Crisanta LN, Drospirenone / Ethinylestradiol, May 2020

For the use of a Registered Medical Practitioner only

Drospirenone and Ethinylestradiol Tablets IP

crisanta LN

BLACK BOX WARNING

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Women over 35 years old who smoke should not use Drospirenone (DRSP) and Ethinylestradiol (EE) tablets. Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use.

QUALITATIVE AND QUANTITATIVE DESCRIPTION
Each film-coated tablet contains:
Drospirenone IP ..... 3.0 mg
Ethinylestradiol IP ..... 0.030 mg
Colourant: Ferric Oxide Red USP, and Titanium Dioxide IP

DOSAGE FORM AND STRENGTH
Tablets for oral use only.

CLINICAL PARTICULARS
Therapeutic Indications
CRISANTA LN is indicated for:
- Use as oral contraceptive in women.
- Treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and who have tolerated other oral hormonal therapies. It should be used only if other treatments have failed.
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women. The effectiveness of DRSP and EE for PMDD when used for more than three individual cycles has not been evaluated. DRSP and EE has not been evaluated for the treatment of pre-menstrual syndrome.

Posology and Method of Administration
CRISANTA LN consists of 21 tablets of a monophasic combined hormonal preparation. The dosage of CRISANTA LN is one tablet daily for 21 consecutive days followed by 7 pill-free days per menstrual cycle.

How to take CRISANTA LN
Take one tablet daily at the same time every day. The tablets can only increase when pills are chosen in taken incorrectly. To achieve maximum contraceptive effectiveness CRISANTA LN must be taken exactly as directed, at the same time daily. Single tablets pills should be taken with water as necessary.

How to Start CRISANTA LN
Take the first tablet of CRISANTA LN on the initiated the patient to take one tablet of CRISANTA LN daily, beginning on Day 1 of the menstrual cycle (the first day of menstrual bleeding is Day 1).
The tablets should be taken in the sequence indicated on the blister pack. Subsequently, one tablet should be taken for 21 days, then a 7 pill-free period follows. Pill-free period is followed by 4 pill-free days. Withdrawal bleeding will normally occur in the pill-free period, which usually begins on the 2nd day after the last tablet. Withdrawal bleeding usually starts on the first day of the menstrual period. Start the next pack of CRISANTA LN on the same day of the week as the last tablet of the previous pack. Start the next pill-free period after the first 7 consecutive days of tablet administration. Start the next pill-free period after the first 7 consecutive days of tablet administration. Start the next pill-free period after the first 7 consecutive days of tablet administration

PMCD Clinical Trials
Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal haemorrhage, menorrhagia, metrorrhagia, disorder, amenorrhea/oligomenorrhea and metrorrhagia, 4.2%), fatigue (1.4%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions
Contraception Clinical Trials: migraine and cervical dysplasia
Acne Clinical Trials: none reported in the clinical trials
PMCD Clinical Trials: cervical dysplasia

Table 3 Adverse drug reactions which have been associated with the use of DRSP+EE as oral contraceptive or in the treatment of moderate acne vulgaris

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known (cannot be estimated from the available data)
Infections and Infestations			Candidiasis	
Blood and Lymphatic System Disorders			Anaemia Thrombocythemia	
Immune System Disorder			Allergic reaction	Hypersensitivity
Endocrine Disorders			Endocrine disorder	
Metabolism and Nutrition Disorders			Increased appetite Anorexia Hyperkalaemia Hyponatremia	
Psychiatric Disorders	Emotional lability	Depression Insomnia Nervousness	Anorgasmia Anorexia Confusional state	
Nervous system Disorders	Headache	Paresthesia	Vertigo Tremor	
Eye disorders			Conjunctivitis Dry eye Eye irritation Tachycardia	
Cardiac Disorders				
Vascular Disorders		Migraine Venous vein Hypertension	Phlebitis Vascular disorder Epistaxis Syncope VTE	
Gastrointestinal disorders	Nausea	Abdominal pain Dyspepsia Diarrhoea Flatulence Vomiting Diarrhoea	Abdomen enlarged Gastroenteritis Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth	
Hepatobiliary Disorders			Biliary pain Cholecystitis	
Skin and Subcutaneous tissue disorders		Chloasma Rash	Acne Alopecia Vaginal candidiasis Dry skin Dermatitis Hyperhidrosis Skin disorder Skin rash Contact dermatitis Photosensitive dermatitis Skin reticular	Erythema multiforme
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps		
Reproductive system and breast disorders	Breast pain Metrorrhagia Amenorrhoea	Vaginal haemorrhage Pelvic pain Breast enlargement Dysmenorrhoea Menorrhagia Vaginal discharge Premenstrual syndrome Breast cyst Breast hypertrophy Breast neoplasm Genital discharge Genital pruritus Vaginitis Menstrual disorder Dysmenorrhoea Hypomenorrhoea Menorrhagia Vaginal dryness Papanicolaou smear suspicious Libido decreased	Dyspareunia Vulvovaginitis Intermenstrual bleeding Polyp of cervix Breast hypertrophy Breast neoplasm Cervicitis Endometrial atrophy Endometrial polyp Uterine enlargement	
General disorders and administration sites conditions		Oedema Fatigue Bleeding increased Oedema Generalized oedema Peripheral oedema Face oedema Weight increased	Malaise	
Investigations		Weight increased	Weight decrease	

