitations, pulmonary embolism, retinal thrombosis, tachycardia, thrombophlebitis

Skin & Mucous Membranes	acne, hirsutism, alopecia, pruritis, rash, urticaria
Allergy	hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angioedema)
Miscellaneous	oedema/fluid retention, bloating, weight gain, pyrexia, change in appetite, change in libido, hypercalcaemia, malaise

4.9 Overdose

Overdosage may be manifested by nausea, vomiting, breast enlargement and later vaginal bleeding. There is no specific antidote and treatment should be symptomatic.

Gastric lavage may be employed if the overdosage is large and the patient is seen sufficiently early (within four hours).

5. Pharmacological properties

5.1 Mechanism of Action

Inhibits pituitary gonadotropin release, transforms proliferative to secretory endometrium, thickens cervical mucus. In carcinoma norethisterone may act by pituitary inhibition or by direct action on tumour deposits.

5.2 Pharmacodynamic properties

Pharmotherapeutic group (ATC code) L02A B.

Norethisterone given at intermediate doses (5-10mg) suppresses ovulation via its effect on the pituitary. The endogenous production of oestrogens and progesterones are also suppressed, and the ectopic endometrium is converted to a decidua resembling that of pregnancy. In carcinoma norethisterone may act by pituitary inhibition or by direct action on tumour deposits.

5.3 Pharmacokinetic properties

Norethisterone is rapidly and completely absorbed after oral administration, peak plasma concentration occurring in the majority of subjects between 1 and 3 hours. Due to first-pass metabolism, blood levels after oral administration are 60% of those after i.v. administration. The half-life of elimination varies from 5 to 12 hours, with a mean of 7.6 hours. Norethisterone is metabolised mainly in the liver. Approximately 60% of the administered dose is excreted as metabolites in urine and faeces.

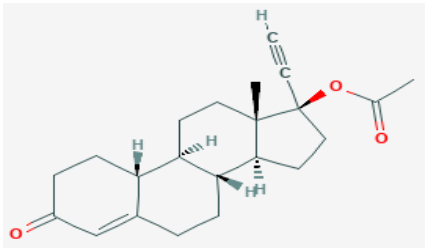
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

The toxicity of norethisterone is very low. Reports of teratogenic effects in animals are uncommon. No carcinogenic effects have been found even in long-term studies.

7. Description

Norethisterone Acetate is [(8R,9S,10R,13S,14S,17R)-17-ethynyl-13-methyl-3-oxo-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-yl] acetate having molecular formula of $C_{22}H_{28}O_3$ and molecular weight of 340.5 g/mol with the chemical structure as below:



Norethindrone Acetate Controlled Release Tablets are uncoated, round, white, flat on both sides with bevelled edges. They are embossed with the letters 'HCG' on one side and scored on other side. The excipients used are Lactose, Maize Starch, Vitamin E Acetate, Polyvinyl Pyrrolidone K-30 and Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not later than the date of expiry**.**

8.3 Packaging information

REGESTRONE is available in blister strip of 10 tablets.

8.4 Storage and handing instructions

Store protected from light & moisture at a temperature not exceeding 30°C.

9. Patient Counselling Information

REGESTRONE 5 mg Tablets

Norethindrone

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 any further questions, ask your doctor or your pharmacist.

• 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 are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What REGESTRONE is and what it is used for

REGESTRONE is one of a group of medicines called 'Progestogens'. Progestogens are similar to the natural female hormone progesterone. REGESTRONE contains the progestogen called norethisterone as the active ingredient. REGESTRONE has many uses.

You can take REGESTRONE to treat or manage:

At low dose: Dysfunctional uterine bleeding, endometriosis, polymenorrhoea, menorrhagia, metropathia, haemorrhagia, postponement of menstruation and premenstrual syndrome.

At high dose: Disseminated carcinoma of the breast.

Your doctor may also prescribe REGESTRONE if you want to delay your next period.

9.2 What you need to know before you take REGESTRONE

REGESTRONE may not be suitable for all women. Please read the following list carefully to see if any of these apply to you. Consult your doctor if you are not sure.

Do not take REGESTRONE:

- If you are allergic to norethisterone or other similar hormone medicines, or any of the other ingredients of this medicine.

- If you are pregnant, or think you might be pregnant. Your doctor may give you a pregnancy test before starting treatment or if you miss a period during treatment.

- If you have now or have ever had any vaginal bleeding (not a period) for which your doctor could not find a cause.

