Drospirenone and Ethinylestradiol Tablets I.P.
DORIS® Tablets

PHYSICIAN LABELING

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

1. TRADENAME OF THE MEDICINAL PRODUCT

DORIS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DORIS provides an oral contraceptive regimen consisting of 21 active uncoated tablets each tablet containing:

Drospirenone I.P. …….3.0 mg
Ethinylestradiol I.P. ……..0.03 mg

For full list of excipients , refer section 6.1
All strengths/ presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Uncoated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DORIS is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

4.2 Posology and Method of Administration

How to take DORIS

To achieve maximum contraceptive effectiveness, DORIS (drospirenone and ethinyl estradiol) must be taken exactly as directed at intervals not exceeding 24 hours.
DORIS consists of 21 tablets of a monophasic combined hormonal preparation. The dosage of DORIS is one tablet daily for 21 consecutive days followed by 7 pill-free days per menstrual cycle. A patient should begin to take DORIS on the first day of her menstrual period (Day 1 Start).

How to start DORIS

Day 1 Start. During the first cycle of DORIS use, the patient should be instructed to take one DORIS tablet daily, beginning on day one 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 DORIS be taken at the same time each day, preferably after the evening meal or at bedtime. If DORIS is first taken later than the first day of the menstrual cycle, DORIS should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 21-day regimens of DORIS 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. Anytime a subsequent cycle of DORIS is started later than the day following 7 pill-free days, the patient should use another method of contraception until she has taken a DORIS tablet daily for seven consecutive days.

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

Withdrawal bleeding usually occurs within 3 days following the last tablet. If spotting or breakthrough bleeding occurs while taking DORIS, the patient should be instructed to continue taking her DORIS as instructed and by 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 her physician.

Although the occurrence of pregnancy is unlikely if DORIS 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 active 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.

In the non- lactating mother, DORIS may be initiated 4 weeks postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (**See Section 4.3 CONTRAINDICATIONS and Section 4.4 Special Warnings and Special Precautions for Use concerning thromboembolic disease.**)

Management of Missed Tablets

The risk of pregnancy increases with each tablet missed. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient forgets to take a tablet at the usual time, the tablet may be taken within the next 12 hours. If more than 12 hours have elapsed from the time of usual administration, the patient must discard the missed tablet and continue to take the remaining tablets in the pack at the usual time in order to avoid premature withdrawal bleeding during this cycle. A supplementary nonhormonal method of contraception must be employed until the pack is empty to prevent pregnancy, which would necessitate immediate discontinuation of DORIS treatment.

If she **MISSES 1** tablet,
- Ask her to take the dose as soon as she remembers or to take two pills at the time of her next regularly scheduled dose.
- She does not need to use backup birth control.

If she **MISSES 2** tablets in a row in **WEEK 1 OR 2,**
- Ask her to take two tablets each for the next two regularly scheduled doses (one missed tablet plus one regularly scheduled tablet for 2 days in a row).
- Ask her to use another form of birth control for at least 7 days following the missed tablets.

If she **MISSES 2** tablets in a row in **WEEK 3**, or if she **MISSES 3** tablets in a row during any of the first **3 WEEKS**,
- Ask her to throw out the rest of the pack and start a new package on the same day.
- She may not have a period that month, but this is expected. However, if she misses her period 2 months in a row, she might be pregnant.

If she misses a pill, she may become pregnant if she has sex in the 7 days after her missed pill. She MUST use another birth control method (such as condoms or spermicides) as a back-up for those 7 days.

4.3 Contraindications

DORIS should not be used in women who have the following:
- Renal insufficiency
- Hepatic dysfunction
- Adrenal insufficiency

- Thrombophlebitis or thromboembolic disorders
- A past history of deep-vein thrombophlebitis or thromboembolic disorders
- Cerebral-vascular or coronary-artery disease
- Valvular heart disease with thrombogenic complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Known or suspected carcinoma of the breast Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Liver tumor (benign or malignant) or active liver disease
- Known or suspected pregnancy
- Heavy smoking (≥15 cigarettes per day) and over age 35

4.4 Special Warnings and Special Precautions for Use

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

DORIS contains 3 mg of the progestin drospirenone that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. DORIS should not be used in patients with conditions that predispose to hyperkalemia (i.e. renal insufficiency, hepatic dysfunction and adrenal insufficiency).

Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium, should have their serum potassium level checked during the first treatment cycle. Drugs that may increase serum potassium include ACE inhibitors, angiotensin–II receptor antagonists, potassium-sparing diuretics, heparin, aldosterone antagonists, and NSAIDs.

