CRISANTA Tablets (Drospirenone + Ethinylestradiol)

For the use of a Registered Medical Practitioner only

Black Box Warning

Cigarette Smoking and Serious Cardiovascular Events Women over 35 years old who smoke should not use Drospirenone and Ethinylestradiol. Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke.

Qualitative and Quantitative Composition

Each film coated tablet contains

Drospirenone……3.0 mg

Ethinylestradiol ……. 0.03 mg

Dosage Form and Strength

Tablets for oral use.

Clinical Particulars

Therapeutic Indications

CRISANTA is indicated for use as oral contraceptive in women.

Posology and Method of Administration

To achieve maximum contraceptive effectiveness, **CRISANTA** must be taken as directed in the order on the blister pack.

A patient should begin to take **CRISANTA** on the first day (Day 1) of her menstrual period. During the first cycle of **CRISANTA** use, the patient should be instructed to take one tablet daily, beginning on day 1 of her menstrual cycle (the first day of menstruation is day one). She should take one tablet daily for 21 consecutive days, followed by 7 pill-free days. It is recommended that **CRISANTA** be

taken at the same time each day, preferably after the evening meal or at bedtime.

If **CRISANTA** is first taken later than the first day of the menstrual cycle, it should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The patient should use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of **CRISANTA** on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her tablets on the next day after the 7 pill-free days, regardless of whether or not a menstrual period has occurred or is still in progress. Any time a subsequent cycle of **CRISANTA** is started later than the day following 7 pill-free days, the patient should use another method of contraception until she has taken a tablet daily for 7 consecutive days.

When Switching from a Different Birth Control Pill

When switching from another birth control pill, **CRISANTA** should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When Switching from a Method other than Birth Control Pills

When switching from a transdermal patch or vaginal ring, **CRISANTA** should be started when the next application would have been due. When switching from an injection, **CRISANTA** should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, **CRISANTA** should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last tablet. If spotting or breakthrough bleeding occurs while taking **CRISANTA**, the patient should be instructed to continue taking **CRISANTA** as instructed and as per the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult the physician.

Although the occurrence of pregnancy is low if **CRISANTA** is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed one or more tablets or started taking them on a day later than she should have), the possibility of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraception should be discontinued if pregnancy is confirmed.

The risk of pregnancy increases with each active tablet missed. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence.

Following First -Trimester Abortion

The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following Delivery or Second-Trimester Abortion

Women should be advised to start at day 21-28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days.

However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of Missed Tablet

If the user is **less than 12 hours** late in taking any tablet, contraceptive protection is not reduced. The woman 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.

Accordingly, the following advice can be given in daily practice:

- *Week 1*

  The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the regular tablet-free interval, the higher the risk of a pregnancy.

- *Week 2*

  The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- *Week 3*

  The risk of reduced reliability is imminent because of the forthcoming 7-day tablet-free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use extra precautions for the next 7 days as well.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. The next blister pack must be started as soon as the current blister pack is finished, i.e., no gap should be left between packs. The user is unlikely to have a withdrawal bleed until the end of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The woman may also be advised to discontinue tablet-taking from the current blister pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next blister pack.

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 Gastrointestinal Bleeding

In case of severe gastrointestinal disturbances (e.g. vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3-4 hours after tablet taking, this can be regarded as a missed tablet and a new (replacement) tablet should be taken as soon as possible. The new tablet should be taken within 12 hours of the usual time of tablet-taking if possible. If more than 12 hours elapse, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to Postpone Withdrawal Bleeding

To delay a period the woman should continue with another blister pack of **CRISANTA** without a tablet-free interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of **CRISANTA** is then resumed after the usual 7-day tablet-free interval.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming tablet-free interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the subsequent pack (just as when delaying a period).

Contraindications

Do not prescribe DRSP+EE to women who are known to have the following. Combined hormonal contraceptives (CHCs) 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 (on anticoagulants) or history of VTE (e.g. deep venous thrombosis or pulmonary embolism)
  - 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 immobilization
  - A high risk of venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE)
  - Current, or history of ATE (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack)
  - Known hereditary or acquired predisposition for ATE, such as hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - High risk of ATE due to multiple risk factors or due to the presence of one serious risk factor

such as
  - Diabetes mellitus with vascular symptoms/disease.
  - Severe hypertension
  - Severe dyslipoproteinaemia

- Women who are known to smoke, if over age 35 (high risk of arterial or venous thrombotic diseases)
- Renal impairment, severe renal insufficiency or acute renal failure.
- Presence or history of liver tumours (benign or malignant) Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Breast cancer or other oestrogen- or progestin-sensitive cancer (of the genital organs), now or in the past
- Known (now or in the past) or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts)
- Undiagnosed abnormal uterine and vaginal bleeding
- Uncontrolled hypertension
- Headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35
- Adrenal insufficiency
- Coronary artery disease
- Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g. subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
- Inherited or acquired hypercoagulopathies
- Pregnancy, because there is no reason to use COCs during pregnancy
- Hypersensitivity to the active substances or to any of the excipients.
- Use of Hepatitis C drug combinations containing ombitasvir, paritaprevir / ritonavir, with or without dasabuvir due to the potential for ALT (transaminase) elevations. DRSP+EE is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir

Special Warnings and Precautions of Use

General

- If any of the conditions or risk factors mentioned below is present, the suitability of DRSP+EE should be discussed with the woman.
- In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of DRSP+EE should be discontinued.
- In case of suspected or confirmed VTE or ATE, CHC use should be discontinued. In case anticoagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

Medical Examination / Consultation

Prior to the initiation or reinstitution of DRSP+EE a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured, and

a physical examination should be performed, guided by the contraindications and warnings. It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of DRSP+EE compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Circulatory Disorders

Thromboembolic Disorders and other Vascular Problems

Stop DRSP+EE if an arterial or venous thrombotic event occurs.

Risk of VTE

The use of any CHC increases the risk of VTE compared with no use. The risk of VTE is highest during the first year of use. The greatest risk of VTE is present after a woman initially starts using a COC or when she restarts the same or a different COC use after a pill-free interval of at least a month.

Based on presently available information on DRSP and EE, DRSP-containing COCs may be associated with a higher risk of VTE than COCs containing the progestin levonorgestrel or some other progestins.

Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as DRSP+EE may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with DRSP+EE, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a 3-fold increase.

Before initiating use of DRSP+EE in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop DRSP+EE at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start DRSP+EE no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

Use of COCs also increases the risk of arterial thromboembolism such as strokes, myocardial infarctions and TIA, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and haemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

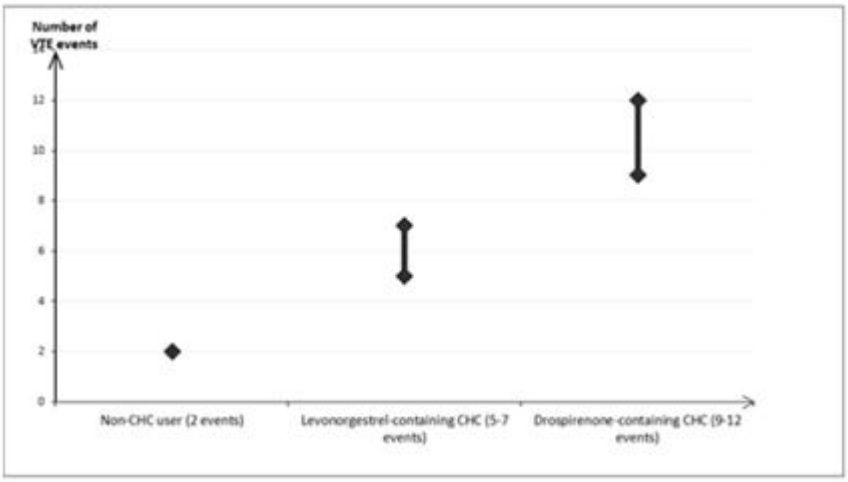
Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop DRSP+EE if there is unexplained loss of vision, proptosis, diplopia, papilloedema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

In women who do not use a CHC and are not pregnant, about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors.

It is estimated that out of 10,000 women who use a CHC containing drospirenone, between 9 and 12 women will develop a VTE in one year; this compares with about 6 in women who use a levonorgestrel-containing CHC. In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period. VTE may be fatal in 1-2% of the cases.

Number of VTE events per 10,000 women in one year



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

Risk Factors for VTE

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.

DRSP+EE 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 factor	Comment
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Yasmin has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered.

Symptoms of VTE

In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

- Symptoms of DVT can include: unilateral swelling of the leg and/or foot 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 discoloured skin on the leg.
- Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may be associated with haemoptysis; sharp chest pain; severe light headedness or dizziness; rapid or irregular heartbeat; vertigo; ‘acute’ abdomen.
- Some of these symptoms (e.g. shortness of breath, coughing) are nonspecific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).
- Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discolouration of an extremity.
- If the occlusion occurs in the eye, symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of ATE

Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal.

Risk Factors for ATE

The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). DRSP+EE is contraindicated if a woman has one

serious or multiple risk factors for ATE that puts her at high risk of arterial 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 should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factor	Comment
Increasing age	Particularly above 35 years
Smoking	Women should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

- 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 trouble walking, dizziness, loss of balance or coordination; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure, etc.
- Temporary symptoms suggest the event is a TIA.
- Symptoms of myocardial infarction (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; feeling of being full, having indigestion or choking; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Hyperkalaemia

DRSP is an aldosterone antagonist with potassium sparing properties. It has anti-mineralocorticoid activity, including the potential for hyperkalaemia in high-risk patients, comparable to a 25 mg dose of spironolactone. DRSP+EE is contraindicated in patients with conditions that predispose to hyperkalaemia (i.e. renal impairment, hepatic impairment and adrenal insufficiency). Women 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 during the first treatment cycle. Medications that may increase serum potassium concentration include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists and NSAIDs. Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and

concomitantly. Strong CYP3A4 inhibitors include azole antifungals (e.g. ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (e.g., indinavir, boceprevir), and clarithromycin.

In most cases, no increase of potassium levels is to be expected. However, in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicinal products, serum potassium levels slightly, but not significantly, increased during DRSP intake. Therefore, it is recommended to check serum potassium during the first treatment cycle in patients presenting with renal insufficiency and pre-treatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicinal products.

Tumours

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 hepatic 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.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk of hepatic adenomas is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Carcinoma of Breast and other Reproductive Organs

Women who currently have or have had breast cancer should not use DRSP+EE because breast cancer is a hormonally-sensitive tumour. There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings. A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer 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 diagnoses 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-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Some epidemiological studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepitheliaal neoplasia in long-term users of COCs (> 5 years). However, there is controversy about the extent to which these findings may be due to differences in sexual behaviour and other factors such as human papilloma virus (HPV).

With the use of the higher-dose COCs (50 mcg EE) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dose COCs remains to be confirmed.

Liver Disease

Discontinue DRSP+EE if jaundice develops. Steroid hormones may be poorly metabolized in patients

with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of COCs.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir / paritaprevir / ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinylestradiol-containing medications, such as COCs. Discontinue DRSP+EE prior to starting therapy with the combination drug regimen ombitasvir / paritaprevir / ritonavir, with or without dasabuvir. DRSP+EE can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

High Blood Pressure

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. For women with well-controlled hypertension, monitor blood pressure and stop DRSP+EE if blood pressure rises significantly. If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

Gallbladder Diseases

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

Carbohydrate and lipid Metabolic Effects

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 EE). However, diabetic women should be carefully observed, particularly in the early stage of COC use.

Carefully monitor prediabetic and diabetic women who are taking DRSP+EE. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidaemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridaemia or a family history thereof, may be at an increased risk of

pancreatitis when using COCs.

Headache

If a woman taking DRSP+EE develops new headaches that are recurrent, persistent or severe, evaluate the cause and discontinue DRSP+EE if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Bleeding Irregularities / Reduced Cycle Control

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first (3) months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles. If bleeding irregularities persists or occurs 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.

If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions, it is unlikely that the woman 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.

The average duration of scheduled bleeding episodes in the majority of subjects (86%- 88%) was 4-7 days. Women who use DRSP+EE may experience absence of withdrawal bleeding episodes, even if they are not pregnant. Based on subject diaries from contraceptive efficacy trials, during cycles 2–13, 1-11% of women per cycle experienced no withdrawal bleeding. Some women may encounter post-pill amenorrhoea or oligomenorrhoea, especially when such a condition was pre-existent. If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more 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 take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

COC use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect when COCs are taken inadvertently during early pregnancy, particularly in so far as cardiac anomalies and limb-reduction defects are concerned.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy.

