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

DROSPERT

1. Generic Name:

Drospirenone Tablets 4 mg with Inert Tablets

2. Qualitative and quantitative composition:

28 film coated tablets
For Oral Use
(A) 24 white colour tablets
Each film coated tablet contains:
Drospirenone I.P. ……4mg
Excipients…….q.s.
Colour: Titanium Dioxide I.P.
(B) 4 green colour film coated tablets:
(Inert Tablets)
Each film coated inert tablet contains:
These tablets do not contain active substance
Excipients…….q.s.
Colours: Brilliant Blue Lake, Yellow Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Starch, Lactose, Microcrystalline Cellulose, PVP K-30, Isopropyl Alcohol, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, Titanium Dioxide and Methylene Dichloride.Each Film coated tablet contains:

3. Dosage form and strength:

Dosage form: Film coated tablet

Strength: Drospirenone 4 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Drospirenone is a Progestin intended for its use by females of reproductive potentials to prevent pregnancy.

4.2 Posology and method of administration:

Drospirenone is dispensed in a blister card. Drospirenone should be started using a Day 1 start.

4.3 Contraindications:

Drospirenone is contraindicated in females with the following conditions:

- Renal impairment
- Adrenal insufficiency
- Presence or history of cervical cancer or progestin sensitive cancers.
- Liver tumors, benign or malignant, or hepatic impairment.
- Undiagnosed abnormal uterine bleeding.

The combination of DROSPERT with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.

4.4 Special warnings and precautions for use:

Hyperkalemia

Drospirenone, a progestin, which has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk females, comparable to a 25 mg dose of spironolactone. Drospirenone is contraindicated in females with conditions that predispose to hyperkalemia (e.g. renal impairment, hepatic impairment, and adrenal insufficiency). Females receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration should have their serum potassium concentration checked prior to starting treatment and during the first treatment cycle. Consider monitoring serum potassium concentration in females at increased risk for hyperkalemia i.e., those females who take a strong CYP3A4 inhibitor long-term and concomitantly with Drospirenone. Strong CYP3A4 inhibitors include azole antifungals (e.g. ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (e.g., indinavir, boceprevir), and clarithromycin. Monitor females taking Drospirenone who later develop medical conditions and/or begin medication that put them at an increased risk for hyperkalemia.

Most females with hyperkalemia in the clinical development studies of Drospirenone had mild potassium elevations and/or isolated increases that returned to normal while still on study medication. No concurrent adverse reactions were attributed to hyperkalemia. In the pivotal trial, two females (0.2%) with persistent potassium elevations discontinued Drospirenone.

Thromboembolic Disorders

Epidemiological studies have not indicated an association between progestin-only preparations and an increased risk of myocardial infarction, cerebral thromboembolism, or venous thromboembolism.

Combined oral contraceptives containing Drospirenone and ethinyl estradiol may be associated with a higher risk of venous thromboembolism (VTE) than those containing some other progestins in combination with ethinyl estradiol. It is unknown whether the risk of VTE is increased with Drospirenone alone; however, if there is a risk, it is expected to be lower than that of Drospirenone in combination with ethinyl estradiol.

When prescribing Drospirenone, consider the increased risk of thromboembolism inherent in the postpartum period and in females with a history of thromboembolism

Discontinue Drospirenone if arterial or venous thromboembolic events occur. Consider discontinuing Drospirenone, if feasible, in case of Drospirenone prolonged immobilization due to surgery or illness.

Bone Loss

Treatment with Drospirenone leads to decreased estradiol serum levels. It is unknown if this may cause a clinically relevant loss of bone mineral density.

Cervical Cancer

Some studies suggest that use of combination hormonal contraceptives containing progestin and estradiol has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

Liver Disease

Discontinue Drospirenone if jaundice or acute or chronic disturbances of liver function

develop. Do not resume use until markers of liver function return to normal and Drospirenone causation has been excluded.

Drospirenone is contraindicated in females with liver tumors, benign or malignant, or hepatic impairment.

Ectopic Pregnancy
Be alert to the possibility of ectopic pregnancy in females who become pregnant or complain of lower abdominal pain while on Drospirenone.

Risk of Hyperglycemia in Patients with Diabetes
Some patients receiving progestins, including Drospirenone, may exhibit a decrease in insulin sensitivity. Therefore, patients with diabetes may be at greater risk of hyperglycemia and may require additional medication adjustments or monitoring.

