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

CESTEL 30

1. Generic Name:

Dienogest and Ethinylestradiol Tablets

2. Qualitative and quantitative composition:

Each film-coated tablet contains:
Dienogest I.P. …..2 mg
Ethinylestradiol I.P. …30 mcg
Excipients…….q.s.
Colours: Titanium Dioxide I.P.
The excipients used are Mannitol, Starch, Microcrystalline Cellulose, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate, Talcum, Crospovidone, Super coat, Titanium Dioxide, Isopropyl Alcohol and Methylene Chloride.

3. Dosage form and strength:

Dosage form: Film coated tablet
Strength: Dienogest and Ethinylestradiol: 2 mg and 30 mcg

4. Clinical particulars:

4.1 Therapeutic indication:

It is indicated for use as an oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception.

4.2 Posology and method of administration:

Posology

Dienogest and Ethinylestradiol tablet must be taken orally.

The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. Bleeding usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

4.3 Contraindications:

Combined oral contraceptive (COCs) including Dienogest/Ethinylestradiol combination, should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product should be stopped immediately.

Presence or risk of venous thromboembolism (VTE)

- Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE].
- Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
- Major surgery with prolonged immobilisation.
- A high risk of venous thromboembolism due to the presence of multiple risk factors.

Presence or risk of arterial thromboembolism (ATE)

- Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA]).
- Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipinantibodies and lupus anticoagulant).
- History of migraine with focal neurological symptoms.
- A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms.
    - severe hypertension.
    - severe dyslipoproteinaemia.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the ingredients contained in Dienogest and Ethinylestradiol tablet.

4.4 Special warnings and precautions for use:

If any of the conditions/risk factors mentioned below are present, the benefits of Dienogest/Ethinylestradiol combination use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it.

Circulatory disorders

Reported epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing Ethinylestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Based on the new data it can be assumed that the VTE risk in OC users is roughly twice as high as for non- pregnant non OC users. The absolute attributable risk (approximately 4 VTEs per 10,000 WY of use) was found to be slightly higher in these studies than reported in the past.

It is important that women understand that VTE associated with CHC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with CHC use.

An additional increase in VTE risk for CHCs containing ≥ 50 μg Ethinylestradiol cannot be

excluded.

VTE may be life-threatening or may have a fatal outcome (in 1-2% of cases).

Extremely rarely, thrombosis has been reported to occur in CHG users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors.

Dinoges/Ethinylestradiot combination is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors- in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m^2). Risk increases substantially as BMI rises.
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
- Other medical conditions associated with VTE include:
  - Cancer
  - Systemic lupus erythematosus
  - Haemolytic uraemic syndrome
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
  - Sickle cell disease
- Increasing age, particularly above 35 years.
- Smoking.

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism {e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. Dienogest/Ethinylestradiol combination is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis.

Risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at

relatively early age e.g. below 50).

- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
  - o Diabetes mellitus
  - o Hyperhomocysteinaemia
  - o Valvular heart disease
  - o Atrial fibrillation
  - o Dystipoproteinaemia
  - o Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHG. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some reported 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.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare.

In women with hereditary angiooedema exogenous estrogens may induce or exacerbate symptoms of angiooedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers 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.

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.

Sexually transmitted infections (ST1s) including Human Immunodeficiency Virus (HIV) infections and AIDS

Dienogest/Ethinylestradiol combination is intended to prevent pregnancy. It does not protect against STIs including HIV infections (AIDS). The woman should be advised that additional

barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced efficacy

The efficacy of COCs may be reduced in the event of missed tablets, vomiting, diarrhoea or concomitant medication.

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

4.5 Drug-Interaction:

Effect of other medicines on Dienogest/Ethinylestradiol combination

Interactions can occur with medicines that induce microsomal enzymes which can result in Increased clearance of sex hormones and which may lead to breakthrough bleeding_and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Women prescribed any of these medicines should temporarily -use a barrier method in addition to the COC, or choose another method of contraception." The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

Substances Increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, fetbamate, griseofulvin and products containing St. John's Wort.

Substances with variable effects on the clearance of COCs, e.g.

When co-administered with COCs, many HIV/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of CO Cs (enzyme Inhibitors)

Dienogest is a substrate of cytochrome P450 (CYP) 3A4.