- If you or a member of your family have ever had a problem with blood clots, including deep vein thrombosis (DVT).

- If you have now or have had in the past, a heart attack or angina.

- If you have liver problems.

- If you have ever had a pregnancy where you had jaundice, or an itchy rash known as pemphigoid gestationis. This rash appears as small blisters on your abdomen.

- If you have severe generalised itching all over your body (pruritis)

- If you have a condition known as porphyria (a rare inherited blood disease).

Warnings and precautions

Talk to your doctor or pharmacist before taking Utolvan if you have any of the following conditions. This will help them decide if REGESTRONE is suitable for you:

- Epilepsy

- Migraine headaches

- Asthma

- Heart problems

- Kidney problems.

Psychiatric disorders

Some women using hormonal contraceptives including REGESTRONE have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

Risk of Venous Thromboembolism (VTE)

All women have a small chance of having a blood clot in the veins of the leg, in the lung or other part of the body. The chances of getting a clot are very slightly higher if you are taking a hormone medicine like REGESTRONE. You are more likely to get a clot whether or not you are taking REGESTRONE if you:

- are very overweight

- have systemic lupus erythematosus. (This is a condition where the immune system attacks healthy tissues, typically causing symptoms such as painful joints and muscles, tiredness, fever and rashes).

- have had a blood clot in the veins or lungs before

- have relatives who have had blood clots

- are unable to move for long periods of time (for example after an operation)

- have a serious injury or have major surgery

- have a history of repeated miscarriage.

Tell your doctor if you have just had an operation or if you are going to have an operation while taking REGESTRONE. Section 4 of this leaflet ('possible side effects') also has more information on the warning signs of blood clots.

Other medicines and REGESTRONE

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

This includes the following medicines, as the effect of REGESTRONE may be altered when they are taken at the same time:

- Medicines to treat epilepsy (e.g. phenytoin, carbamazepine)

- Antibiotic medicines to treat an infection (e.g. tetracyclines, rifampicin, co-trimoxazole)

- Antiviral medicines to treat HIV (e.g. ritonavir, nelfinavir)

- Anticancer medicines

- Herbal preparations containing St John's wort (Hypericum perforatum)

- Aminoglutethimide, sometimes used in Cushing 's syndrome.

- Ciclosporin (for suppressing the immune system)

- Non-steroidal anti-inflammatory drugs (NSAIDs) for treating pain and inflammation

- Medicines for high blood pressure.

REGESTRONE can also interfere with some laboratory tests, so tell your doctor if you are having any blood tests or hospital investigations.

Tell your doctor or pharmacist if you are taking any other medicines not listed above, including those bought without a prescription**.**

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy

REGESTRONE must not be taken if you are pregnant as hormonal medicines can affect the developing baby. It is important you use some form of contraception (e.g. a condom) while taking REGESTRONE, as it is not a contraceptive.

Breast-feeding

If you are breast-feeding, ask your doctor for advice before taking this medicine, so they can advise whether you should use an alternative method of feeding your baby.

Driving and using machines

No effect on the ability to drive or use machinery has been seen with REGESTRONE**.**

REGESTRONE contains lactose

Lactose is a type of sugar. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

9.3 How to take REGESTRONE

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose will depend on the condition you are being treated for. This information can also be found on the label on the box the tablets come in. The following information will help **you see what the usual dose is for a particular problem.**

Taking REGESTRONE for heavy bleeding and other period problems - You will usually take 1 tablet 3 times a day (15 mg) for 10 days. A few days after you stop taking the tablets you will usually have bleeding like a period. To stop your periods causing problems again, your doctor may tellm you to take REGESTRONE for a few days after your next two periods. You will probably take 1 tablet twice a day (10 mg) for 8 days. You will need to start taking these tablets 19 days after your last period began.

Taking REGESTRONE for premenstrual tension - You will usually take one 5 mg tablet a day for 10 days, starting 16 days after your last period began.

Taking REGESTRONE for endometriosis - You will usually take 1 tablet 3 times (15 mg) a day for at least 6 months. If you have any irregular bleeding or spotting, your doctor may increase the dose to 4 or 5 tablets (20-25 mg) a day until this bleeding stops.

Taking REGESTRONE for breast cancer - You will usually take 8 tablets (40 mg) a day. Your doctor may increase this to 12 tablets (60 mg).

Taking REGESTRONE to delay your periods - You will usually take 1 tablet 3 times (15 mg) a day.