Depression

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use. Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms,

including shortly after initiating the treatment. Women with a history of depression should be carefully observed and DRSP+EE discontinued if depression recurs to a serious degree.

Interference with 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, glucose tolerance, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. If you need a blood test, tell your doctor or the laboratory staff that you are taking the pill because hormone contraceptives can affect the results of some tests.

ALT Elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as CHCs.

Reduced Efficacy

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

Other Conditions

- In women with hereditary angio-oedema, exogenous oestrogens may induce or exacerbate symptoms of angio-oedema.
- 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 while taking COCs.
- 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; gallstones; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Worsening of endogenous depression, epilepsy, Crohn's disease and of ulcerative colitis has been reported during COC use.

Drug Interactions

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

Influence of other Medicinal Products on DRSP+EE

Substances Diminishing the Efficacy of COCs (increasing the clearance of COCs)

Drugs or herbal products that induce microsomal enzymes, including CYP3A4, can result in increased clearance of sex hormones and may decrease the effectiveness of COCs (contraceptive failure) or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, primidone,

carbamazepine, bosentan, HIV-medication ritonavir, nevirapine and efavirenz, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St. John's wort (*Hypericum perforatum*). Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure.

Maximal enzyme induction is generally seen within a few weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy. Counsel women to use an alternative method of contraception or a back-up / barrier method when enzyme inducers are used with COCs, and to continue back-up / barrier contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability. If the drug therapy runs beyond the end of the tablets in the COC pack, the next COC pack should be started right after the previous one without the usual tablet-free interval.

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Substances Increasing the Plasma Concentrations (Decreasing the Clearance) of COCs

The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both.

Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days increased the $AUC_{(0\text{-}24h)}$ of DRSP+EE 2.7 fold and 1.4 fold respectively.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6- fold, respectively when taken concomitantly with a CHC containing 0.035 mg ethinylestradiol.

HIV / HCV Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Significant changes (increase or decrease) in the plasma concentrations of oestrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with NNRTIs. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Antibiotics

There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, However, clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma

concentrations of synthetic steroids.

Effects of COCs on other Drugs

COCs containing EE may inhibit the metabolism of other compounds.

COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. COCs have also been shown to increase concentrations of cyclosporine. Consult the labelling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

COCs Increasing the Plasma Concentrations of CYP450 Enzymes

In clinical studies, administration of a hormonal contraceptive containing EE did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g., midazolam) while plasma concentrations of CYP2C19 substrates (e.g., omeprazole and voriconazole) and CYP1A2 substrates (e.g., theophylline and tizanidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Based on *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of DRSP at doses of 3 mg with the cytochrome P450 mediated metabolism of other active substances is unlikely.

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Potential to Increase Serum Potassium Concentration

There is a potential for an increase in serum potassium concentration in women taking DRSP and EE with other drugs that may increase serum potassium concentration.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations. Therefore, DRSP+EE users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. DRSP+EE can be restarted 2 weeks following completion of treatment with this combination drug regimen. In patients without renal insufficiency, the concomitant use of DRSP and ACE-inhibitors or NSAIDs did not show a significant effect on serum potassium. Nevertheless, concomitant use of DRSP+EE with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle.

Use in Special Populations

Patients with Renal Impairment

DRSP+EE is contraindicated in patients with renal impairment.

In subjects with creatinine clearance (CLcr) of 50–79 mL/min, serum DRSP concentrations were comparable with those in a control group with CLcr ≥ 80 mL/min. In subjects with CLcr of 30–49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalaemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium-sparing drugs.

DRSP treatment was also well tolerated by women with mild and moderate renal impairment. DRSP treatment did not show any clinically significant effect on serum potassium concentration.

Patients with Hepatic Impairment

DRSP+EE is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. DRSP+EE has not been studied in women with severe hepatic impairment.

In a single dose study, oral clearance (CL/F) was decreased approximately 50% in volunteers with moderate hepatic impairment as compared with those with normal liver function. The observed decline in DRSP clearance in volunteers with moderate hepatic impairment did not translate into any apparent difference in terms of serum potassium concentrations. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalaemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that DRSP is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

Pregnant Women

DRSP+EE is not indicated during pregnancy.

If pregnancy occurs during use of DRSP+EE, the preparation should be withdrawn immediately. There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. 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 pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Animal studies have shown undesirable effects during pregnancy and lactation. Based on these animal data, undesirable effects due to hormonal action of the active compounds cannot be excluded. However, general experience with COCs during pregnancy did not provide evidence for an actual undesirable effect in humans.

The available data regarding the use of DRSP+EE during pregnancy are too limited to permit conclusions concerning negative effects of DRSP+EE on pregnancy, health of the foetus or neonate. To date, no relevant epidemiological data are available.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than 4 weeks postpartum. The increased risk of VTE during the postpartum period should be considered when re-startling DRSP+EE.

Lactating Women

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be recommended and, when possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of the contraceptive steroids and/or their metabolites are present in breast milk. These amounts may affect the child.

After oral administration of DRSP + EE, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Paediatric Patients

Safety and efficacy of DRSP + EE has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 years and for those 18 years and older. Use of this product before menarche is not indicated.

Geriatric Patients

DRSP + EE has not been studied in postmenopausal women and is not indicated in this population.

Effects on Ability to Drive and Use Machinery

There is no information suggesting that use of DRSP+EE affects driving or use of machines.

Undesirable Effects

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labelling:

- Serious cardiovascular events and stroke
- Vascular events
- Liver disease

Adverse reactions commonly reported by COC users are as below:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The data provided reflect the experience with the use of 3 mg DRSP/0.03 mg EE in the adequate and well-controlled studies for contraception (N = 2,837).

The US pivotal clinical study (N=326) was a multicenter, open-label trial in healthy women aged 18 - 35 who were treated for up to 13 cycles. The second pivotal study (N=442) was a multicenter, randomized, open-label comparative European study of 3 mg DRSP/0.03 mg EE vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles. The most common adverse reactions (≥ 2% of users) were: premenstrual syndrome (13.2%), headache/migraine (10.7%), breast pain/tenderness/discomfort (8.3%), nausea/vomiting (4.5%) abdominal pain/discomfort/tenderness (2.3%) and mood changes (depression, depressed mood, irritability, mood swings, mood altered and affect lability (2.3%).