Bleeding Irregularities and Amenorrhea
Females using Drospirenone may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy. Based on subject diaries from four clinical trials of Drospirenone, 64.4% of females experienced unscheduled bleeding at Cycle 1. This percentage decreased to 40.3% by cycle 13.
A total of 91 out of 2593 subjects (0.4%) discontinued Drospirenone due to menstrual bleeding disorders including metrorrhagia, menstrual irregular, vaginal hemorrhage, menorrhagia, uterine hemorrhage, and amenorrhea.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have, consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

Depression
Carefully observe females for a history of depression and discontinue Drospirenone if depression recurs to a serious degree. Data on the association of progestin-only contraceptive products with onset of depression and exacerbation of depression are limited.

4.5 Drug-Interaction:

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Hormonal Contraceptives

Substances decreasing the systemic concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the systemic concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.

Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, rifabutin, rufinamide, aprepitant, and products containing St. John's wort.

Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel females to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the systemic concentrations of hormonal contraceptives (HCs):

In a clinical drug-drug interaction study conducted in premenopausal females, once daily

co-administration of DRSP 3 mg/ethinyl estradiol (EE) 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure.

Influence of Drospirenone on other Medicinal Products

Based on in vitro studies and in vivo interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone with the metabolism of other active substances is unlikely.

Potential to increase serum potassium concentration:

There is a potential for an increase in serum potassium concentration in females taking Drospirenone with other drugs that may increase serum potassium concentration (for example, ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS

4.6 Use in special populations

Pregnancy

Risk Summary

Based on epidemiologic studies and meta-analyses, there is little or no increased risk of birth defects in the children of females who inadvertently use oral progestins during early pregnancy.

Discontinue Drospirenone if pregnancy occurs, because there is no reason to use hormonal contraceptives during pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Data

Human Data

Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following maternal use of oral progestins before conception or during early pregnancy.

Lactation

Risk Summary

Negligible amounts of Drospirenone are excreted in the breast milk [see Data]. Thus, at therapeutic doses of Drospirenone, no effects on breastfed newborns/infants are anticipated. In general, no adverse effects have been found on milk production or on the health growth, or development of the infant with use of POPs.

Human Data

After daily administration of 4 mg Drospirenone tablets, the average DRSP concentration in breast milk over 24-hour period is 5.6 ng/mL. Based on this concentration, the estimated average infant daily dosages for an exclusively breastfed infant is 840 ng/kg/day (relative infant dose is 1.5%).

Pediatric Use

Safety and efficacy of Drospirenone have been established in females of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and users 16 years and older.

Study CF111/304 evaluated the bleeding associated with Drospirenone in females ≥12 years of age. Bleeding data were generally consistent with those from Study CF111/303 in adult females.

Use of this product before menarche is not indicated.

Geriatric Use

Drospirenone has not been studied in postmenopausal females and is not indicated in this population.

Hepatic Impairment

Drospirenone is contraindicated in females with hepatic impairment. The mean exposure to Drospirenone (DRSP) in females with moderate liver impairment is approximately three times higher than the exposure in females with normal liver function. Drospirenone has not been studied in females with severe hepatic impairment.

Renal Impairment

Drospirenone is contraindicated in females with renal impairment.

4.7 Effects on ability to drive and use machines:

No data are available for effects on ability to drive and use machines.

4.8 Undesirable effects:

The following are clinically significant adverse reactions:

- Hyperkalemia
- Bleeding Irregularities and Amenorrhea
- weakness or numbness in an arm or leg o palpitations (feel like your heart is racing or fluttering) or irregular heartbeat
- nausea
- vomiting o severe pain in your chest
- shortness of breath
- Blood clot forming in blood vessels (thromboembolism problems)
- leg pain that will not go away
- a sudden, severe headache unlike your usual headaches
- sudden, severe shortness of breath
- sudden change in vision or blindness o chest pain

- weakness or numbness in your arm or leg
- trouble speaking
- Bone loss.
- Cervical cancer
- Ectopic pregnancy (pregnancy in your tubes)
- Risk of high blood sugar levels in people with diabetes
- Changes in menstrual bleeding
- Depression, especially if you have had depression in the past
- acne
- menstrual cramps
- headache
- nausea
- breast pain and tenderness
- severe vaginal bleeding
- weight gain
- less sexual desire

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:

There have been no reports of effects from overdosage of Drospirenone. Symptoms that may occur include are nausea, vomiting, and vaginal bleeding. There are no antidotes and treatment should be to provide symptomatic support.

Drospirenone is a spironolactone analogue which has antimineralocorticoid properties. Therefore, serum potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

5. Pharmacological properties:

5.1 Mechanism of Action:

Drospirenone progestin-only oral contraceptive lowers the risk of becoming pregnant primarily by suppressing ovulation.

5.2 Pharmacodynamic properties:

Drospirenone is a spironolactone analogue with anti-mineralocorticoid activity.

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, serum levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis.