Strong and moderate CYP 3A4 inhibitors like azole antifungals (e.g. ketoconazole itraconazole, voriconazole, fluconazole), cimetidine, verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem, antidepressants and grapefruit juice may increase Plasma levels of the estrogen or progestogen or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol by 1.4 to 1.6-fotd respectively, when taken concomitantly with a COC containing 35µg ethinylestradiol.

Effects of Dienogest/Ethinylestradiol combination on other medication

Oral contraceptives may affect the metabolism of certain other medicines. Accordingly, plasma

and tissue concentrations may increase (e.g. cyclosporin)ordecrease (e .g. lamotrigine).

ln clinical studies, administration of a hormonal contraceptive containing ethinylestradiol lead to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g theophylline) to moderate (e.g. melatonin, tizanidine) increase of CYP1 A2 substrates.

Pharmacodynamic Interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these has been shown to be associated with increases in alanine aminotransferase (ALT) levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women.

4.6 Use in special populations

Pregnancy: Pregnancy Category B3

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Dienogest/Ethinylestradiol combination is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of Dienogest/Ethinylestradiol combination. Dienogest/Ethinylestradiol combination must be discontinued immediately.

Nursing Mothers

Oienogest is excreted into rat milk. Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or metabolites may be excreted with the milk. Therefore, the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

Pediatric Use(< 18 years of age)

DinogesVEthinylestradiol combination is only indicated after menarche.

Geriatric Use(> 65years of age)

DinogesVEthinylestradiol combination is not indicated after menopause.

Hepatic Impairment

Dienogest/Ethinylestradiol combination is contraindicated in women with severe hepatic diseases whilst liver function values have not returned to normal.

Renal impairment

Dienogest/Ethinylestradiol combination has not been specifically studied in renally impaired patients.

Effect on laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g. corticosteroid binding, globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.7 Effects on ability to drive and use machines:

No information available.

4.8 Undesirable effects:

In Study for Contraception, Adverse events (whether attributable to the medication or not) reported at a frequency of ≥ 1% of the events occurred with Dienogest/Ethinylestradiol combination are listed below.

Adverse Effect	% Of Adverse Effect
Skin and appendage disorders	
Acne	3.90
Alopecia	1.39
Peripheral nervous system	
Headache	8.1
Migraine	1.49
Psychiatric system	
Depressive moods	1.2
Gastrointestinal system disorders	
Nausea /vomiting	2.1
Enteritis	1.39
Cardiovascular disorders	
Hypertension	1.11
Hypotension	1.95
Respiratory system disorders	
Bronchitis	4.36
Pharyngitis	5.48
Rhinitis	1.86
Sinusitis	1.76
Urinary system disorders	
Cystitis	2.32
Urinary tract infection	1.49
Reproductive system	
Breast tenderness	5.4
Dysmenorrhoea	1.02
Leukorrhoea	1.21
Salpingitis	1.58
Vaginitis	3.62
Neoplasm	
Ovarian cyst	1.39
Body as a whole	
Reduced libido	1.1
Allergy	2.51
Back pain	1.21
Influenza-like symptoms	16.16
Resistance mechanism disorders	
Fungal infection	2.32
Moniliasis	1.95

In Study for acne, Adverse events (whether attributable to the medication or not) reported at a frequency of ≥1 % of the events occurred with Dienogest/Ethinylestradiol combination are listed below.

Adverse Reaction	Ethinylestradiol Combination % of Patients	Placebo% of Patients
Gastrointestinal disorders		
Nausea	4.2 %	2.7 %
Vomiting	3.0 %	1.9 %
Diarrhoea	1.3 %	2.3 %
Infections and infestations		
Influenza	2.1 %	1.1 %
Nasopharyngitis	1.7 %	3.0 %
Respiratory tract infection viral	1.5 %	1.1 %
Nervous system disorders		
Headache	5.3 %	5.3 %
Reproductive system and breast disorders		
Breast pain	2.1 %	0.0 %
Metrorrhagia	2.1 %	0.0 %
Breast tenderness	1.5 %	0.8 %

Post-marketing data

The following undesirable effects have been reported in users of Dienogest/Ethinylestradiol combination or other COCs and the association has been neither confirmed nor refuted.

Cardiovascular: deep venous thrombosis, pulmonary embolism, cerebral infarction, thrombosis, migraine, stroke, occlusion retinal artery, hepatic haemangioma, superficial thromophlebitis, hypertension, peripheral vascular disease.