*Bleeding irregularities usually subside during continued treatment.

Description of Selected Adverse Reactions
An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs.

The following serious events have been reported in women using CHCs:
- Venous thromboembolic disorders,
- Arterial thromboembolic disorders,
- Hypertension,
- Liver tumors,
- Occurrence or deterioration of conditions for which association with CHC 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 angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema,
- 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 unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Adverse reactions are presented by System Organ Classes, and ordered by frequency.

Vascular Disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary Disorders: Gallbladder disease, liver function disturbances, liver tumours

Immune System Disorder: Hypersensitivity (including anaphylactic reaction)

Metabolism and Nutrition Disorders: Hyperglycaemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and Subcutaneous Tissue Disorders: Chloasma, angio-oedema, erythema nodosum, erythema multiforme

Gastrointestinal Disorders: Inflammatory bowel disease

Musculoskeletal and Connective Tissue Disorders: Systemic lupus erythematosus

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@zydus.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800267779 (Cipla Number) or please 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 serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females you are sexually active.
DRSP is a spironolactone analogue having anti-mineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis should be monitored in cases of overdose.
There has not yet been any experience of overdose with DRSP +EE. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur are: nausea, vomiting and in case of female or adolescent if active tablets are nausea, vomiting and withdrawal bleeding. Withdrawal bleeding may even occur in girls before the menarche, if they accidentally take the medicinal product. There are no antidotes and further treatment should be symptomatic.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Drospirenone is a spironolactone analogue with anti-mineralocorticoid and anti-androgenic activity. The oestrogen in CRISANTA+LS is ethynylestradiol.
COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that reduce sperm penetration and the endometrial changes that reduce the likelihood of implantation.

Contraception
Two studies assessed the efficacy of 3 mg DRSP / 0.02 mg EE combination on the suppression of ovarian activity as assessed by measurement of follicle size via transvaginal ultrasound and serum hormone (progesterone and estradiol) analyses during two treatment cycles (21-day active tablet period plus 7-day pill-free period). More than 90% of subjects in these studies demonstrated ovulation inhibition.

Acne
Acne vulgaris is a skin condition with a multifactorial aetiology, including androgen stimulation of sebum production. While the contributions of the different processes are known to be influenced by androgens, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the anti-androgenic activity of DRSP on acne is not known.

Pharmacokinetic properties

Absorption
The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 42% as a result of presystemic conjugation and first-pass metabolism. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after the administration.

The pharmacokinetics of DRSP are dose-proportional following single doses ranging from 1-10 mg. Following daily dosing of DRSP and EE, steady-state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{max} and $AUC_{(0-24)}$ values of DRSP following multiple-dose administration of DRSP and EE.
For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of DRSP and EE, serum C_{max} and $AUC_{(0-24)}$ values of EE accumulate by a factor of about 1.5-2.

