Dyestadiol

(Cyproterone acetate 2mg & Ethinylestradiol 35mcg)

NAME OF THE MEDICINAL PRODUCT
Dyestadiol 35 mcg/2.0mg coated tablets

COMPOSTION
21 hormone-containing beige coated tablets.
Each coated tablet contains 35 mcg ethinylestradiol, 2.0 mg cyproterone acetate

PHARMACEUTICAL FORM
Coated tablet

CLINICAL PARTICULARS
Indication(s)
Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age. This includes patients with ploycystic ovary syndrome requiring treatment of these symptoms.
For the treatment of acne, Dyestadiol should be used when topical therapy or system antibiotic treatments are not considered appropriate. Since Dyestadiol is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 'Contraindications').

Dosage and method of administration
Method of administration.
Oral use

Dosage regimen
How to take Dyestadiol
Dyestadiol is to be taken regularly in order to achieve the therapeutic efficacy and the required contraceptive protection. Previously used hormonal contraception should be discontinued. The dose regimen of Dyestadiol is similar to the usual regimen of most of the combined oral contraceptives. Thus, the same administration rules must be considered. Combined oral contraceptives, when taken correctly, have a failure rate approximately 1% per year. The irregular intake of Dyestadiol can lead to intermenstrual bleedings and could deteriorate the therapeutic and contraceptive reliability.
Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet- free interval.
How to start Dyestadiol: Tablet-taking has to start on date 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding).
Management of missed tablets
If the user is less than 12 hours late in taking any tablet, contraceptive protection is not reduced. The women should take the tablet as soon as she remembers and should take further tablets at the usual time.
If she is more than 12 hours late in taking any tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
1. tablet-taking must never be discontinued for longer than 7 days.
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary- ovarian-axis.
If the woman missed tablets and subsequently has no withdrawal bleed in the first normal tablet-free interval, the possibility of a pregnancy should be considered.
Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets, as given in section 'Management of missed tablets',is applicable.
The length of use depends on the severity of the symptoms of androgenization and their response to treatment. In general, treatment should be carried out over several months. Time to relieve of symptoms is at least three months. Acne and seborrhea usually respond sooner than hirsutism. The need to continue treatment should be evaluated periodically by the treating physician. Should there be a recurrence of symptoms, weeks or months after discontinuation of tablet-taking, treatment with Dyestadiol may be resumed. In case of a restart of Dyestadiol (following a 4 week or a greater pill free Interval), the increased risk of VTE should be considered (see 'section 'special warnings and precautions for use). Additional Information on special populations Children and adolescents. Dyestadiol is only indicated after menarche.
Geriatric patients.
Not applicable. Dyestadiol is not indicated after menopause.
Patients with hepatic impairment.
Dyestadiol is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section 'Contraindications'.
Patients with renal impairment. Dyestadiol has not been specifically studied in renally impaired patients. Available date do not suggest a change in treatment in this patient population.
Contraindications
Preparations containing estrogen/progestogen combinations should not be used in the presence of any of the conditions listed below. If any of the conditions appear for the first time during their use, the product 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 a history of prodromi 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 tumors (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Concomitant use with another hormonal contraceptive (see section' Indication (s)')
- Known or suspected pregnancy.
- Lactation
- Hypersensitivity to the active substances or to any of the excipients.

Dyestadiol is not for use in men.
Special warnings and precautions for use
Dyestadiol is composed of the progestogen cyproterone acetate and the estrogen ethinylestradiol and administered for 21 days of a monthly cycle. It has a similar composition to that of a combined oral contraceptive (COC). The clinical and epidemiological experience with estrogen/progestogen combinations like Dyestadiol is predominantly based on combined oral contraceptives (COC). Therefore, the following warnings related to the use of COC apply also for Dyestadiol.
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. 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. Date from a large, prospective 3-armed cohort study suggest that this increased risk mainly present during the first 3 months. Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 ug ethinylestradiol) COCs is two to three fold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery. VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. 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. There is no consensus as to whether the occurrence of these events is associated with the use of COCs. Symptoms of deep venous thrombosis (DVT) can 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) can 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). An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can 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 or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen. Symptoms of MI can 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, anxiety, or shortness of breath; rapid or irregular heartbeats. Arterial thromboembolic events may be life-threatening or may have a fatal outcome. The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factor or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. Dyestadiol should not be prescribed in case of a negative risk benefit assessment. (see section, 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');
- 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 women should be referred to a specialist for advice before deciding about any COC use;
- Prolonged immobilization, major surgery any surgery to the legs, or major trauma. In these situations it is
- advisable to discontinue COC use (in the case of elective surgery at least four 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);
- dyslipoproteinemia;
- hypertension:
- migraine;
- valvular heart disease;
- atrial fibrillation;