Genital tract: intermenstrual bleeding (consisting of vaginal haemorrhage and metrorrhagia), menstrual disorders, vaginal mycosis.

Digestive: nausea, vomiting, diarrhoea, cholelithiasis, liver neoplasm, fatty liver, pancreatitis, hepatitis, hepatic cyst, decreased cholinesterase, gingivitis and abdominal pain (including upper and lower abdominal pain, abdominal discomfort/distention).

Nervous system: depression, mood altered, headache, migraine, galactorrhoea, paresthesia and changes in libido.

Musculoskeletal: articular swelling

Respiratory tract: voice alteration, dyspnoea, asthma.

Skin: dermatitis, rash, urtticaria, erythema nodosum, erythema multiforme, atopic eczema (exacerbation), papulous exanthema, chloasma.

Eyes: contact lens intolerance, blurred vision.

Metabolic: hypertriglyceridemia, oedema, change in weight, fluid retention.

Haemic and lymphatic: haemorrhagicpurpura, leucopoenia.

Body as a Whole: anaphylactic reaction, pain in extremities.

Breast disorders: breast pain (including breast discomfort and breast tenderness), hypertrophy breast and breast discharge.

Immune system disorders: hypersensitivity.

Special senses: acute deafness

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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.

4.9 Overdose:

No information available.

5. Pharmacological properties:

5.1 Mechanism of Action:

The contraceptive effect of combined oral contraceptives (COCs) is based on the interaction of various factors. The primary mechanisms are inhibition of ovulation (by suppression of gonadotrophins) and changes in the cervical secretion (blocking the entry of sperm into the uterus).

5.2 Pharmacodynamic properties:

For the majority of users, the cycle is more regular, the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Dienogest has beneficial properties in addition to contraception. Dienogest exerts antiandrogenic activity leading to a positive effect on the skin and to a reduction in acne lesions and sebum production.

In addition, with the higher-dosed COCs (50 µg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer.

5.3 Pharmacokinetic properties:

Bioavaitability studies have been conducted with Dienogest/Ethinylestradiol combination.

Dienogest

Absorption

After single oral administration of 2 mg dienogest in combination with 30 µg ethinylestradiol, dienogest is absorbed rapidly are almost completely. Maximum plasma concentrations of 51.6 ± 9.5 ng/ml are reached in 2.4 ± 1.4 hours after single dose oral administration. A high absolute bioavailability of about 96% was demonstrated in a bioavailability study.

Distribution

10% is present in plasma in free form, whilst approx. 90% is bound non-specifically to albumin. dienogest does not bind to the specific transport proteins, sex hormone-binding globulin (SHBG)

and corticosteroid-binding globulin (CBG).

Metabolism

Dienogest is metabolised mainly by hydroxylation but also by hydrogenation, conjugation and aromatisation, to endocrinologically largely inactive metabolites. The contribution of the metabolites to the pharmacological and toxicological effects of dienogest is insignificant.

Excretion

After an oral dose of 0.1 mg/kg body weight, the ratio of renal to faecal excretion is 3.2. The total clearance is 3.66 ± 0.71 L/h after a single dose.

Half-Life: The half-life of dienogest is 9.3 ± 1.8 hours, which is relatively short compared to other progestogens. There is thus very little accumulation with daily administration.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly in the small intestine. 50-60% of it is converted primarily to sulphate metabolites in the wall of the small intestine and in the liver (first-pass effect). After administration of the ethinylestradiol-dienogest combination, the absolute bioavailability of ethinylestradio is about 44 %.

After a sing le administration of 30 μg ethinylestradiol and 2 mg dienogest, maximum plasma concentrations are reached after 1.5 to 4 hours.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5 %), and induces an increase in the serum concentrations of SHBG.

Metabolism

Ethinytestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulphate. The metabolic clearance rate of ethinylestradiol is about 5 mUmin/kg.

Excretion

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted 30-50% via the kidneys, with 30-40% being excreted with the faeces.

Half-Life: Serum ethinylestradiol levels decrease in two phases, with an elimination half-life of 11.7 ± 6.5 hours following single administration of 30 μg ethinylestradiol and 2 mg dienogest.

