Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name : **Dianofem Tablet**
1.2 Generic Name : Cyproterone Acetate BP / Ph. Eur. and Ethinylestradiol BP / Ph. Eur.
1.3 Strength : 2.0 mg Cyproterone Acetate BP / Ph. Eur. and 0.035 mg Ethinylestradiol BP / Ph. Eur.
1.4 Dosage Form : Tablet (Film-Coated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

The **Dianofem Tablet** are constituted by the active ingredient of Cyproterone Acetate BP / Ph. Eur. and Ethinylestradiol BP / Ph. Eur.

2.2 Quantitative Declaration

The **Dianofem Tablet** contains the active ingredient 2.0 mg Cyproterone Acetate BP / Ph. Eur. and 0.035 mg Ethinylestradiol BP / Ph. Eur.

Each film-coated tablet contains 2.0 mg Cyproterone Acetate BP / Ph. Eur. and 0.035 mg Ethinylestradiol BP / Ph. Eur.
Excipients: For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet (Film-Coated)
White, round biconvex tablet, one side contains “R” logo and other side contains break line.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of women with severe acne, unresponsive to oral antibiotic and other available treatments, with associated symptoms of androgenization, including seborrhea and mild hirsutism.

Note: Dianofem should not be prescribed solely for its contraceptive properties. However, when taken as recommended (see Dosage) Dianofem will provide reliable contraception in patients treated for the above clinical conditions. If patient compliance is uncertain and contraception is necessary, then a supplementary nonhormonal contraceptive method should be considered. Dianofem has many properties in common with estrogen/progestogen-combination oral contraceptives and the same Contraindications, Warnings and Precautions applicable to this class of drugs should be considered. Estrogen and/or progestogen should not be taken during treatment with Dianofem. (see section 4.3).

4.2 Posology and method of administration

Method of Administration: Oral use

Dosage

Dianofem should not be prescribed solely for its contraceptive properties. If patient compliance is uncertain and contraception is necessary, then a supplementary nonhormonal contraceptive method should be considered.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

Dianofem is supplied in blister pack units consisting of 21 tablets; each tablet containing cyproterone acetate 2 mg and ethinyl estradiol 0.035 mg. Each cycle consists of 21 days on medication and a 7 day interval without medication (3 weeks on, 1 week off).

First Treatment Course:
The patient is instructed to take 1 tablet daily for 21 consecutive days beginning on day 1 of her menstrual cycle. (For the first cycle only the first day of menstrual flow is
considered Day 1.) The tablets are then discontinued for 7 days (1 week). Withdrawal bleeding should usually occur during the period that the patient is off the tablets. The first cycle will be somewhat shorter than usual, whereas all following cycles will last 4 weeks.

Subsequent Courses:
The patient begins her next and all subsequent 21-day course of tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets 7 days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.
Treatment should be continued for several months, since improvement may not be observed with 4 or 5 cycles. It is recommended to continue treatment with Dianofem for at least another 3 to 4 cycles after signs have subsided.

Pregnancy should be ruled out before continuing treatment with Dianofem in patients who have missed a menstrual period, if pregnancy is suspected, medication should be discontinued.

Special Notes on Administration:
It is recommended that Dianofem tablets be taken at the same time each day. Irregular tablet-taking, vomiting or intestinal affections with diarrhea, very rare individual metabolic disturbances or prolonged simultaneous use of certain medical preparations can affect the contraceptive action (see Precautions, Drug Interactions).
If spotting or breakthrough bleeding occurs during the 3 weeks in which Dianofem is being taken, the patient is instructed to continue taking the medication. This type of bleeding usually is transient and without significance. However, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

In exceptional cases, menstruation may fail to occur during the 7-day tablet-free interval. The patient is advised not to resume tablet-taking and to consult her physician.
Although the occurrence of pregnancy is highly unlikely if the tablets are taken according to directions, the possibility of pregnancy should be ruled out before continuing treatment with Dianofem in patients who have missed a period of withdrawal bleeding. The patient should consult her physician and, in the meantime, a supplementary nonhormonal method of contraception should be employed.

Management of missed tablets
If the patient forgets to take a tablet at the usual time, the tablet may be taken within the next 12 hours. If more than 12 hours have elapsed from the time of usual administration, the patient must discard the missed tablet and continue to take the remaining tablets in the pack at the usual time in order to avoid a premature withdrawal bleeding during this cycle. A supplementary nonhormonal method of contraception must be employed until the pack is empty to prevent pregnancy which would necessitate immediate discontinuation of Dianofem treatment.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

4.3 Contraindications

Thrombophlebitis, thromboembolic disorders, or a history of these conditions; cerebrovascular disorders, myocardial infarction or coronary artery diseaes; active liver disease or hepatic adenomas or carcinomas; history of cholestatic jaundice; known or suspected carcinoma of the breast; known or suspected estrogen-dependent neoplasia; undiagnosed abnormal vaginal bleeding; any ocular lesion arising from ophthalmie vascular disease, such as partial or complete loss of vision or defect in visual fields; when pregnancy is suspected or diagnosed; previous or existing liver tumors; severe diabetes with vascular changes; a history of otosclerosis with deterioration during pregnancy.

