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

Drospirenone and Ethinylestradiol Tablets IP

Yamini®

Composition

Each film coated tablet contains:
Drospirenone IP .....3 mg
Ethinylestradiol IP .....0.03 mg
Excipients .....q.s.
Colours: Yellow Oxide of Iron & Titanium Dioxide IP

Yamini like all oral contraceptives is intended to prevent pregnancy. Please note that it does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Yamini is different from other birth-control pills because along with ethinyl estradiol it contains the progestin drospirenone which is closer to natural progesterone.

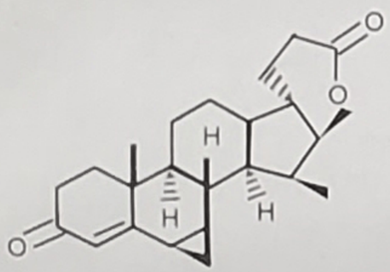
Description

Yamini is an oral contraceptive. This regimen consists of 21 yellow tablets each containing 3.0 mg of drospirenone and 0.030 mg of ethinyl estradiol.

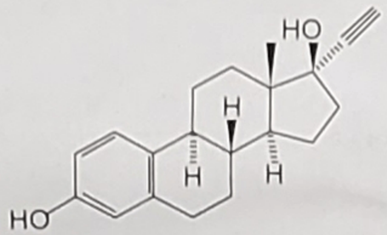
Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro-10,13 dimethylspiro-[17H-dicyclopropa-6,7:15,16] cyclopenta[a]phenanthrene- 17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$. Drospirenone differs from other synthetic progestins in that its pharmacological profile in preclinical studies shows it to be closer to the natural progesterone. As such it has anti-mineralocorticoid properties, counteracts the estrogen-stimulated activity of the renin-angiotensin-aldosterone system, and is not androgenic.

Ethinyl estradiol (19-nor-17- pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

The structural formula of these two are as follows:



Drospirenone



Ethinyl estradiol

Clinical Pharmacology

Pharmacodynamics

Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and in vitro have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

Pharmacokinetics

Absorption

The absolute bioavailability of drospirenone from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of **Yamini** which is a combination tablet of drospirenone and ethinylestradiol has not been evaluated. Serum concentrations of drospirenone and ethinyl estradiol reached peak levels within 1-3 hours after administration of **Yamini**. After single dose administration of **Yamini**, the relative bioavailability, compared to a suspension, was 107% and 117% for drospirenone and ethinyl estradiol , respectively.

The pharmacokinetics of drospirenone are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of **Yamini**, steady state drospirenone concentrations were observed after 10 days. There was about 2 to 3 fold accumulation in serum Cmax and AUC (0-24h) values of drospirenone following multiple dose administration of **Yamini**.

For ethinyl estradiol , steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of **Yamini** serum Cmax and AUC(0-24h) values of ethinyl estradiol accumulate by a factor of about 1.5 to 2.0.

Effect of Food

The rate of absorption of drospirenone and ethinyl estradiol following single administration of two **Yamini** tablets was slower under fed conditions with the serum Cmax being reduced about 40% for both components. The extent of absorption of drospirenone , however, remained unchanged. In contrast the extent of absorption of ethinyl estradiol was reduced by about 20% under fed conditions.

Distribution

Drospirenone and Ethinylestradiol serum levels decline in two phases. The apparent volume of distribution of drospirenone is approximately 4 L/kg and that of ethinyl estradiol is reported to be approximately 4-5 L/kg.