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, gallbladder disease, and hypertension, although the risk of serious morbidity or mortality is very small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is based principally on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and

progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. *Myocardial infarction*
An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary- artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 among women who use oral contraceptives.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users. Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism
An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery.

c. Cerebrovascular diseases
Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives
A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest estrogen content which provides satisfactory results in the individual.

e. Persistence of risk of vascular disease
There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE
One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages. These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable

to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is below that associated with childbirth.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of COCs. However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not appear to increase with duration of use and no consistent relationships have been found with dose or type of steroid. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history. Some studies have found a small increase in risk for women who first use COCs before age 20.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormonally-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular

lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE 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, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

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

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed dosing schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS
Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.

Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (**see section 4.4 Special Warnings and Special Precautions for Use-1a and 1d**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE
An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely, and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. BLEEDING IRREGULARITIES
Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. GENERAL
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. PHYSICAL EXAMINATION AND FOLLOW-UP
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

3. LIPID DISORDERS
Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

4. LIVER FUNCTION

If jaundice develops in any woman receiving oral contraceptives, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

5. FLUID RETENTION
Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

6. EMOTIONAL DISORDERS
Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. CONTACT LENSES
Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

8. PEDIATRIC USAGE
Safety and efficacy of DORIS have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Effects of Other Drugs on Combined Hormonal Contraceptives

Rifampin
Metabolism of ethinylestradiol and some progestins (e.g., norethindrone) is increased by rifampin. A reduction in contraceptive effectiveness and an increase in menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants
Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine have been shown to increase the metabolism of ethinylestradiol and/or some progestins, which could result in a reduction of contraceptive effectiveness.

Antibiotics
Pregnancy while taking combined hormonal contraceptives has been reported when the combined hormonal contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effects of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin
Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinylestradiol by approximately 30% and 20%, respectively.
St. John's Wort

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of oral contraceptives and emergency contraceptive pills. This may also result in breakthrough bleeding.

Other
Ascorbic acid and acetaminophen may increase plasma concentrations of some synthetic estrogens, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and an increased incidence of menstrual irregularities has been suggested with phenylbutazone.

Effects of Drospirenone on Other Drugs

Metabolic Interactions

Metabolism of DRSP and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in *in vitro* and *in vivo* studies (see **Metabolism**). In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19 and CYP3A4 with CYP2C19 being the most sensitive enzyme.

Interactions with Drugs That Have the Potential to Increase Serum Potassium

There is a potential for an increase in serum potassium in women taking DRSP and EE with other drugs. Of note, occasional or chronic use of NSAID medication was not restricted in any of the DRSP and EE clinical trials.

Effects of Combined Hormonal Contraceptives on Other Drugs

Combined oral contraceptives containing ethinylestradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance on temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

INTERACTIONS WITH LABORATORY TESTS

Certain endocrine- and liver-function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by

radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex-hormone-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
e. Triglycerides may be increased.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

4.6 Pregnancy and Lactation

Pregnancy category X.

Estrogens and progestins should not be used during pregnancy. Fourteen pregnancies that occurred with DRSP and EE exposure *in utero* (none with more than a single cycle of exposure) have been identified. One infant was born with esophageal atresia. A causal association with DRSP and EE is unknown.

A teratology study in pregnant rats given drospirenone orally at doses of 5, 15 and 45 mg/kg/day, 6 to 50 times the human exposure based on AUC of drospirenone, resulted in an increased number of fetuses with delayed ossification of bones of the feet in the two higher doses. A similar study in rabbits dosed orally with 1, 30 and 100 mg/kg/day drospirenone, 2 to 27 times the human exposure, resulted in an increase in fetal loss and retardation of fetal development (delayed ossification of small bones, multiple fusions of ribs) at the high dose only. When drospirenone was administered with ethinylestradiol (100:1) during late pregnancy (the period of genital development) at doses of 5, 15 and 45 mg/kg, there was a dose dependent increase in feminization of male rat fetuses. In a study in 36 cynomolgous monkeys, no teratogenic or feminization effects were observed with orally administered drospirenone and ethinylestradiol (100:1) at doses up to 10 mg/kg/day drospirenone, 30 times the human exposure.

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

After oral administration of DORIS about 0.02% of the drospirenone dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 3 mcg drospirenone in an infant.

4.7 Effects on Ability to Drive and Use Machines

There is no clinical data available on effect of drospirenone and ethinylestradiol on ability to drive or use machines.

4.8 Undesirable Effects

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

Thrombophlebitis, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease and hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:
Mesenteric thrombosis and retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:
Nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, temporary infertility after discontinuation of treatment, edema, melasma which may persist, breast changes: tenderness, enlargement, secretion, change in weight (increase or decrease), change in cervical erosion and secretion, diminution in lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), mental depression, reduced tolerance to carbohydrates, vaginal candidiasis, change in corneal curvature (steepening) and intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and a causal association has been neither confirmed nor refuted:
Acne, Budd-Chiari syndrome, cataracts, changes in appetite, changes in libido, colitis, cystitis-like syndrome, dizziness, erythema multiforme, erythema nodosum, headache, hemolytic uremic syndrome, hemorrhagic eruption, hirsutism, impaired renal function, loss of scalp hair, nervousness, porphyria, pre-menstrual syndrome and vaginitis.