5.3 Pharmacokinetic properties:

Absorption

The pharmacokinetics of oral drospirenone is dose-proportional following single doses ranging from 1-10 mg. Maximum concentrations (Cmax) of drospirenone in plasma of about 27 ng/ml are reached at about 2-6 hours after single ingestion of Drospirenone. During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 41 ng/ml are reached after about 10 days of treatment. Plasma drospirenone Cmax and area under the curve (AUC) accumulate by a factor of about 1.5 to 2 following multiple dose administration of Drospirenone. Concomitant ingestion of food has no influence on the extent of absorption of drospirenone.

Distribution

Drospirenone is 95% to 97% bound to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG). The apparent volume of distribution of drospirenone is approximately 4 L/kg.

Elimination

Metabolism

Drospirenone is extensively metabolized after oral administration. The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active.

Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

Excretion

DRSP serum concentrations are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces.

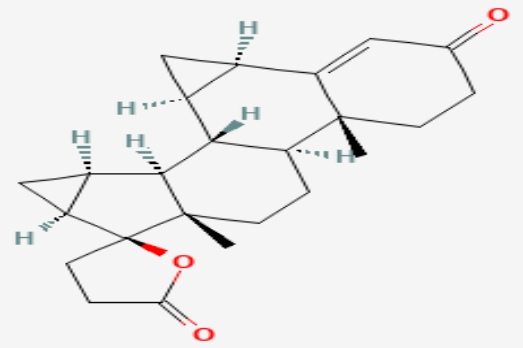
6. Nonclinical properties:

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a reported 24-month oral carcinogenicity study in mice with doses up to 10 mg/kg/day DRSP, equating to 2 times the maximum clinical exposure (based on AUC), there was an increase in carcinomas of the harderian gland in the high dose DRSP group. In a similar study in rats given doses up to 10 mg/kg/day DRSP, 10 times the maximum clinical exposure (based on AUC), there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the high dose DRSP group. Mutagenesis studies for DRSP were conducted in vivo and in vitro and no evidence of mutagenic activity was observed.

7. Description:

Drospirenone is (1R,2R,4R,10R,11S,14S,15S,16S,18S,19S)-10,14-dimethylspiro[hexacyclo[9.8.0.0^{2,4}.0^{5,10}.0^{14,19}.0^{16,18}]nonadec-5-ene-15,5'-oxolane]-2',7-dione having molecular weight of 366.5 and empirical formula of $C_{24}H_{30}O_3$ and the chemical structure is:



Drospirenone Tablets 4 are White to off White coloured, round, biconvex, film coated tablets, plain on both sides. The excipients used are Starch, Lactose, Microcrystalline Cellulose, PVP K-30, Isopropyl Alcohol, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, Titanium Dioxide and Methylene Dichloride.

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:

DROSPERT is available in Blister strip of 28 tablets (24 active tablets + 4 inert tablets)

8.4 Storage and handing instructions:

Store below 30°C. Protect from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

DROSPERT
DrospirenoneTablets

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.

What is in this leaflet?

9.1 What DROSPERT is and what it is used for

9.2 What you need to know before you take DROSPERT

9.3 How to take DROSPERT

9.4 Possible side effects

9.5 How to store DROSPERT

9.6 Contents of the pack and other information

9.1 What DROSPERT is and what it is used for

DROSPERT is a birth control pill (oral contraceptive) also called a POP (progestin only pill) that is used by females who can become pregnant to prevent pregnancy.

The progestin drospirenone may increase potassium levels in your blood. You should not take DROSPERT if you have kidney, liver or adrenal disease because this could cause serious heart problems as well as other health problems. Other medicines may also increase potassium levels in your blood. If you are currently on daily, long-term treatment for a chronic health condition with any of the medicines listed below, talk to your healthcare provider about whether DROSPERT is right for you. If you take any of the medicines listed below for a chronic health condition you should have a blood test to check the potassium level in your blood before you start taking DROSPERT and during the first month that you take DROSPERT.

- medicines to treat fungal infections, such as ketoconazole, itraconazole, or voriconazole
- medicines to treat Human Immunodeficiency Virus (HIV) infection or Hepatitis C infection, such as indinavir or boceprevir
- clarithromycin

9.2 What you need to know before you take DROSPERT

Do not take DROSPERT if you:

- have kidney disease or kidney failure.
- have reduced adrenal gland function (adrenal insufficiency).
- have or have had cervical cancer or any cancer that is sensitive to female hormones.
- have liver disease, including liver tumors.
- have unexplained vaginal bleeding.
- Tell your healthcare provider if you have or have had any of these conditions. Your healthcare provider can suggest a different method of birth control.