There is no consensus about the possible role of varicose veins and superfacial thrombophlebitis in venous thromboembolism. The increased risk of thromboembolism in the puerperium must considered (for information on pregnancy and lactation see section 'Pregnancy and lactation').
The user group of Dyestadiol is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovary syndrome. Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
An increase in frequency or severity of migraine during Dyestadiol use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of Dyestadiol.
Biochemical factor that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, 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 low-dose COCs (<0.05 mg ethinylestradiol).
Tumors
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs 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. A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24)of having breastcancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age the excess number of breast cancer diagnosis in current and recent COC users 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 COC users,
the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-user tend to be less advanced clinically than the cancers diagnose in never-users. In rare cases, benign Liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra- abdominal hemorrhage occur in women taking COCs.
Malignancies may be life-threatening or may have a fatal outcome.
Other conditions
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.
Although small increase in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clincally significant hypertension develops during use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.
The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestation; otosclerosis-related hearing loss.
In women with hereditary angioedema exogenous estrogens inducer or exacerbate symptoms of angioedema. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until marker 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 COCs.
Although COCs 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 using low-dose COCs (containing < 0.05 mg ethinylestradiol) However, diabetic women should be carefully observed while taking COCs. Crohn's disease and ulcerative colitis have been associated with COC use. Chloasma may occasionally occur, 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 taking COCs.
Medical examination/consultation
Women should be advised that preparations like Dyestadiol do not protect against HIV infections (AIDS) and other sexually transmitted diseases.
Reduced efficacy
The contraceptive effect of Dyestadiol may be reduced in the event of e.g. missed tablets (section 'Management of missed tablets'), gastro-intestinal disturbances (section 'Advice in case of gastro-instestinal disturbances') during tablets taking or concomitant medication (section 'Interaction with other medicinal products and other forms of intertaction').
Reduced cycle control
With estrogern/progestogen combinations, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first month of use. In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section 'Dosage and method of administration'. it is unlikely that the women is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.
Interaction with other medicinal products and other forms of Interaction
Effects of other medicaments on Dyestadiol
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. Women on treatment with any of these drugs should temporarily use a barrier method in addition to Dyestadiol or chose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the tablets in the Dyestadiol pack, the next pack should be started without the usual tablet-free Interval. Substances increasing the clearance of Dyestadiol (diminished efficacy of Dyestadiol by enzyme-induction). e.g.:
Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate,
felbamate, griseofulvin and products containing St. john'wort) Substances with variable effects on the clearance of Dyestadiol, e.g.:
When co-administered with Dyestadiol, many HIV/HCV protease inhibitors and non-nucleosider reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.
Effects of estrogen/progestogen combinations on other medicaments
Estrogen/progestogen combinations like Dyestadiol may affect the metabolism of certain other drugs. Accordingly, Plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).
Other forms of interactions
Laboratory tests
The use of preparations like Dyestadiol may influence the results of certain laboratory tests.
Pregnancy
Dyestadiol is not indicated during pregnancy. If pregnancy occurs during treatment with Dyestadiol, further intake must be stopped.
Lactation
The administration of Dyestadiol is contraindicated during lactation. Cyproterone acetate is transferred into the milk of lactating women. About 0.2 % of the maternal dose will reach the newborn via milk corresponding to a dose of about 1 pg/kg. 0.02 % of the daily maternal dose of ethinylestradiol could be transferred to the newborn via milk during established lactation.
Effects on ability to drive or use machines
Undesirable effects
Side effects that have been reported in users of COCs but for which the association has been neither confirmed not refuted are:

System Organ Class	Common > 1/100)	Uncommon (>1/1000 and <1/100)	Rare (< 1/100)
Eye disorders			Contact lens intolerance
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting Diarrhea	
Immune system disorders			Hypersensitivity
Investigations	Weight increased		Weight decreased
Metabolism and nutrition disorders		Fluid retention	
Nervous system disorders	Headache	Migraine	
Psychiatric disorders	Depressed mood Mood altered	Libido decreased	Libido increased
Reproductive system and breast disorders	Breast pain, Breast tenderness	Breast hypertrophy	Vaginal discharge Breast discharge
Skin and subcutaneous tissue disorders		Rash Urticaria	Erythema nodosum Erythema multiforme
Vascular Disorders			Thromboembolism

The following serious adverse events have been reported in women using COCs, which are discussed in section 'Special warnings and precautions for use':
- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Cerebrovascular accidents
- Hypertension
- Hypertriglyceridemia
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Liver tumours (benign and malignant)
- Liver function disturbances
- Chloasma
- In women with hereditary angioedema exogenous may induce or exacerbate symptoms of angioedema. Occurrence or deterioration of conditions for which association with COC use is not conclusive: Jaundice and/for pruritus related to cholestasis: gallstone formation: porphyria: systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestation: otosclerosis-related hearing loss, Crohn's disease, ulcerative colitis, cervical cancer

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 numbers is small in relation to the overall risk of breast cancer. Causation with COC use is unknown. For further information, see sections Contraindications, and 'Special warnings and Precautions for use'.

Overdose
There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are: nausea,vomiting and in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

DOSAGE: As prescribed by the physician.

INSTRUCTIONS: Store in a dry place below 30°C and protect from sunlight.
Keep all medicines out of reach of children. To be sold on the prescription of a registered medical practitioner only.

Presentation
Dyestadiol: 1 x 21 's Tablets

خوراک:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:
خشک جگہ پر ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
سورج کی روشنی سے بچائیں۔ بچوں کی دسترس سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
Dyson Research Laboratories (Pvt) LTD.
28th-KM Ferozepur Road, Lahore,Pakistan.
ISO 9001:2015 Certified Company