Table 1. Pharmacokinetic Parameters of DRSP 3 mg and EE 0.02 mg

DRSP:					
Cycle/day	No. of subjects	C_{max} (ng/ml)	T_{max} (h) (IQR)	$AUC_{(0-24)}$ (ng·h/ml)	$t_{½}$ (h)
1/1	23	38.4 (25)	1.5 (1-2)	268 (19)	NA
1/21	23	70.3 (16)	1.5 (1-2)	763 (17)	30.8 (22)
EE:					
Cycle/day	No. of subjects	C_{max} (pg/ml)	T_{max} (h) (IQR)	$AUC_{(0-24)}$ (pg·h/ml)	$t_{½}$ (h)
1/1	23	32.8 (45)	1.5 (1-2)	108 (52)	NA
1/21	23	45.1 (35)	1.5 (1-2)	220 (57)	NA

NA = Not available

= geometric mean (geometric coefficient of variation)

= median (range)

Effect of Food
The rate of absorption of DRSP and EE following single administration of a formulation similar to DRSP and EE was slower under the high (5 times) 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.

Distribution
DRSP and EE serum concentrations decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4-5 L/kg.
DRSP does not bind to SHBG or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in a doubling of the serum SHBG concentrations (as measured at through concentrations). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98%) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced sheep SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2-3 mg.

Metabolism
The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4, 5-dihydrodrospirenone-3-sulphate formed by reduction and subsequent sulfation. These metabolites were shown to be pharmacologically active. Drospirenone is also subject to oxidative metabolism catalysed by CYP3A4.

EE has been reported to be subject to significant gut and the liver hepatic first-pass metabolism. Metabolism of EE and its oxidative metabolites occur primarily by conjugation with sulphate and glucuronide and subsidiary. CYP3A4 is 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.

Excretion
DRSP serum concentrations are characterized by a terminal disposition phase (half-life of approximately 30 hours after both single- and multiple-dose regimens). Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in females compared to males. DRSP is extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and faeces. 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 17-22% of the metabolites were excreted as glucuronides and sulphates.
For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and faeces as glucuronide and sulphate conjugates and undergoes enterohepatic circulation.

NON-CLINICAL PROPERTIES
Animal Toxicology
Data from 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+LS is an oral contraceptive. Each pack consists of 24 tablets, and each tablet contains 3 mg of drospirenone (DRSP) and 0.02 mg of ethinylestradiol (EE).

PHARMACEUTICAL PARTICULARS
Shelf life
See on pack.

Packaging Information
CRISANTA+LS is available in a pack of 24 tablets.

Storage and Handling Information
Store at temperature not exceeding 25°C. Protect from moisture.

PATIENT COUNSELLING INFORMATION
What CRISANTA+LS is and what it is used for?
CRISANTA+LS is a contraceptive pill and is used to prevent pregnancy, as well as to treat moderate acne and symptoms of premenstrual dysphoric disorder (PMDD).
It Each of the 24 tablets 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+LS

General notes
Before you start using CRISANTA+LS, you should read the information on blood clots mentioned below. It is particularly important to read the information on blood clots in your legs.

Before you can begin taking CRISANTA+LS, 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+LS, or where the reliability of CRISANTA+LS 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+LS alters the monthly changes of body temperature and of cervical mucus.

CRISANTA+LS, 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 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 and 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 embolism, PE) or other organs;
- if you think you may have a blood clot, or you are being treated with a blood thinner;
- if you have a severe disorder of your blood fat (cholesterol, lipids) or a disorder of your blood clotting (such as protein C deficiency, protein S deficiency, antithrombin 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 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 ischemic 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 hyperhomocysteinemia
  - 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 and EE if you have hepatitis C and are taking the medicinal products containing ombitasvir/paritaprevir/ritonavir or dasabuvir.

Warnings and Precautions
When should stop using 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), 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.
In some situations, you need to take special care while using DRSP and EE or any other combination pill, and your doctor may need to examine you regularly. If the condition develops or gets worse when you are using DRSP and EE, you should ask your doctor if:
- if a close relative has or has ever had breast cancer
- if you have a disease of the liver or the gallbladder
- if you have diabetes
- if you have depression
- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease)
- if you have haemolytic uremic syndrome (HUS) (a disease affecting your natural defense system)
- if you have sickle cell anemia (an inherited disease of the red blood cells)
- if you have systemic lupus erythematosus (SLE) (a disease affecting your natural defense system)
- if you have had porphyria (an inherited disease of the red blood cells causing failure of enzymes)
- 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 caused porphyria, skin rash with blisters during pregnancy (herpes gestationis), or a severe disease causing sudden movements of the body (Sydenham's chorea)
- if you have or have ever had pimples on your skin (acne vulgaris), or "pregnancy patches" especially on the face, if yes the case, avoid prolonged exposure to sunlight or ultraviolet light
- if you have hereditary angioedema, products containing oestrogens 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 pharynx and/or difficulty swallowing or difficulty breathing
- talk to your doctor before taking DRSP and EE

Blood Clots
Using a combined hormonal contraceptive such as DRSP and EE increases your risk of developing a blood clot compared with not using one. It can have a blood clot (blood clot) in a blood vessel and cause serious problems.
- 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 and EE is small.