If any of these conditions happen while you are taking DROSPERT, stop taking DROSPERT right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking DROSPERT.

Before you take DROSPERT, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or think you may be pregnant.
- have ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism) or a stroke or heart attack (myocardial infarction).
- have or have had depression

Tell your healthcare provider about all the medicine you take including prescription and over-the-counter medicines, vitamins and herbal supplements, such as St. John's Wort.

DROSPERT may affect the way other medicines work, and other medicines may affect how well DROSPERT works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

9.3 How to take DROSPERT

Drospirenone (white active and Brilliant Blue inert (Placebo) tablets) is swallowed whole once a day. Take one tablet daily for 28 consecutive days; one white active tablet daily during the first 24 days and one brilliant blue inert (Placebo) tablet daily during the 4 following days. Tablets must be taken every day at about the same time of the day so that the interval between two tablets is always 24 hours.

9.4 Possible side effects

DROSPERT may cause serious side effects, including:

- **High potassium levels in your blood (hyperkalemia).** Certain medicines and conditions can also increase the potassium levels in your blood. Your healthcare provider may check the potassium levels in your blood before and during treatment with DROSPERT**. Call you healthcare provider or go to a hospital emergency room right away if you have signs or symptoms of high potassium levels in your blood including:**
  - weakness or numbness in an arm or leg o palpitations (feel like your heart is racing or fluttering) or irregular heartbeat
  - nausea
  - vomiting o severe pain in your chest
  - shortness of breath.
- **Blood clot forming in blood vessels (thromboembolism problems).** Tell your healthcare provider if you have had a blood clot. Tell your healthcare provider if you plan to have surgery or are not able to be active due to illness or injury. **Call your healthcare provider or go to a hospital emergency room right away if you have:**
  - leg pain that will not go away
  - a sudden, severe headache unlike your usual headaches
  - sudden, severe shortness of breath
  - sudden change in vision or blindness o chest pain
  - weakness or numbness in your arm or leg
  - trouble speaking
- **Bone loss.** It is not known if the decrease in a sex hormone that happens with DROSPERT can result in decreased bone density (bone loss).
- **Cervical cancer.** See “Do birth control pills cause cancer?”
- Liver problems, including rare liver tumors. Call your healthcare provider right away if you have yellowing of your skin or eyes.
- **Ectopic pregnancy (pregnancy in your tubes).** If you get pregnant while using DROSPERT, you might have an ectopic pregnancy. That means that the pregnancy is not in the uterus. Ectopic pregnancy is a medical emergency that often requires surgery. If you have severe abdominal (belly) pain, call your healthcare provider or go to a hospital emergency room right away.
- **Risk of high blood sugar levels in people with diabetes.** If you have diabetes, you may need to monitor your blood sugar level more often or adjust your diabetes medicine.
- **Changes in menstrual bleeding.** Irregular vaginal bleeding, especially between menstrual periods, and irregular periods or the absence of menstrual periods are common side effects of DROSPERT, but can sometimes be serious. Tell your healthcare provider if you have any of these changes in menstrual bleeding.
- **Depression, especially if you have had depression in the past.** Call your healthcare provider immediately if you have any thoughts of harming yourself

What are the most common side effects of DROSPERT?

The most common side effects of DROSPERT include: •

- acne
- menstrual cramps
- headache
- nausea
- breast pain and tenderness
- severe vaginal bleeding
- weight gain
- less sexual desire

These are not all the possible side effects of DROSPERT. Call your doctor for medical advice about side effects.

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 DROSPERT

Store below 30°C. Protect from light and moisture.

9.6 Contents of the pack and other information

What DROSPERTcontains

28 film coated tablets
For Oral Use
(A) 24 white colour tablets
Each film coated tablet contains:
Drospirenone I.P. ……4mg
Excipients…….q.s.
Colour: Titanium Dioxide I.P.
(B) 4 green colour film coated tablets:
(Inert Tablets)
Each film coated inert tablet contains:
These tablets do not contain active substance
Excipients…….q.s.
Colours: Brilliant Blue Lake, Yellow Oxide of Iron & Titanium Dioxide I.P.

The excipients used are Starch, Lactose, Microcrystalline Cellulose, PVP K-30, Isopropyl Alcohol, Crospovidone, Colloidal Silicon Dioxide, Magnesium Stearate, Supercoat White-F, Titanium Dioxide and Methylene Dichloride.

DROSPERT is available in Blister strip of 28 tablets (24 active tablets + 4 inert tablets)

10. Details of manufacturer

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

11. Details of permission or licence number with date

Mfg Lic No 27/UA/SC/P-2018 issued on 13.08.2021

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/DROSPERT 4 mg/OCT-21/01/PI