4.4 Special warnings and precautions for use

Physical Examination and Follow up:

Before estrogen/progestogen combinatiojns are used, a throrough history and physical examination should be made including a blood pressure determination. Breasts, liver, extremities, abdomen and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active and a urinalysis should be done.

The first follow up examination should be done 3 months after the initial prescription. Thereafter, examinations should be conducted at regular intervals during long-term treatment and more frequently for those patients at greater risk for adverse effects. At each annual visit examination should include those procedures outlined above that were done at the initial visit.

Hepatic Function:

Patients who have had jaundice should be given estrogen/progestogen combinations with great care and under close observation.

If there is a clear-cut history of cholestatic jaundice, especially if it occurred during pregnancy, other methods of treatment should be prescribed. The development of servere generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If the jaundice should prove to be cholestatic in type, therapy should not be resumed. In patients taking estrogen/progestogen combinations, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported, Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of estrogen/progestogen combinations. Although these lesions are uncommon, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Return to Fertility:

After discontinuing therapy, the patient should delay pregnancy until at least 1 normal menstrual cycle has occurred. The patient should be instructed to use a nonhormonal method of contraception during this time period.

Amenorrhea:

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following estrogen / progestogen-combination therapy. Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

Thromboembolic Complications-Post-surgery:
Retrospective studies have reported an increased risk of post-surgery thromboembolic complications in estrogen/progestogen combination users. If feasible, such drugs should be discontinued at least 1 month prior to elective major surgery. Medication should not be resumed until at least 2 weeks after hospital discharge following surgery.

Warnings

Predisposing Factors for Coronary Artery Diseases:
In women with predisposing factors for coronary artery disease (such as cigarette smoking, hypertension, hypercholesterolemia, obesity, diabetes and increasing age), the use of estrogen/progestogen combinations have been reported as an additional risk factor.

After the age of 35 years, estrogen/progestogen combinations should be considered only in exceptional circumstances and when the risk/benefit ratio has been carefully weighed by both the patient and the physician Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from the use of this class of medication. This risk increases with age and heavy smoking (15 or more cigarettes per day) and is more marked in women over 35 years of age. Women who use such medication should not smoke.

Estrogen/progestogen combinations may cause an increase in plasma lipoproteins and should be administered with caution to women known to have pre-existent hyperlipoproteinemia. Lipid profiles should be determined regularly in these patients. The combination of obesity, hypertension and diabetes is particularly hazardous to women who are taking this class of medication. Should this triad of conditions develop, the patient should be placed on an alternate form of therapy.

Discontinue medication at the earliest manifestation of:

A. Thromboembolic and cardiovascular disorders such as: thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis. The use of estrogen/progestogen-combination products should be avoided in conditions which predispose to vensus stasis and to vascular thrombosis, e.g., immobilization after accidents or confinement to bed during long-term illness.

   Under such conditions other nonhormonal methods of treatment should be considered. For use when surgery is contemplated, see Precautions.

B. Visual defects, partial or complete.
C. Papilledema, or ophthalmic vascular lesions.
D. Severe headache of unknown etiology, or worsening of pre-existing migraine headache.
E. Onset of jaundice or hepatitis.
F. Itching of the whole boby.

Pregnancy:
Fetal abnormalities have been reported to occur in the offspring of women who have taken estrogen/progestogen combinations in early pregnancy. Rule out pregnancy as soon as it is suspected.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

Lactation:
The use of estrogen/progestogen combinations during the period a mother is breast-teeding her infant may not beadvisable. The hormonal components are excreted in breast milk and may reduce its quantity and quality. The long-term effects on the developing child are not known.
This drug may casue fluid retention. Conditions such as epilepsy.

Adverse Effects:

General:
An increased risk of the following serious adverse reactions has been associated with the use of estrogen/progestogen combinations: thrombophlebitis; arterial thromboembolism; pulmonary embolism; mesenteric thrombosis; neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis; myocardial infarction; cerebral thrombosis; cerebral hemorrhage; hypertension; liver tumors; gallbladder disease and congenital anomalies.

The following adverse reactions also have been reported in patients receiving estrogen/progestogen-combination oral contraceptives:
nausea and vomiting, usually the most common adverse reaction occurring in approximately 10% or less of patients during the first cycle.