6. Nonclinical properties:

6.1 Animal Toxicology or Pharmacology

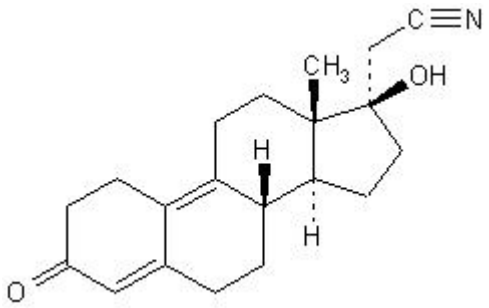
No information available.

7. Description:

Dienogest

Dienogest is 2-[(8S, 13S, 14S, 17R)-17-hydroxy-13-methyl-3-oxo-1,2,6,7,8,11,12,14,15,16-decahydrocyclopentaphenanthren-17-yl]acetonitrile.

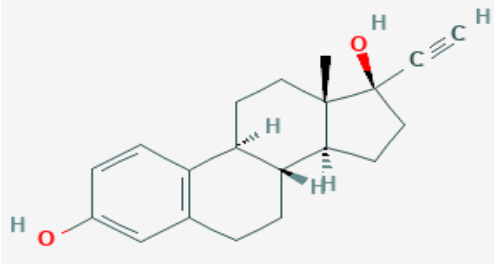
The molecular weight is 311.4 and empirical formula is $C_{20}H_{25}NO_2$. The chemical structure is as below:



Dienogest is off-white to slightly yellow powder. It is slightly soluble in dichloromethane and practically insoluble in water.

Ethinylestradiol

Ethinylestradiol is chemically 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17β-diol. The molecular weight is 296.4 and empirical formula is $C_{20}H_{24}O_2$. The chemical structure is as below:



Ethinylestradiol is a white or slightly yellowish-white, crystalline powder which is freely soluble in ethanol 95% and in ether; sparingly soluble in chloroform; practically insoluble in water.

Dienogest and Ethinylestradiol Tablets are white coloured, round, biconvex, film coated tablets, plain on both sides. The excipients used are Mannitol, Strach, Microcrystalline Cellulose, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate, Talcum, Crospovidone, Super coat, Titanium Dioxide, Isopropyl Alcohol and Methylene Chloride.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

Not applicable.

8.2 Shelf-life:

Do not use later than the date of expiry.

8.3 Packaging information:

CESTEL 30 is packed in blister strips of 21 tablets.

8.4 Storage and handing instructions:

Store protected from light and moisture at a temperature not exceeding 30ºC.
Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user
CESTEL 30
Dienogest and Ethinylestradiol Tablets

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 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. See section 4.

What is in this leaflet?

9.1. What CESTEL 30 is and what it is used for

CESTEL 30 contains the active substance Dienogest and Ethinylestradiol.

It is used as an oral contraceptive and in the treatment of mild to moderate acne in women who seek oral contraception.

9.2. What you need to know before you take CESTEL 30

The CESTEL 30 tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack.

Do not take CESTEL if:

- there is presence of current venous thromboembolism (VTE) (on anticoagulants) or history of deep venous thrombosis (DVT) or pulmonary embolism (PE).
- there is presence of current arterial thromboembolism (ATE) or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or
- transient ischaemic attack [TIA]).
- you have known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
- you have known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipinantibodies and lupus anticoagulant).
- you have undergone any major surgery with prolonged immobilisation.
- you are at a high risk of venous thromboembolism due to the presence of multiple risk factors.
- you have history of migraine with focal neurological symptoms.
- you are at a high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk
- factor such as:

  • diabetes mellitus with vascular symptoms.

• severe hypertension.

• severe dyslipoproteinaemia.

- you have pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- there is presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- you have used direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these.
- there is presence or history of liver tumours (benign or malignant).
- there is known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- you have undiagnosed vaginal bleeding.
- you are pregnant or suspected to be pregnant.
- you have hypersensitivity to any of the ingredients contained in CESTEL tablet.