Adverse Reactions (≥1%) Leading to Study Discontinuation

Of 2,837 women, 6.7% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was headache/migraine (1.5%).

Serious Adverse Reactions

Depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma.

The following adverse drug reactions have been reported during use of DRSP and EE:

System Organ Class (MedDRA)	**Frequency of Adverse Reactions**		
	Common ≥1/100 to <1/10	**Uncommon ≥ 1/1,000 to <1/100**	**Rare ≥ 1/10,000 to < 1/1000**
Immune system			Hypersensitivity Asthma
Psychiatric disorders	Depressive mood	Libido increased Libido decreased	
Nervous system	Headache		
Ear and labyrinth			Hypoacusis
Vascular system	Migraine	hypertension, hypotension	Venous thromboembolism Arterial thromboembolism
Gastrointestinal system	Nausea	Vomiting, Diarrhoea	
Skin and subcutaneous system		Acne, eczema, pruritus, alopecia	Erythema nodosum, Erythema multiforme
Reproductive system and breast	Menstrual disorders, premenstrual syndrome, intermenstrual bleeding, breast pain/tenderness/ discomfort, leucorrhoea, vaginal discharge, moniliasis, vulvovaginal candidiasis	Breast enlargement, Vaginal infection	Breast discharge

General disorders and administration site Conditions		Fluid retention, Weight increased, Weight decreased	

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs.

The following serious adverse events have been reported in women using COCs:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice
- Chloasma
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal
- In women with hereditary angiooedema exogenous oestrogens may induce or exacerbate symptoms of angiooedema

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 number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of DRSP and EE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions, including fatalities, are grouped into System Organ Classes and ordered by frequency.

Vascular Disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, intracardiac thrombosis, intracranial venous sinus thrombosis, sagittal sinus thrombosis, retinal vein occlusion, myocardial infarction and stroke), hypertension

Hepatobiliary Disorders: Gallbladder disease

Immune System Disorders: Hypersensitivity

Metabolism and Nutrition Disorders: Hyperkalaemia

Skin and Subcutaneous Tissue Disorders: Chloasma

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024. By reporting side-effects, you can help provide more information on the safety of this product.

Overdose

There have been no reports of overdose or serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea. On the basis of general experience with COCs, symptoms that may possibly occur in this case are: nausea, vomiting and, withdrawal bleeding. Withdrawal bleeding may even occur in girls before their menarche, if they accidentally take the medicinal product. There are no antidotes and further treatment should be symptomatic.

DRSP is a spironolactone analogue that has anti-mineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Pharmacological Properties

Pharmacodynamic Properties

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

CRISANTA is a COC with ethinylestradiol and the progestogen, drospirenone. In a therapeutic dosage, DRSP, a spironolactone analogue, also possesses anti-androgenic and mild anti-mineralocorticoid properties. It has no oestrogenic, glucocorticoid and anti-glucocorticoid activity. This gives DRSP a pharmacological profile closely resembling the natural hormone, progesterone.

There are indications from clinical studies that the mild anti-mineralocorticoid properties of DRSP+EE result in a mild anti-mineralocorticoid effect.

No specific pharmacodynamic studies were conducted with DRSP+EE

Pharmacokinetic Properties

Drospirenone

Absorption

The absolute bioavailability of the combination tablet of DRSP and EE has not been evaluated. Orally administered DRSP is rapidly and almost completely absorbed. Maximum concentrations of the active substance in serum of about 38 ng/ml are reached at about 1-2 hours after single ingestion. Bioavailability is between 76 and 85%. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after administration of DRSP+EE.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1 to 10 mg. Following daily dosing of DRSP+EE, steady-state DRSP concentrations were observed after 8 days. There was about 2- to 3- fold accumulation in serum C_{max} and $AUC_{(0-24h)}$ values of DRSP following multiple-dose administration of DRSP+EE.

Mean pharmacokinetic parameters of DRSP

Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0-24h) (ng*h/mL)	$t_{1/2}$ (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA*
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)

*NA – Not Available

Distribution

After oral administration, serum DRSP levels decrease with a terminal half-life of 31 hours. DRSP is bound to serum albumin (97%) and does not bind to sex hormone-binding globulin (SHBG) or corticoid binding globulin (CBG). Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough concentrations). Only 3-5 % of the total serum concentrations of the active substance are present as free steroid. The EE-induced increase in SHBG does not influence the serum protein-binding of DRSP. The mean apparent volume of distribution of DRSP is 3.7 ± 1.2 l/kg.

Metabolism

DRSP is extensively metabolized after oral administration. The major metabolites in the plasma are the acid form of DRSP, generated by opening of the lactone ring, and the 4,5-dihydro-drospireno-e-3-sulphate, both of which are formed without involvement of the P450 system. DRSP is metabolized to a minor extent by cytochrome (CY) P450 3A4 and has demonstrated a capacity to inhibit this enzyme and CYP450 1A1, CYP450 2C9 and CYP450 2C19 *in vitro*.

Elimination

The metabolic clearance rate of DRSP in serum is 1.5 ± 0.2 ml/min/kg. Excretion of DRSP was nearly complete after 10 days and amounts excreted were slightly higher in faeces compared to urine. DRSP is extensively metabolized and is excreted only in trace amounts in unchanged form. The metabolites of DRSP are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with urine and faeces is about 40 hours. At least 20 different metabolites were observed in urine and faeces. About 38-47% of the metabolites in urine were glucuronide and sulphate conjugates. In faeces, about 17-20% of the metabolites were excreted as glucuronides and sulphates.

Steady-State Conditions

During a treatment cycle, maximum steady-state concentrations of DRSP in serum of about 70 ng/ml are reached after about 8 days of treatment. Serum DRSP levels accumulated by a factor of about 3

as a consequence of the ratio of terminal half-life and dosing interval.

Ethinylestradiol

Absorption

EE is rapidly and completely absorbed after ingestion. After administration of 30 µg, peak plasma concentrations of 100 pg/ml are reached 1 - 2 hours after ingestion. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. EE undergoes an extensive first-pass effect, which displays great inter-individual variation. The absolute bioavailability is approximately 45 %. Following daily administration of DRSP+EE serum C_{max} and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2.