Other reactions, as a general rule, are seen less frequently or only occasionally:
gastrointestinal symptoms (such as abdominal cramps and bloating); breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; amenorrhea during and after treatment; temporary infertility after discontinuance of treatment; edema; chloasma or melasma which may persist; breast changes: tenderness, enlargement, and secretion; change in weight (increase or decrease); change in cervical erosion and secretion; endocervical hyperplasia; possible dimirution in lactation when given immediately postpartum; cholestatic jaundice; migraine; increase in size of uterine leiomyomata; rash (allergic); mental depression; reduced tolerance to carbohydrates; vaginal candidiasis; premenstrual-like syndrome; intolerance to contact lenses; change in corneal curvature (steepening); cataracts; optic neuritis; retinal thrombosis; changes in libido; chorea; changes in appetite; cystitis-like syndrome; rhinitis; headache; nervousness; dizziness; hirsutism; loss of scalp hair; erythema multiforme; erythema nodosum; hemorrhagic eruption; vaginitis; porphyria; impaired
renal function; Raynaud's phenomenon; auditory disturbances; hemolytic uremic syndrome and pancreatitis.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent use of the following drugs may result in reduced efficacy of Dianofem and increased incidence of breakthrough bleeding:
ampicillin, analgesics, antihistamines, antimigraine preparations, chloramphenicol, griseofulvin, isoniazid, neomycin, nitrofurantoin, penicillin V, phenylbutazone, sulfonamides and tetracycline.
Concurrent use of anticoagulants with estrogen/progestogen combinations may reduce the anticoagulant effect.

Effectiveness of the following drugs may be altered when used concurrently:
antihy pertensives, benzodiazepines (those that undergo oxidative degradation) beta-adrenergic blockers, caffeine, corticosteroids, hypoglycemics, phenothiazines, theophyllines, tricyclic antidepressants and vitamins.

Concurrent use of the following drugs may reduce the efficacy of Dianofem because of accelerated estrogen metabolism caused by the induction of hepatic enzymes:
carbamazepine, phenobarbital, phenytoin, primidone and rifampin.

Diabetics using estrogen/progestogen combinations may require adjustment of their antidiabetic medication.

Concurrent administration of vitamin C (ascorbic acid) with estrogen/progestogen combinations has been reported to result in a significant rise in plasma ethinyl estradiol levels.

4.6 Pregnancy and lactation
Rule out pregnancy before treatment is begun.
Because of the antiandrogenic action of Dianofem, feminization of male fetuses has occurred in animal studies and may possibly occur in humans.

4.7 Effects on ability to drive and use machines
Not Known.

4.8 Undesirable effects
There is an increased risk of thromboembolism for all women who use Dianofem (see section 4.4).
The most serious undesirable effects associated with the use of COCs are listed in s*ection 4.4, Special warnings and precautions for use.*

Other side effects that have been reported in users of Dianofem are:

System Organ Class	Common (≥ 1/100)	Uncommon (≥ 1/1000 and < 1/100)	Rare (≥ 1/10,000 to < 1/1000)	Not known (cannot be estimated from available data)
Vascular Disorders			Thromboembolism	Increase in blood pressure
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, Uticaria	Erythema nodosum, Erythema multiforme	

4.9 Overdose
Symptoms and Treatment: There have been no reports of overdose with Dianofem There are no specific antidotes and treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Sex hormones and modulators of the genital system, antiandrogens and oestrogens.

ATC code: G03HB01

Dianofem blocks androgen-receptors. It also reduces androgen synthesis both by negative feedback effect on the hypothalamo-pituitiary-ovarian systems and by the inhibition of androgen-synthesising enzymes.

Although Dianofem also acts as an oral contraceptive, it is not recommended in women solely for contraception, but should be reserved for those women requiring treatment for the androgen-dependent skin conditions described.

5.2 Pharmacokinetic properties
Cyproterone Acetate
Following oral administration cyproterone acetate is completely absorbed in a wide dose range. The ingestion of Dianofem affects a maximum serum level of 15 ng cyproterone acetate/ml at 1.6 hours. Thereafter, drug serum levels decrease in two disposition phases characterized by half-lives of 0.8 hours and 2.3 days. The total clearance of cyproterone acetate from serum was determined to 3.6 ml/min/kg. Cyproterone acetate is metabolized by various pathways including hydroxylations and conjugations. The main metabolite in human plasma is the 15ß-hydroxy derivative.

Some dose parts are excreted unchanged with bile fluid. Most of the dose is excreted in form of metabolites at a urinary to biliary ratio of 3:7. The renal and biliary excretion was determined to proceed with a half-life of 1.9 days. Metabolites from plasma were eliminated at a similar rate (half-life of 1.7 days).