How to recognize 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 color of the skin, for the leg (e.g. turning pale, red or blue)

Pulmonary embolism
- sudden unexplained breathlessness or rapid breathing
- sudden cough without an obvious cause (may bring up blood)
- sharp chest pain which may increase with deep breathing
- severe pain in the stomach
- dizziness or light-headedness
- 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
- blurred vision, which usually occurs in one eye
- immediate loss of vision or
- painless blurring of vision which can progress to loss of vision (blood clot in the eye)

Heart attack
- chest pain, discomfort, pressure, stress, weight, arms or below the breastbone
- sensation of squeezing or fullness in the chest, arm or shoulder
- 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 a stroke are like an early warning sign of a stroke. Be alert and full recovery, but you should still seek urgent medical attention as you may be at risk of a stroke in the future.

Blood clots blocking other blood vessels
- swelling and slight blue discoloration 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 forms 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 do risk of developing a blood clot in a vein is higher?
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 to form a blood clot is always slightly higher than if you were not using a combined hormonal contraceptive. When you stop DRSP and EE pills the 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) is only higher in women who use a combined hormonal contraceptive and are not pregnant. About 1 out of 10,000 women who are not using a combined hormonal contraceptive and are not pregnant, about 1 will develop a blood clot in a vein.
- About 2 out of 10,000 women who are not using a combined hormonal contraceptive that contains levonorgestrel, norethisterone, or norgestrel develop a blood clot in a vein.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains drospirenone, between about 9 and 12 women will develop a blood clot in a vein.
- 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 developing a blood clot in a vein is small but some conditions will increase the risk. Your risk is higher:
- if you are very overweight (if your body mass index or BMI is very high)
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g. 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 and EE may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop DRSP and EE talk 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 and EE needs to be stopped.
If any of the above conditions change while you are using DRSP and EE, for example a close family member experiences a thrombosis for no known reason, or you gain a lot of weight, tell your doctor.

Breast cancer is an early 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 these women are given more medical examinations, so that breast cancer is diagnosed more often by their doctor more often. The decreasing of breast tumours becomes gradually less after stopping the combination hormonal contraceptive. It is important to regularly check your breasts and you should consult your doctor if you feel any lump.
In rare cases, benign liver tumours, and in even lower cases malignant liver tumours have been reported in pill users. Contact your doctor if you have unusual abdominal pain.

Psychiatric disorders
Some women using hormonal contraceptives including DRSP and 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 and EE, you may have unexpected bleeding (bleeding outside the pill-free days). 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 you must do if no bleeding occurs during the pill free days
If you have taken all the active 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. Only start the next pack of tablets when you can be sure that you are not pregnant.

Other medicines and DRSP and EE
Always tell your doctor prescribe 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 and 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 and EE.
- can make it less effective in preventing pregnancy
- can cause unexpected bleeding

These include medicines used for the treatment of
- epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine)
- tuberculosis (e.g. rifampicin)
- HIV and hepatitis C Virus 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 and EE may influence the effect of other medicines, e.g.
- medicines containing cyclosporin
- the anti-epileptic lamotrigine (this could lead to an increased frequency of seizures)
- theophylline (used to treat breathing difficulties)
- tizanidine (used to treat muscle pain and/or muscle cramps)

Do not use DRSP and 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 and EE can be restarted approximately 2 weeks after completion of this treatment.

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

Breastfeeding
Use of DRSP and EE 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.

Driving and Using Machines
There is no information suggesting that use of DRSP and EE affects driving or use of machines

How to take CRISANTA+LS?
Each blister contains 24 active tablets the tablets of CRISANTA+LS are arranged in order. A strip contains 24 tablets. Take one tablet of CRISANTA+LS every day, if necessary, with a small amount of water. You may take the tablets with or without food, but you should take the tablets every day around the same time.