You need to start taking the tablets 3 days before your period is due to start. Your period will usually start within 3 days of finishing the tablets.

If you do not have a period after you finish a course of REGESTRONE, check with your doctor in case you are pregnant.

If you take more REGESTRONE than you should

If you take too many tablets, contact your doctor straight away.

If you forget to take REGESTRONE

Take the tablet as soon as you remember, and carry on taking the tablets at the normal times. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Reasons for stopping REGESTRONE treatment immediately

Very rarely, REGESTRONE may cause a severe allergic reaction, which can be life-threatening in some cases. You can get some or all of the following symptoms:

• wheezing

• Difficulty breathing

• feeling faint

• swelling of the face or tongue

• swelling of the hands and feet

• Intense itchy skin rash.

If you think you are reacting badly to the medicine, get emergency medical help immediately. The following symptoms could be warning signs of thrombosis (a blood clot) which will need urgent treatment:

Symptoms of a blood clot in the lungs:

- Sudden, severe, sharp pain in your chest

- Coughing up blood

- You suddenly become short of breath

- Your heart beats more rapidly

Symptoms of a blood clot in the brain (‘a stroke’):

- You have an unusually severe or long headache

- Your sight is affected in any way

- You find it difficult to speak

- You collapse or faint

- Any part of your body feels weak or numb

Symptoms of a deep-vein thrombosis (DVT):

- You have severe pain, tenderness or swelling in your calf, ankle or foot

- You have purple discolouration of the skin of the leg or the skin becomes red and warm to touch

If you get any of these symptoms, you should stop taking the tablets and see your doctor

Immediately.

Reasons for seeking medical advice during treatment

It is important to see your doctor straightaway if you get:

- Yellowing of the skin or whites of the eyes (jaundice)

- Migraine headache for the very first time

Your doctor may also decide to stop treatment if your blood pressure gets too high.

Other side effects

You can also get the following side effects with medicines like REGESTRONE:

Effects on the reproductive system and breasts: bleeding and spotting between periods, lack of periods (amenorrhoea), unexpected or unusual vaginal bleeding, changes in discharge from the cervix, cervical erosions (this may be seen when you have a smear test), cycles where you don't ovulate (anovulation), breast pain and tenderness, a milky discharge from the breast when not pregnant or breastfeeding (galactorrhoea).

Effects on the nervous system: headache, depression, dizziness, fatigue, difficulty sleeping, confusion, nervousness, a feeling of intense happiness (euphoria), feeling sleepy, loss of concentration, vision problems.

Effects on the stomach and intestines: feeling or being sick, constipation, diarrhoea, dry mouth. Effects on the liver: disturbed liver function, yellowing of the skin or whites of the eyes. Cysts and tumours: a liver disorder, such as a benign liver tumour. These mostly do not cause any symptoms but can sometimes be felt. Benign liver tumours can sometimes cause severe abdominal pain.

Effects on your metabolism: altered fat levels in the blood, alteration of blood sugar levels, increased levels of insulin between meals and existing diabetes getting worse, decreased tolerance to some sugars like glucose, adrenergic-like effects (e.g. fine hand tremors, sweating, cramps in the calves at night), effects on the adrenal glands (e.g. Cushingoid syndrome), cloudy vision, sugar in your urine.

Effects on your heart and circulation: blood clots, including clots in the lung, and swelling in the veins due to blood clots, stroke, heart attacks, congestive heart failure, increased blood pressure, feeling your heartbeat, clots in the blood vessels of the retina (this causes visual problems), heart beating faster (tachycardia).

Effects on your skin and hair: acne, increase in body or facial hair, hair loss, itching, rash, hives.

Miscellaneous: fluid retention and swelling of hands and ankles, bloating, weight gain, raised temperature, change in appetite, changes in sex drive, fatigue, and increase in calcium (seen in blood tests).

9.5 . How to store REGESTRONE

Store protected from light and moisture at a temperature not exceeding 30°C

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

What REGESTRONE contains

- The active substance is norethindrone. Each tablet contains 5 mg of norethisterone.

- The other ingredients are Lactose, Maize Starch, Vitamin E Acetate, Polyvinyl Pyrrolidone K-30 and Magnesium Stearate.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd.

Plot No. 47 & 48, Sector -6A, I.I.E., SIDCUL, Haridwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No. 97/UA/SC/P-2009 issued on 08.05.2017.

12. Date of revision

Not available

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ REGESTRONE 5mg /November-20/01/PI