Mean pharmacokinetic parameters of EE

Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0-24h)}$ (ng*h/mL)	$t_{1/2}$ (h)
1/1	11	53.5 (43)	1.9 (45)	280 (87)	NA*
1/21	11	92.1 (35)	1.5 (40)	461 (94)	NA*
6/21	11	99.1 (45)	1.5 (47)	346 (74)	NA*
9/21	11	87 (43)	1.5 (42)	485 (92)	NA*
13/21	10	90.5 (45)	1.6 (38)	469 (83)	NA*

*NA – Not Available

Distribution

EE has an apparent volume of distribution of 5 l/kg and binding to plasma proteins is approximately 98 %. EE induces the hepatic synthesis of SHBG and CBG. During treatment with 30 µg EE the plasma concentration of SHBG increases from 70 to about 350 nmol/l. EE passes in small amounts into breast milk (0.02 % of the dose). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

EE is metabolized completely (metabolic plasma clearance 5 ml/min/kg). EE has been reported to be subject to significant gut and hepatic first-pass metabolism. Metabolism of EE and its oxidative metabolites occur primarily by conjugation with glucuronide or sulphate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and faecal excretion.

Elimination

EE is not excreted in unchanged form to any significant extent. The metabolites of EE are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day. The elimination half-life is 20 hours.

Steady-state Conditions

Steady-state conditions are reached during the second half of a treatment cycle and serum levels of EE accumulate by a factor of about 1.4-2.1.

Effect of Food

The rate of absorption of DRSP and EE following single administration of the formulation was slower under fed (high-fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

Special Populations

Children and Adolescents

DRSP+EE is indicated after menarche.

Effect of Renal Impairment

Steady-state serum DRSP levels in women with mild renal impairment (creatinine clearance CLcr, 50-80 mL/min) were comparable to those of women with normal renal function. The serum DRSP levels were on average 37% higher in women with moderate renal impairment (CLcr, 30-50 mL/min) compared to those in women with normal renal function. DRSP treatment was also well tolerated by women with mild and moderate renal impairment. DRSP treatment did not show any clinically significant effect on serum potassium concentration.

Effect of Hepatic Impairment

DRSP+EE is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. In a single-dose study, oral clearance (CL/F) was decreased approximately 50% in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in DRSP clearance in volunteers with moderate hepatic impairment did not translate into any apparent difference in terms of serum potassium concentrations. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalaemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that DRSP is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B). DRSP+EE has not been studied in women with severe hepatic impairment.

Non-Clinical Properties

Animal Toxicology or Pharmacology

There are no preclinical safety data which could be of relevance to the prescriber and which are not already included in other relevant sections of the Prescribing Information.

Description

CRISANTA is an oral contraceptive. Each pack consists of 21 tablets and each tablet contains 3 mg of drospirenone (DRSP) and 0.03 mg of ethinylestradiol (EE).

Pharmaceutical Particulars

Incompatibilities

Not applicable

Shelf life

24 months

Packaging Information

CRISANTA is available in a pack of 21 tablets.

Storage and Handling Information

Store at a temperature not exceeding 25°C. Protect from moisture.

Patient Counselling Information

What is CRISANTA and what is it used for?

CRISANTA is a contraceptive pill and is used to prevent pregnancy. Each tablet contains a small amount of two different female hormones, namely drospirenone (DRSP) and ethinylestradiol (EE). Contraceptive pills that contain two hormones are called “combination” pills.

What you need to know before you take CRISANTA?

General notes

Before you start using **CRISANTA** you should read the information on blood clots. It is particularly important to read the symptoms of a blood clot.

Before you can begin taking **CRISANTA**, your doctor will ask you some questions about your personal health history and that of your close relatives. The doctor will also measure your blood pressure, and depending upon your personal situation, may also carry out some other tests.

In this leaflet, several situations are described where you should stop using **CRISANTA**, or where the reliability of **CRISANTA** may be decreased. In such situations you should either not have sex or you should take extra non-hormonal contraceptive precautions, e.g., use a condom or another barrier method. Do not use rhythm or temperature methods. These methods can be unreliable because **CRISANTA** alters the monthly changes of body temperature and of the cervical mucus.

CRISANTA, like other hormonal contraceptives, does not protect against HIV infection (AIDS) or any other sexually transmitted disease.

When you should not use DRSP+EE

You should not use DRSP+EE if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form

of birth control would be more appropriate.

Do not use DRSP+EE

- if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs;
- if you know you have a disorder affecting your blood clotting – for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, Factor V Leiden or antiphospholipid antibodies;
- if you need an operation or if you are off your feet for a long time;
- if you have ever had a heart attack or stroke;
- if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms);
- if you have any of the following diseases that may increase your risk of a clot in the arteries:
  - severe diabetes with blood vessel damage
  - very high blood pressure
  - a very high level of fat in the blood (cholesterol or triglycerides)
  - a condition known as hyperhomocysteinaemia
- if you have (or have ever had) a type of migraine called 'migraine with aura';
- if you have (or have ever had) a liver disease and your liver function is still not normal;
- if your kidneys are not working well (renal failure);
- if you have (or have ever had) a tumour in the liver;
- if you have (or have ever had) or if you are suspected of having breast cancer or cancer of the genital organs;
- if you have any unexplained bleeding from the vagina;
- if you are allergic to ethinylestradiol or drospirenone, or any of the other ingredients of this medicine. This may cause itching, rash or swelling.

Do not use **DRSP+EE** if you have hepatitis C and are taking the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir.

Use in children

CRISANTA is not intended for use in females whose periods have not yet started

Warnings and Precautions

When should you contact your doctor?

Seek urgent medical attention if you notice possible signs of a blood clot that may mean you are suffering from a blood clot in the leg (i.e. deep vein thrombosis), a blood clot in the lung (i.e. pulmonary embolism), a heart attack or a stroke.

Tell your doctor if any of the following conditions apply to you.

Talk to your doctor, pharmacist or nurse before taking DRSP+EE. In some situations, you need to take special care while using DRSP+EE or any other combination pill, and your doctor may need to examine you regularly. If the condition develops or gets worse while you are using DRSP+EE, you should also tell your doctor.

- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease);
- if you have systemic lupus erythematosus (SLE – a disease affecting your natural defence system);
- if you have haemolytic uraemic syndrome (HUS - a disorder of blood clotting causing failure of the

kidneys);
- if you have sickle cell anaemia (an inherited disease of the red blood cells);
- if you have elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);
- if you need an operation or you are off your feet for a long time;
- if you have just given birth you are at an increased risk of blood clots. You should ask your doctor how soon after delivery you can start taking DRSP + EE;
- If you have an inflammation in the veins under the skin (superficial thrombophlebitis);
- If you have varicose veins;
- if a close relative has or has ever had breast cancer;
- if you have a disease of the liver or gallbladder;
- if you have other kidney problems and are taking medicines which increase potassium levels in the blood;
- if you have diabetes;
- if you have depression;
- if you have epilepsy;
- if you have a disease that first appeared during pregnancy or earlier use of sex hormones [for example, hearing loss, a blood disease called porphyria, yellowing of the skin or eyes (jaundice), itching of the whole body (pruritis), skin rash with blisters during pregnancy (gestational herpes), a nerve disease causing sudden movements of the body (Sydenham's chorea)];
- if you have ever had a discolouration of the skin especially on the face or neck known as "pregnancy patches" (chloasma). If so, avoid direct sunlight or ultraviolet light.
- if you have hereditary angioedema, products containing estrogens may cause or worsen the symptoms. You should see your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives together with difficulty breathing.

Blood clots

Using a combined hormonal contraceptive such as DRSP+EE increases your risk of developing a blood clot compared with not using one. In rare cases a blood clot can block blood vessels and cause serious problems. Blood clots can develop:

- in veins (referred to as a 'venous thrombosis', 'venous thromboembolism' or VTE);
- in the arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or very rarely, they may be fatal. **It is important to remember that the overall risk of a harmful blood clot due to DRSP+EE is small.**

How to recognise a blood clot

Seek urgent medical attention if you notice any of the following signs or symptoms.

Deep vein thrombosis

Swelling of one leg or along a vein in the leg or foot especially when accompanied by:

- pain or tenderness in the leg which may be felt only when standing or walking
- increased warmth in the affected leg
- change in colour of the skin on the leg e.g. turning pale, red or blue.

Pulmonary embolism

- sudden unexplained breathlessness or rapid breathing;
- sudden cough without an obvious cause, which may bring up blood;
- sharp chest pain which may increase with deep breathing;
- severe light headedness or dizziness;
- rapid or irregular heartbeat;
- severe pain in your stomach;

If you are unsure, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').

Retinal vein thrombosis (blood clot in the eye)

Symptoms most commonly occur in one eye:

- immediate loss of vision or
- painless blurring of vision which can progress to loss of vision

Heart attack

- chest pain, discomfort, pressure, heaviness;
- sensation of squeezing or fullness in the chest, arm or below the breastbone;
- fullness, indigestion or choking feeling;
- upper body discomfort radiating to the back, jaw, throat, arm and stomach;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Stroke

- sudden weakness or numbness 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.

Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.

Blood clots blocking other blood vessels

- swelling and slight blue discolouration of an extremity;
- severe pain in your stomach (acute abdomen)

Blood clots in a vein

What can happen if a blood clot forms in a vein?

The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently,

they occur in the first year of use of a combined hormonal contraceptive;

- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT);
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism;
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?

The risk of developing a blood clot in a vein is highest during the first year of taking a combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more. After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.

When you stop DRSP+EE your risk of a blood clot returns to normal within a few weeks.

What is the risk of developing a blood clot?

The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are taking. The overall risk of a blood clot in the leg or lung (DVT or PE) with DRSP+EE is small.

- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains levonorgestrel, norethisterone or norgestimate, about 5-7 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains drospirenone such as DRSP + EE, between about 9 and 12 women will develop a blood clot in a year.
- The risk of having a blood clot will vary according to your personal medical history.

Factors that increase your risk of a blood clot in a vein

The risk of a blood clot with DRSP+EE is small but some conditions will increase the risk. Your risk is higher:

- if you are very overweight (body mass index or BMI over 30kg/m^2);
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (eg. below the age of about 50). In this case you could have a hereditary blood clotting disorder;
- if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of DRSP+EE may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop DRSP+EE ask your doctor when you can start using it again.
- as you get older (particularly above about 35 years);
- if you gave birth less than a few weeks ago.

The risk of developing a blood clot increases the more conditions you have.

Air travel (>4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.

It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that DRSP+EE needs to be stopped.

If any of the above conditions change while you are using DRSP+EE, for example a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

Blood clots in an artery

What can happen if a blood clot forms in an artery?

Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery

It is important to note that the risk of a heart attack or stroke from using DRSP+EE is very small but can increase:

- with increasing age (beyond about 35 years);
- if you smoke. When using a combined hormonal contraceptive like DRSP+EE you are advised to stop smoking. If you are unable to stop smoking and are older than 35, your doctor may advise you to use a different type of contraceptive;
- if you are overweight;
- if you have high blood pressure;
- if a member of your immediate family has had a heart attack or stroke at a young age (less then about 50). In this case you could also have a higher risk of having a heart attack or stroke;
- if you or someone in your immediate family have a high level of fat in the blood (cholesterol or triglycerides);
- if you get migraines, especially migraines with aura;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation);
- if you have diabetes.

If you have more than one of these conditions or if any of them are particularly severe, the risk of developing a blood clot may be increased even more. If any of the above conditions change while you are using DRSP+EE, for example you start smoking, a close family member experiences a thrombosis for no known reason or you gain a lot of weight, tell your doctor.

DRSP+EE and Cancer

Breast cancer has been observed slightly more often in women using combination pills but it is not known whether this is caused by the treatment. For example, it may be that more tumours are detected in women on combination pills because they are examined by their doctor more often. The occurrence of breast tumours becomes gradually less after stopping the combination hormonal contraceptives. It is important to regularly check your breasts and you should contact your doctor if you feel any lump.

In rare cases, benign liver tumours and in even fewer cases malignant liver tumours have been reported in pill users. Contact your doctor if you have unusually severe abdominal pain or abdominal swelling (which may be due to enlargement of liver).