After the four pill free days, you must start a new strip. For the correct order, follow the direction of the arrows on the strip.

During the 4 pill free days, bleeding should begin (so-called withdrawal bleeding). This usually starts on the 2nd or 3rd day after the last tablet of CRISANTA+LS.

After the 4 pill free days, you should start with the following strip, whether you have bleeding or not. This means that you should start every strip on the same day of the week and your withdrawal bleed should occur on the same days each month, if you use CRISANTA+LS in this manner. you are protected against pregnancy also during the 4 days when you are pill free.

When can you start with the first strip?
If you have not used a contraceptive with hormones in the previous month
begin with CRISANTA+LS on the first day of the cycle (that is the first day of your period). If you start CRISANTA+LS on the first day of your menstruation 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 combined hormonal contraceptive, or combined contraceptive vaginal ring or patch
You can start CRISANTA+LS 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 combined 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 IUD)
You may switch any time from the progestogen-only pill (from an implant or an IUD on the day of its removal, from an injection when the next injection would be due) but in all of these cases you must use extra protective measures (for example, a condom) for the first 7 days of tablet-taking.

After a miscarriage
Follow the advice of your doctor.

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

If you are breastfeeding and want to start CRISANTA+LS (again) after having a baby
Ask your doctor what to do if you are not sure when to start.

If you take more CRISANTA+LS that you should
There are no reports of serious harmfulls of taking too many CRISANTA+LS tablets.
If you take several tablets at once then you may feel sick or vomit or 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+LS tablets, or you discover (because that a child has taken some, ask your doctor for advice.

If you forget to take CRISANTA+LS
If you are less than 24 hours late in taking any tablet, contraceptive protection is not reduced. Take the tablet as soon as you remember and should take the further tablets at the usual time. If you forget a tablet in the first week of your period, if you start CRISANTA+LS on the first day of your menstruation 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.
- The recommended hormone-free tablet interval (pill free days) must never be discontinued for longer than 7 days
- 7 days of uninterrupted tablet-taking are required to retain adequate suppression of the hypothalamic-pituitary-ovarian axis.

The risk of pregnancy increases with a missed tablet.
If your MISS one tablet:
Take it as soon as you remember. Take the next tablet at your regular time. This means you may take two tablets in one day. You do not need to use a back-up birth control method if you have sex.
If you MISS two tablets in a row in WEEK 1 OR WEEK 2 of the pack:
- Take two tablets on the day you remember and two tablets the next day.
- Then take one tablet a day until you finish the pack.
- You should become pregnant if you have sex the 7 days after you restart the tablets. However, if you miss your period 2 months in a row, contact your doctor or clinic because you might be pregnant.
If you MISS two tablets in a row in WEEK 3 OR WEEK 4 of the pack:
- Throw out the rest of the pack and start a new pack that same day.
- You should become pregnant if you have sex the 7 days after you restart the tablets. You must use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.
- You may not have your period, but this is expected. However, if you miss your period 2 months in a row, contact your doctor or clinic because you might be pregnant.
If you MISS three (or more) tablets in a row during ANY Week:
- Throw out the rest of the pack and start a new pack that same day.
- You could become pregnant if you have sex the 7 days after you restart the tablets. You must use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.
- You may not have your period, but this is expected. However, if you miss your period 2 months in a row, contact your doctor or clinic because you might be pregnant.
Finally, if you are still not sure what to do about the tablets you have missed:
- Use a back-up method (such as condoms or spermicides) anytime you have sex.
- Continue taking 1 tablet daily until you finish the pack.

Advice in Case of Gastrointestinal Disturbances
In case of 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, a new (replacement) tablet should be taken as soon as possible. This new tablet should be taken within 24 hours of the usual time of tablet-taking if possible. If more than 24 hours elapse, the advice concerning missed tablets is applicable. If you do not want to change your hormone tablet-taking schedule, you have to take the extra tablet(s) from another tablet blister pack.