The following are the most common adverse events reported with use of DRSP and EE during the clinical trials, occurring in > 1% of subjects and which may or may not be drug related:

Headache, Menstrual Disorder, Breast Pain, Abdominal Pain, Nausea, Leukorrhea, Flu Syndrome, Acne, Vaginal Moniliasis, Depression, Diarrhea, Asthenia, Dysmenorrhea, Back Pain, Infection, Pharyngitis, Intermenstrual Bleeding, Migraine, Vomiting, Dizziness, Nervousness, Vaginitis, Sinusitis, Cystitis, Bronchitis, Gastroenteritis, Allergic Reaction,

Urinary Tract Infection, Pruritus, Emotional Lability, Surgery, Rash, Upper Respiratory Infection.

4.9 Overdosage

Serious ill effects have not been reported following acute ingestion of large doses of other oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. Drospirenone, however, is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).
Drospirenone is a spironolactone analogue with antimineralocorticoid activity. Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

NON-CONTRACEPTIVE HEALTH BENEFITS
The following non-contraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.

Effects on menses
- increased menstrual cycle regularity
- decreased blood loss and decreased incidence of iron-deficiency anemia
- decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation
- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancies

Effects from long-term use
- decreased incidence of fibroadenomas and fibrocystic disease of the breast
- decreased incidence of acute pelvic inflammatory disease
- decreased incidence of endometrial cancer
- decreased incidence of ovarian cancer

5.2 Pharmacokinetic Properties

Absorption

The absolute bioavailability of drospirenone (DRSP) from a single entity tablet is about 76%. The absolute bioavailability of ethinyl estradiol (EE) is approximately 40% as a result

of presystemic conjugation and first-pass metabolism. The absolute bioavailability of DORIS which is a combination tablet of drospirenone and ethinyl estradiol has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1–3 hours after administration of DORIS. After single dose administration of DORIS, the relative bioavailability, compared to a suspension, was 107% and 117% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1–10 mg. Following daily dosing of DORIS, steady state DRSP concentrations were observed after 10 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 DORIS (**see TABLE I**).
For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of DORIS serum C_{max} and AUC(0–24h) values of EE accumulate by a factor of about 1.5 to 2.

TABLE I- TABLE OF MEAN PHARMACOKINETIC PARAMETERS OF DORIS (Drospirenone 3 mg and Ethinyl Estradiol 0.03 mg)

Drospirenone
Mean (%CV) Values

Cycle / Day	**No. of Subjects**	**C_{max} (ng/mL)**	**T_{max} (h)**	**AUC(0–24h) (ng•h/mL)**	**t1/2 (h)**
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA[a]
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)

Ethinyl Estradiol
Mean (%CV) Values

Cycle / Day	**No. of Subjects**	**C_{max} (pg/mL)**	**T_{max} (h)**	**AUC(0–24h) (pg•h/mL)**	**t1/2 (h)**
1/1	11	53.5 (43)	1.9 (45)	280.3 (87)	NA[a]
1/21	11	92.1 (35)	1.5 (40)	461.3 (94)	NA[a]
6/21	11	99.1 (45)	1.5 (47)	346.4 (74)	NA[a]
9/21	11	87 (43)	1.5 (42)	485.3 (92)	NA[a]
13/21	10	90.5 (45)	1.6 (38)	469.5 (83)	NA[a]

a) NA = Not available

Effect of Food
The rate of absorption of DRSP and EE following single administration of two DORIS tablets was slower under fed conditions with the serum Cmax 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 levels 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 sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough levels). 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

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In in vitro studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by cytochrome P450 3A4 (CYP3A4).
EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver are responsible for the 2hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum levels are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38–47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17–20% of the metabolites were excreted as glucuronides and sulfates.
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 feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Pharmacokinetics in Special Patient Groups

Hepatic Dysfunction

DORIS is contraindicated in patients with hepatic dysfunction. The mean exposure to DRSP in women with moderate liver impairment is approximately three times the exposure in women with normal liver function.

Renal Insufficiency
DORIS is contraindicated in patients with renal insufficiency.

5.3 Preclinical Safety Data

Preclinical studies in animals and *in vitro* have shown that drospirenone has no androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. Preclinical studies in animals have also shown that drospirenone has antiandrogenic activity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose IP (70 mesh) , Microcrystalline Cellulose IP (pH 101) , Indion 234 , Magnesium Stearate IP

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

24 months

6.4 Special Precautions for Storage

Store below 30°C . Protect from moisture.

6.5 Nature and Contents of Container

1. Printed Aluminium Foil

2.PVC/PVdC Film

6.6. Instruction for Use/Handling

None specific