Psychiatric Disorders

Some women using hormonal contraceptives including DRSP+EE have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts, If you experience mood changes and depressive symptoms contact your doctor for further medical advice

as soon as possible.

Bleeding Between Periods

During the first few months that you are taking DRSP+EE, you may have unexpected bleeding (bleeding outside the gap week). If this bleeding occurs for more than a few months or if it begins after some months, your doctor must find out what is wrong.

What to do if no Bleeding Occurs during the 7 pill-free days

If you have taken all the tablets correctly, have not had vomiting or severe diarrhoea and you have not taken any other medicines, it is highly unlikely that you are pregnant. If the expected bleeding does not happen twice in succession, you may be pregnant. Contact your doctor immediately. Do not start the next strip until you are sure that you are not pregnant.

Other Medicines and DRSP+EE

Always tell your doctor which medicines or herbal products you are already using.. Also tell any other doctor or dentist who prescribes another medicine (or the pharmacist) that you take DRSP+EE. They can tell you if you need to take additional contraceptive precautions (for example condoms) and if so, for how long or whether the use of another medicine you need must be changed.

Some medicines can have an influence on the blood levels of DRSP+EE and can make it less effective in preventing pregnancy, or can cause unexpected bleeding. These include:

- medicines used for the treatment of -
  - epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, etc.);
  - tuberculosis (e.g. rifampicin);
  - HIV and Hepatitis C infections (so called protease inhibitors and non nucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz)
  - fungal infections (e.g. griseofulvin, ketoconazole);
  - arthritis, arthrosis (etoricoxib);
  - high blood pressure in the blood vessels in the lungs (bosentan).
- the herbal remedy St. John's wort.

DRSP+EE may influence the effect of other medicines,

- medicines containing ciclosporin;
- the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures);
- theophylline (used to treat breathing problems);
- tizanidine (used to treat muscle pain and/or muscle cramps).

Do not use DRSP+EE if you have hepatitis C and are taking the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir as this may cause increases in liver function blood test results (increase in ALT liver enzyme). Your doctor will prescribe another type of contraceptive prior to start of the treatment with these medicinal products. DRSP+EE can be restarted approximately 2 weeks after completion of this treatment.

DRSP+EE with Food and Drink

DRSP+EE may be taken with or without food, if necessary with a small amount of water.

Laboratory Tests

If you need a blood test, tell your doctor or the laboratory staff that you are taking the pill, because hormonal contraceptives can affect the results of some tests.

Pregnancy and Breastfeeding

Pregnancy

If you are pregnant, you must not take DRSP+EE. If you become pregnant while taking DRSP+EE, stop immediately and contact your doctor. If you want to become pregnant, you can stop taking DRSP+EE at any time.

Breastfeeding

Use of DRSP+EE is generally not advisable when a woman is breast-feeding. If you want to take the pill while you are breastfeeding you should contact your doctor.

Driving and using machines

There is no information suggesting that use of DRSP+EE affects driving or use of machines.

How to take CRISANTA?

Take CRISANTA every day for 21 days

CRISANTA comes in strips of 21 pills, each marked with a day of the week.

- Take your pill at the same time every day.
- Start by taking a pill marked with the correct day of the week.
- Follow the direction of the arrows on the strip. Take one pill each day, until you have finished all 21 pills.
- Swallow each pill whole, with water if necessary. Do not chew the pill.

Then have seven pill-free days

After you have taken all 21 pills in the strip, you have seven days when you take no pills. So, if you take the last pill of one pack on a Friday, you will take the first pill of your next pack on the Saturday of the following week.

Within a few days of taking the last pill from the strip, you should have a withdrawal bleed like a period. This bleed may not have finished when it is time to start your next strip of pills.

You don’t need to use extra contraception during these seven pill-free days – as long as you have taken your pills correctly and start the next strip of pills on time.

Then start your next strip

Start taking your next strip of CRISANTA after the seven pill-free days – even if you are still bleeding. Always start the new strip on time.

During the seven pill-free days, when you take no tablets, bleeding should begin (so-called withdrawal bleeding). This usually starts on the 2nd or 3rd day after the last tablet of CRISANTA. Start the following strip after the last day of the seven pill-free days, whether your bleeding has stopped or not.

When can you start with the first strip?

- *If you have not used a contraceptive with hormones in the previous month*

Begin with CRISANTA on the first day of your cycle (that is, the first day of your period). If you start CRISANTA on the first day of your period you are immediately protected against pregnancy. You may also begin on day 2-5 of the cycle, but then you must use extra protective measures (for example, a condom) for the first 7 days.

- *Changing from a combination hormonal contraceptive, or combination contraceptive vaginal ring or patch*

You can start CRISANTA preferably on the day after the last active tablet (the last tablet containing the active substances) of your previous pill, but at the latest on the day after the tablet-free days of your previous pill finish (or after the last inactive tablet of your previous pill). When changing from a combination contraceptive vaginal ring or patch, follow the advice of your doctor.

- *Changing from a progestogen-only-method (progestogen-only pill, injection, implant or a progestogen-releasing intrauterine system IUS)*

You may switch any day from the progestogen-only pill (from an implant or an IUS on the day of its removal, from an injectable when the next injection would be due) but in all of these cases use extra protective measures (for example, a condom) for the first 7 days of taking CRISANTA.

- *After a miscarriage or abortion*

If you have had a miscarriage or abortion during the first three months of pregnancy, your doctor may tell you to start taking CRISANTA straight away. This means that you will have contraceptive protection with your first pill.

- *After having a baby*

You can start taking CRISANTA between 21 and 28 days after having a baby. If you start later than day 28, use a so-called barrier method (for example, a condom) during the first seven days of taking CRISANTA. If, after having a baby, you have had sex before starting CRISANTA (again), you must first be sure that you are not pregnant or wait until your next period.

- *If you are breastfeeding and want to start* CRISANTA *after having a baby*

Use of CRISANTA is generally not advisable when a woman is breastfeeding. If you want to take the pill while you are breastfeeding you should contact your doctor.

If you take more CRISANTA than you should

There are no reports of serious harmful results of taking too many DRSP+EE tablets.

If you take several tablets at once then you may feel sick or vomit or you may bleed from the vagina.

Even girls who have not yet started to menstruate but have accidentally taken this medicine may experience such bleeding.