Cyproterone acetate is almost exclusively bound to plasma albumins. About 3.5 - 4.0 % of total drug levels are present unbound. Because protein binding is non-specific, changes in SHBG (sex hormone binding globulin) levels do not affect the pharmacokinetics of cyproterone acetate.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

Due to the long half-life of the terminal disposition phase from plasma (serum) and the daily intake, cyproterone acetate accumulates during one treatment cycle. Mean maximum drug serum levels increased from 15 ng/ml (day 1) to 21 ng/ml and 24 ng/ml, at the end of treatment cycles 1 and 3, respectively. The area under the concentration versus time profile increased 2.2 fold (end of cycle 1) and 2.4 fold (end of cycle 3). Steady-state conditions were reached after about 10 days. During long-term treatment cyproterone acetate accumulates over treatment cycles by a factor of 2.

The absolute bioavailability of cyproterone acetate is almost complete (88 % of dose). The relative bioavailability of cyproterone acetate from Dianofem was 109 % when compared to an aqueous microcrystalline suspension.

Ethinylestradiol
Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of Dianofem, maximum drug serum levels of about 80 pg/ml are reached at 1.7 hours. Thereafter, ethinylestradiol plasma levels decrease in two phases characterized by half-lives of 1 - 2 hours and about 20 hours. For analytical reasons these parameters can only be calculated for higher dosages.
For ethinylestradiol an apparent volume of distribution of about 5 l/kg and a metabolic clearance rate from plasma of about 5 ml/min/kg were determined.

Ethinylestradiol is highly but non-specifically bound to serum albumin. 2% of drug levels are at present unbound. During absorption and first-liver passage ethinylestradiol is metabolized resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about one day.

Due to the half-life of the terminal disposition phase from plasma and the daily ingestion, steady-state plasma levels are reached after 3 - 4 days and are higher by 30 - 40 % as compared to a single dose. The relative bioavailability (reference: aqueous microcrystalline suspension) of ethinylestradiol from Dianofem was almost complete.

The systemic availability of ethinylestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of vitamin C.

Ethinylestradiol induces the hepatic synthesis of SHBG (sex hormone binding globulin) and CBG (corticoid binding globulin) during continuous use. The extent of SHBG induction, however, is dependent upon the chemical structure and dose of the coadministered progestin. During treatment with Dianofem SHBG concentrations in serum increased from about 100 nmol/l to 300 nmol/l and the serum concentrations of CBG increased from about 50 mcg/ml to 95 mcg/ml.

5.3 Preclinical safety data
Not stated.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

SN	Name of ingredients	Grade	Used as
1.	Povidone (K-30)	BP/Ph. Eur.	Binder
2.	Maize Starch (1500)	BP/Ph. Eur.	Disintegrant
3.	Starch, Pregelatinised	BP/Ph. Eur.	Disintegrant
4.	Lactose Monohydrate	BP/Ph. Eur.	Filler
5.	Silica, Colloidal Anhydrous	BP/Ph. Eur.	Glidant
6.	Magnesium Stearate	BP/Ph. Eur.	Lubricant
7.	Hypromellose	BP/Ph. Eur.	Film Former
8	Titanium Dioxide	BP/Ph. Eur.	Pigment
9	Polyethylene Glycol (6000)	USP-NF	Plasticizer
10	Acetone	BP/Ph. Eur.	Solvent
11	Dichloromethane	BP/Ph. Eur.	Solvent
12	Purified water	BP/Ph. Eur.	Solvent

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

Two (2) years from the date of manufacturing.

6.4 Special precautions for storage

Store in a dry and cool place (below 30°C), away from light and children.

6.5 Nature and contents of container

Alu-PVDC blister pack contains 21 coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Phone : +88-02-48037862-64
Fax : +88-02-9004369
E-mail : plant@renata-ltd.com
Website: www.renata-ltd.com
Plant: Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216**. Corporate Headquarter:** Plot # 1, Milk Vita Road, Section-7, Mirpur, Dhaka-1216, Bangladesh

7.1 NAME AND ADDRESS OF MANUFACTURER

Renata Limited
Plot# 1, Milk Vita Road,
Section –VII, Mirpur,
Dhaka-1216, Bangladesh
Tel: 9031012-3, 9034352
Fax: 880-2-9031956, 9004369

7.2 NAME AND ADDRESS OF PRINCIPAL

Renata Limited
Plot# 1, Milk Vita Road,
Section –VII, Mirpur
Dhaka-1216, Bangladesh
Tel: 9031012-3, 9034352
Fax: 880-2-9031956, 9004369

8. REGISTRATION NUMBER:

002-478-85

9. CATEGORY FOR DISTRIBUTION:

Prescription only medicine

10. DATE OF PUBLICATION OF THIS PACKAGE INSERT:

November, 2023