Warnings and precautions

Talk to your doctor before taking CESTEL if:

- you are suffering from circulatory disorders such as such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism.
- you are at a risk of venous thromboembolism (VTE). Risk factors for VTE are as follows:
    - Obesity (body mass index over 30 kg/m1). Risk increases substantially as BMI rises. Prolonged immobilisation. major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.
    - Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.
    - Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).
    - Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
    - Other medical conditions associated with VTE include:
        - Cancer
        - Systemic lupus erythematosus
        - Haemolytic uraemic syndrome
        - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
        - Sickle cell disease
    - Increasing age, particularly above 35 years.
    - Smoking.
- you are at a risk of arterial thromboembolism (ATE). Risk factors for ATE are as follows:

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include:
- hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant)
- Migraine
- Other medical conditions associated with adverse vascular events:
    - Diabetes mellitus
    - Hyperhomocysteinaemia
    - Valvular heart disease
    - Atrial fibrillation
    - Dystipoproteinaemia
    - Systemic lupus erythematosus

- in case of presence or history of liver tumours (benign or malignant).
- you have hypertriglyceridaemia or have a family history of it because you may be at an increased risk of pancreatitis when taking CESTEL.
- there is hereditary angioedema as exogenous estrogens may induce or exacerbate symptoms of angiooedema.
- you have acute or chronic disturbances of liver function.

Pregnancy and breast-feeding

Pregnancy

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used Combined oral contraceptive (COCs) prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

Dienogest/Ethinylestradiol combination is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of Dienogest/Ethinylestradiol combination. Dienogest/Ethinylestradiol combination must be discontinued immediately.

Breast feeding

Dienogest is excreted into rat milk. Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or metabolites may be excreted with the milk. Therefore, the use of COCs should

generally not be recommended until the nursing mother has completely weaned her child.

9.3. How to take CESTEL 30

CESTEL 30 tablet must be taken orally.

How much to take

One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7-day tablet-free interval, during which time a withdrawal bleed usually occurs. Bleeding usually starts on day 2-3 after the last tablet and may not have finished before the next pack is started.

9.4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following undesirable effects have been reported in users of DinogesVEthinylestradiol combination or other COCs and the association has been neither confirmed nor refuted.

Cardiovascular: deep venous thrombosis, pulmonary embolism, cerebral infarction, thrombosis, migraine, stroke, occlusion retinal artery, hepatic haemangioma, superficial thromophlebitis, hypertension, peripheral vascular disease.

Genital tract: intermenstrual bleeding (consisting of vaginal haemorrhage and metrorrhagia), menstrual disorders, vaginal mycosis.

Digestive: nausea, vomiting, diarrhoea, cholelithiasis, liver neoplasm, fatty liver, pancreatitis, hepatitis, hepatic cyst, decreased cholinesterase, gingivitis and abdominal pain (including upper and lower abdominal pain, abdominal discomfort/distention).

Nervous system: depression, mood altered, headache, migraine, galactorrhoea, paresthesia and changes in libido.

Musculoskeletal: articular swelling

Respiratory tract: voice alteration, dyspnoea, asthma.

Skin: dermatitis, rash, urtticaria, erythema nodosum, erythema multiforme, atopic eczema (exacerbation), papulous exanthema, chloasma.

Eyes: contact lens intolerance, blurred vision.

Metabolic: hypertriglyceridemia, oedema, change in weight, fluid retention.

Haemic and lymphatic: haemorrhagicpurpura, leucopoenia.

Body as a Whole: anaphylactic reaction, pain in extremities.

Breast disorders: breast pain (including breast discomfort and breast tenderness), hypertrophy breast and breast discharge.

Immune system disorders: hypersensitivity.

Special senses: acute deafness

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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

9.5. How to store CESTEL 30

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep the medicine out of reach of children.

9.6. Contents of the pack and other information

What CESTEL 30 contains

The active substance is Dienogest and Ethinylestradiol.

The other ingredients are

Mannitol, Starch, Microcrystalline Cellulose, Low substituted Hydroxypropyl Cellulose, Magnesium Stearate, Talcum, Crospovidone, Super coat, Titanium Dioxide, Isopropyl Alcohol and Methylene Chloride.
Colours: Titanium Dioxide I.P.

10. Details of manufacturer

Manufactured in India by:
Synokem Pharmaceuticals Ltd.
Plot No. 56-57, Sector 6A, I.I.E (SIDCUL),
Ranipur (BHEL), Hardiwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No. 27/UA/SC/P-2018 issued on 05.07.2019

12. Date of revision

Not applicable

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TORRENT PHARMACEUTICALS LTD.
IN/CESTEL 2mg, 30 mcg/SEP-20/01/PI