Delaying your period: what you need to know
Even if it is not recommended, you can delay your period by exceeding the 4 pill free days and going straight to a new strip of CRISANTA+LS and finishing it.
You may experience light or premenstrual-like bleeding while using this second strip.
You might ask your doctor for advice before deciding to delay your menstrual period.
Changing the first day of your period to a later day than the usual one is only for females according to the instructions, your period will begin during the pill free days. If you have to change this day, reduce the number of pill free but never increase them – it is the maximum!!!
For example, if you stop taking tablets on a Friday, and you want to change this to a Tuesday (3 days earlier) you must start a new strip 3 days earlier than usual. You might experience bleeding during this time. You may then experience a premenstrual-like bleeding. If you are not sure what to do, ask your doctor.

If you stop taking CRISANTA+LS
You can stop taking CRISANTA+LS 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+LS and wait for a menstrual period before trying to become pregnant. This will be able to calculate the expected delivery date more easily. If you have any further questions on the use of this medicine, ask your doctor.

Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effect, particularly if severe and persistent, or have any other change in your health that you think may be due to DRSP and EE, please talk to your doctor.
An increased risk of blood clots in your veins (VTE) or blood clots in your arteries (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 and EE.
Common side effects (between 1 and 10 in every 100 users may be affected):
- mood swings
- headache
- nausea
- breast pain
- problems with your periods, such as irregular periods, absence of periods

Uncommon side effects (between 1 and 10 in every 1,000 users may be affected):
- depression, nervousness, sleeplessness
- dizziness, "pins and needles"
- migraine, varicose veins, increased blood pressure
- stomach ache, vomiting, diarrhea, mild nausea, inflammation of the stomach, stomachoss
- acne, itching, rash
- pain in your arms or legs, back pain, limb pain, muscle cramps
- vaginal fungal infection, pelvic pain, breast enlargement, benign breast lumps, uterine/vaginal bleeding (which usually subsides during continued treatment), painful menstruation, painful sex, Bulkiness, inflammation of the vagina (vaginitis), problems with your periods, painful periods, reduced periods, very heavy periods, vaginal dryness, abnormal cervical smear, decreased interest in sex, lack of energy, increased sweating, fluid retention
- weight increase

Rare side effects (between 1 and 10 in every 10,000 users may be affected):
- candida (fungal infection)
- allergic reaction, increase in the number of pimples in the blood
- nervous tension
- hormonal (endocrine) disorder
- increased appetite, loss of appetite, abnormally high concentration of potassium in the blood, abnormally low concentration of sodium in the blood
- failure to experience an orgasm, anorexia
- giddiness, tremor
- eye disorders, e.g. inflammation of the eyelid, dry eyes
- abnormally rapid heartbeat
- inflammation of a vein, nosebleed, flushing
- enlarged abdomen, bowel disorders, bloated, stomach hernia, fungal infection of the mouth, constipation, dry mouth
- pain of bile ducts or the gallbladder, inflammation of the gallbladder
- yellow bowel pigments, dry skin, skin disorders, such as acne, allergic rash, inflammation of the skin, dry skin, lumpy inflammation of the skin, successes hair growth, skin discoloration, reddish or brownish marks on the skin, skin disorder following intensive, withdrawal bleeding, breast pain, difficult or painful sex, inflammation of the vagina (vaginitis), vaginal fungal infection, withdrawal bleeding, breast pain, increased number of breast cancer, benign breast lumps in the breast, abnormal growth in the mucosal surface of the neck of the uterus, shrinkage or swelling of the breasts, uterine cysts, enlargement of the womb, breast cysts
- feeling generally unwell
- water retention
- painful blood clots in a vein or artery for example:
  - in a leg or foot (i.e. DVT)
  - in a lung (i.e. 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 chances of having a blood clot in a blood vessel may be higher if you have any other conditions that increase this risk.
The following side effects have also been reported, but their frequency cannot be estimated from the available data: hypersensitivity, erythema multiforme (rash with target-shaped reddening or spots)

Reporting of side effects
If you experience any side effects, talk to your doctor or pharmacist or write to drugsafety@zydus.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 1800267779. By reporting side effects, you can help provide more information on the safety of this product.

5. How to store CRISANTA+LS

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

6. What CRISANTA+LS contains
Each film-coated tablet contains
Drospirenone IP.....3.0 mg
Ethinylestradiol IP.....0.02 mg

DETAILS OF MANUFACTURER
Manufactured in India by : Sikkim Manipal Pharmaceuticals Ltd.
Plot No.: 58-57, Section-6A, I.E. (SIDCO/IL), Rangpo (BHEL), Hamtabari-264403 (Uttarakhand)

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