Drospirenone does not bind to Sex Hormone Binding Globulin (SHBG) or Corticosteroid Binding Globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). ethinyl estradiol is reported to be highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of both SHBG and CBG. ethinyl estradiol induced effects on SHBG and CBG were not affected by variation of the drospirenone dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of drospirenone found in human plasma were identified to be the acid form of drospirenone generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In in vitro studies with human liver microsomes, drospirenone was metabolized only to a minor extent mainly by cytochrome P450 3A4 (CYP3A4). ethinyl estradiol has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

Drospirenone serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of drospirenone was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. drospirenone was extensively metabolized and only trace amounts of unchanged drospirenone were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For ethinyl estradiol the terminal disposition phase half-life has been reported to be approximately 24 hours. Ehinyl estradiol is not excreted unchanged. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Indications

Yamini is indicated for the preventions of pregnancy in women who elect to use an oral contraceptive.

Dosage and administration

Please read the following directions carefully before starting to take these pills or when you are not sure as to what to do regarding any of the factors related to these pills.

Some important directions before starting the Yamini pill pack

- Take one pill everyday at the same time. This is the correct way of taking these pills.
- If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. When this happens, an additional method of contraception such as usage of condoms or spermicides, is required.
- Many women might experience spotting or light bleeding. Some women might also feel very sick and nauseated during the first 1 – 3 packs of pills. But remember, that even if these happen, do not stop taking the pills. If these persists then please consult your doctor.
- Missing pills can also cause spotting or light bleeding, , even when you make up for these missed pills. On the days you take two pills, to make up for missed pills, you could feel a little nauseated.
- If you have vomiting or diarrhea, or if you take some medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.
- Use a back-up method such as condoms or spermicides until you check with your doctor.
- If you have problem remembering to take the pill, talk to your doctor about how to make pill-taking easier.

Before you start taking Yamini

- Decide what time of the day you would take your pill. Like mentioned here earlier, it is always advised to take the pill at the same time everyday.

How to take Yamini

Yamini consists of 21 tablets of a monophasic combined hormonal preparation. The dosage of Yamini is one tablet daily for 21 consecutive days followed by 7 pill free days per menstrual cycle.

A patient should begin to take Yamini either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

During the first cycle of Yamini use, the patient should be instructed to take one Yamini daily, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) She should take one Yamini daily for 21 consecutive days, followed by 7 pill free days.

What to do during the month

- Take one pill at the same time every day until the pack is empty.
- Do not skip pills even if you get spotting or bleeding between monthly periods or nauseated.
- Do not skip pills even if you do not have sexual intercourse very often.

What to do if you miss pills

If you miss one pill:

1. Take it as soon as you remember. Take the next pill at your regular time.This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sexualintercourse.

If you miss two (2) pills in a row in week 1 or week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You may become pregnant if you have sexual intercourse in the 7 days after you miss pills. You must use another birth control method such as condoms or spermicides as a back-up for those 7 days.

If you miss two (2) pills in a row in the 3rd week:

If you are a Day 1 Starter:
Throw away the rest of the pill pack and start a new pack that same day.

If you are a Sunday Starter:

1. Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected.
3. However, if you miss your period two months in a row, please consult your doctor because you might be pregnant.

If you miss 3 or more pills in a row (during the first 3 weeks):

1. If you are a day 1 starter:
   Throw away the rest of the pill pack and start a new pack that same day.

   If you are a sunday starter:
   Keep taking 1 pill every day until sunday. On sunday, throw out the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period two months in a row, consult your doctor because you might be pregnant.
3. You may become pregnant if you have sexual intercourse in the 7 days after you miss pills. You must use another birth control method such as condoms or spermicides as a back-up for those 7 days.

Finally, if you are still not sure what to do about the pills you have missed:

1. Use a back-up method such as condoms or spermicides anytime you have sexual intercourse.
2. Keep taking one active pill each day until you are able to consult your doctor.

Pregnancy due to pill failure

The incidence of pill failure resulting in pregnancy is approximately less than 1.0% (one pregnancy per 100 women per year of use) if taken every day as directed, but more typical failure rates are about 5%. If failure does occur with **Yamini** use, the risk to the fetus is unknown.

Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

Contraindications, Warnings and Precautions

You should not take the pill if you are:

- hypersensitive to any of the components
- pregnant or suspect you are pregnant
- have unexplained vaginal bleeding, high blood pressure, diabetes, high cholesterol, Clotting disorders, heart attack, stroke, angina pectoris (severe chest pain), cancer of the Breast or sex organs, jaundice, malignant or benign liver tumors
- suffering from ovent obesity.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B and syphilis.

Yamini is different from other birth-control pills because it contains the progestin, drospirenone, Drospirenone may increase potassium.Therefore, you should not take **Yamini** if you have kidney, liver and adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any medication e.g. drugs for high blood pressure, you should consult your doctor about whether **Yamini** is right for you and during the first month that you take **Yamini**, you should have a blood test to check your potassium level.

Overdose

Serious ill effects have not been reported following ingestion of large doses of other oral contraceptives by young children.

Overdosage of **Yamini** may cause nausea and withdrawal bleeding in females and may increase blood levels of potassium or decrease blood levels of sodium, which could be dangerous. In case of overdosage, contact your doctor.

Special Population

Hepatic Dysfunction
Yamini is contraindicated in patients with hepatic dysfunction.

Renal Insufficiency
Yamini is contraindicated in patients with renal insufficiency. Potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range and who are concomitantly using potassium sparing drugs.

Side Effects of conventional oral contraceptives

The most common side effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness and difficulty wearing contact lenses. These side effects, Especially nausea and vomiting may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary anabolism), blockage or rupture of a blood vessels in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. Women with migraine headaches also may be at increased risk of stroke when taking the pill.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually return to normal when the ill is stopped.
4. Cancer of the breast- Various studies give conflicting reports on the relatioship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of getting breast cancer begin to go back down. You should have regular breast examinations by your doctor and examine your own breasts monthly. Tell your doctor if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram.
   Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone sensitive tumor. Some studies have found an increase in the incidence of cancer or precancerous lesions of the cervix in women who use the pill. However, this finding may be related to factors other than the use of the pill. Notify the doctor if you notice any unusual physical disturbances while taking the pill.

Drug Interactions

Tell your doctor if you are taking any of the following medications: Non steroidal anti-inflammatory (NSAIDs) when taken long-term and for treatment of arthritis or other problems (e.g. ibuprofen, naproxen or others)

- Drugs for the treatment of high blood pressure, epilepsy, diabetes
- Drugs for treatment of infections e.g. rifampicin, ritonavir, penicillins, tetracyclines, cyclosporin, griseofulvin
- Cholesterol-lowering drugs e.g. clofibrate
- Prednisolone
- Sedative e.g. meperidine and hypnotics e.g. benzodiazepines, barbifurates, chloral hydrate
- Antacids

Additional Benefits of Yamini

Taking the pill may provide some important non-contraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.
Studies have shown that **Yamini** can be beneficial in the treatment of acne of moderate to severe degree in women who simultaneously desire contraception. It causes lesser fluid retention and is thus useful in women with premenstrual dysphoric disorder.

What you must do while on this medication

Be sure to discuss any medical condition you may have with your doctor. Your doctor will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be displayed to another time if you request it and the doctor believes that it is appropriate to postpone it. You should be re-examined at least once a year while taking oral contraceptives.

Presentation

A strip of 21 tablets.

Storage requirements

Store below 30°C, protected from moisture.
Keep this medicine out of the reach of children.

® Regd. Trade Mark of Lupin Ltd.

In technical assistance with:
BDR PHARMACEUTICALS INTL. PVT. LTD.

Manufactured by:
Ontop Pharmaceuticals Pvt. Ltd.
9-D, Bommasandra Indl. Area
Hosur Road, Bangalore - 560 099
In technical assistance with BDR, India

"To report product complaint or adverse drug reaction dial Toll free no. 1800-209-2505 or email at dsrm@lupin.com"

For Further information contact:

LUPIN LTD.
159, C.S.T. Road,
Kalina, Santacruz (E),
Mumbai - 400 098, INDIA.

R6