If you have taken too many CRISANTA tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice

If you forget to take CRISANTA

- If you are less than 12 hours late taking a tablet, the protection against pregnancy is not reduced. Take the tablet as soon as you remember and then take the following tablets again at the usual time.
- If you are more than 12 hours late taking a tablet, the protection against pregnancy may be reduced. The greater the number of tablets you have forgotten, the greater is the risk of becoming pregnant.

The risk of incomplete protection against pregnancy is greatest if you forget a tablet at the beginning or at the end of the strip. Therefore, you should keep to the following rules:

- More than one tablet forgotten in this strip

Contact your doctor.

- One tablet forgotten between days 1 - 7

Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time and use extra precautions for the next 7 days, for example, a condom. If you have had sex in the week before forgetting the tablet you may be pregnant. In that case, contact your doctor.

- One tablet forgotten between days 8 – 14

Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time. The protection against pregnancy is not reduced, and you do not need to take extra precautions. If you forget more than one tablet use an additional barrier method such as a condom for 7 days.

- One tablet forgotten between days 15 – 21 - You can choose between two possibilities:
  1. Take the forgotten tablet as soon as you remember, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time. Instead of having seven pill-free days start the next strip as soon as you have taken the last tablet.

     Most likely, you will have a period at the end of the second strip – but you may also have light or menstruation-like bleeding during the second strip.

1. You can also stop the tablets and go directly to the tablet-free period (record the day on which you forgot your tablet). If you want to start a new strip on the day you always start, make the tablet-free period less than 7 days.

If you follow one of these two recommendations, you will remain protected against pregnancy.

If you have forgotten any of the tablets in a strip, and you do not have a bleeding during the first tablet-free period, you may be pregnant. Contact your doctor before you start the next strip.

What to do in the case of vomiting or severe diarrhoea

If you vomit within 3-4 hours of taking a tablet or you have severe diarrhoea, there is a risk that the active substances in the pill will not be fully taken up by your body. The situation is almost the same as forgetting a tablet. After vomiting or diarrhoea, take another tablet from a reserve strip as soon as possible. If possible take it within 12 hours of when you normally take your pill. If that is not

possible or 12 hours have passed, you should follow the advice given above.

Delaying your period: what you need to know

Although it is not recommended, you can delay your period by skipping the seven pill-free days and going straight to a new strip of CRISANTA and finishing it. You may experience light or menstruation-like bleeding while using this second strip. After the usual pill-free period of 7 days start your next strip.

Changing the first day of your period: what you need to know

If you take the tablets according to the instructions, then your period will begin during the seven pill-free days. If you have to change this day, make the pill-free period shorter – (but never longer – 7 days is the maximum!). For example, if you start the seven pill-free days on a Friday, and you want to change this to a Tuesday (3 days earlier) start a new strip 3 days earlier than usual. If you make the pill-free period very short (for example 3 days or less) you may not have any bleeding during this time. You may then experience light or menstruation-like bleeding.

If you stop taking CRISANTA

You can stop taking CRISANTA whenever you want. If you do not want to become pregnant, ask your doctor for advice about other reliable methods of birth control. If you want to become pregnant, stop taking CRISANTA and wait for a menstrual period before trying to become pregnant. You will be able to calculate the expected delivery date more easily.

Possible Side Effects

Like all medicines, DRSP+EE can cause side effects, although not everybody gets them. If you get any side effects, particularly if severe and persistent or you have any change to your health that you think may be due to DRSP+EE, please talk to your doctor.

An increased risk of blood clots in your veins (venous thromboembolism (VTE)) or blood clots in your arteries (arterial thromboembolism (ATE)) is present for all women taking combined hormonal contraceptives.

The following is a list of the side effects that have been linked with the use of DRSP+EE:

Serious side effects – see your doctor straight away

Signs of a severe allergic reaction to DRSP+EE:

- swelling of the face, lips, mouth, tongue or throat

Signs of breast cancer include:

- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel.

Signs of cancer of the cervix include:

- vaginal discharge that smells and/or contains blood
- unusual vaginal bleeding
- pelvic pain

- painful sex

Signs of severe liver problems include:

- severe pain in your upper abdomen
- yellow skin or eyes (jaundice)
- inflammation of the liver (hepatitis)
- your whole body starts itching

If you think you may have any of these, see a doctor straight away. You may need to stop taking DRSP+EE.

Common (may affect up to 1 in 10 people):

- menstrual disorders, bleeding between periods, breast pain, breast tenderness;
- headache; migraine
- depressive mood
- nausea
- thick whitish vaginal discharge, vaginal yeast infection.

Uncommon (may affect up to 1 in 100 people):

- breast enlargement
- increased or decreased interest in sex
- high blood pressure, low blood pressure
- being sick (vomiting), diarrhoea
- acne, skin rash, severe itching, hair loss (alopecia)
- vaginal infection
- fluid retention
- body weight changes

Rare (may affect up to 1 in 1,000 people):

- asthma;
- breast secretion;
- hearing impairment;
- the skin conditions erythema nodosum (characterised by painful reddish skin nodules) or erythema multiforme (characterised by rash with target-shaped reddening or sores).
- harmful blood clots in a vein or artery for example:
- in a leg or foot (i.e. deep vein thrombosis (DVT))
- in a lung (i.e. pulmonary embolism (PE))
- heart attack
- stroke
- mini-stroke or temporary stroke-like symptoms, known as a transient ischaemic attack (TIA)
- blood clots in the liver, stomach/intestine, kidneys or eye.

The chance of having a blood clot may be higher if you have any other conditions that increase this risk.

Reporting of side effects

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance

program of India by calling on 1800 180 3024 or you can report to Cipla Ltd on 18002677779. By reporting side effects, you can help provide more information on the safety of this product.

5. How to store CRISANTA

Store at a temperature not exceeding 25°C. Protect from moisture.

6. What does CRISANTA contain?

Each film coated tablet contains

Drospirenone.....3.0 mg

Ethinylestradiol ..... 0.03 mg

Details of Manufacturer

Manufactured in India by: Synokem Pharmaceuticals Ltd.

Plot No.: 56-57, Sector-6A, I.I.E (SIDCUL), Ranipur (BHEL), Haridwar-249403 (Uttarakhand)

Details of Permission or Licence Number with Date

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