

## PRODUCT MONOGRAPH

**PrNIKKI**

3.0 mg drospirenone and 0.020 mg ethinyl estradiol tablets

Manufacturer's Standard

Oral Contraceptive

Acne Therapy

Manufacturer:  
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# PrNIKKI

3.0 mg drospirenone and 0.020 mg ethinyl estradiol

Manufacturer's Standard

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/3.0 mg drospirenone and 0.020 mg ethinyl estradiol	Lactose monohydrate <i>For a complete listing see <b>DOSAGE FORMS, COMPOSITION AND PACKAGING</b> section.</i>

### INDICATIONS AND CLINICAL USE

NIKKI (3.0 mg drospirenone and 0.020 mg ethinyl estradiol) is indicated for:

- Conception control
- Treatment of moderate acne vulgaris in women  $\geq 14$  years of age who have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche

### CONTRAINDICATIONS

NIKKI (3.0 mg drospirenone and 0.020 mg ethinyl estradiol) should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders
- a history of or actual cerebrovascular disorders
- a history of or actual myocardial infarction or coronary artery disease
- valvular heart disease with complications
- a history of or actual prodromi of a thrombosis (eg, transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - severe hypertension (persistent values of  $\geq 160/100$  mmHg)
  - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - severe dyslipoproteinemia
  - smoking, if over age 35
  - diabetes mellitus with vascular involvement
  - major surgery associated with an increased risk of postoperative thromboembolism
  - prolonged immobilization

- active liver disease or history of, or actual benign or malignant liver tumors
- known or suspected carcinoma of the breast
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- undiagnosed abnormal vaginal bleeding
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- known or suspected pregnancy
- current or history of migraine with focal aura
- history of or actual pancreatitis if associated with severe hypertriglyceridemia
- renal insufficiency
- hepatic dysfunction
- adrenal insufficiency
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age particularly in women over 35 years of age and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including NIKKI, should not be used by women who are over 35 years of age and smoke. Women should be counselled not to smoke (see **WARNINGS AND PRECAUTIONS - Cardiovascular** section below).

Hormonal contraceptives **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. While using hormonal contraceptives, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** hormonal contraceptives to protect against STIs.

### General

#### Discontinue Medication at the Earliest Manifestation of:

- A. **Thromboembolic and Cardiovascular Disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis
- B. **Conditions that Predispose to Venous Stasis and to Vascular Thrombosis** (eg, immobilization after accidents or confinement to bed during long-term illness). Other nonhormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **WARNINGS AND PRECAUTIONS - Peri-operative Considerations**.

- C. **Visual Defects - Partial or Complete**
- D. **Papilledema, or Ophthalmic Vascular Lesions**
- E. **Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache**
- F. **Increase in Epileptic Seizures**

The following information is provided from studies of combination oral contraceptives (COCs).

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus, (1) hemolytic uremic syndrome, (2-4) chronic inflammatory bowel disease, (Crohn's disease or ulcerative colitis), (5) sickle cell disease, (6) valvular heart disease, and atrial fibrillation. (7, 8)

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria, (9) systemic lupus erythematosus, (10) hemolytic uremic syndrome, (11) Sydenham's chorea, (12, 13) herpes gestationis, (14, 15) and otosclerosis-related hearing loss. (16)

The information contained in this section is principally from studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered orally remains to be determined.

**NIKKI contains 3 mg of the progestin drospirenone (DRSP) that has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. NIKKI should not be used in patients with conditions that predispose to hyperkalemia (eg, 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.**

### **Carcinogenesis and Mutagenesis**

Malignancies may be life-threatening or may have a fatal outcome.

## ***Breast Cancer***

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.

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than 8 years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended, because, if breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

## ***Cervical Cancer***

The most important risk factor for cervical cancer is persistent human papillomavirus infection (HPV). Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk, but there continues to be controversy about the extent to which this finding is attributable to confounding effects, eg, cervical screening and sexual behaviour including use of barrier contraceptives.

## ***Hepatocellular Carcinoma***

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

See **TOXICOLOGY** for discussion of animal data.

## **Cardiovascular**

### ***Predisposing Factors for Coronary Artery Disease***

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke. For this reason, combination oral contraceptives, including NIKKI, should not be used by women who are over 35 years of age and smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear.

In low-risk, nonsmoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

### ***Hypertension***

Patients with essential hypertension whose blood pressure is well-controlled may be given hormonal contraceptives, but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. 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.

### **Endocrine and Metabolism**

#### ***Diabetes***

Current low-dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

#### ***Lipid and Other Metabolic Effects***

A small proportion of women will have adverse lipid changes while on oral contraceptives. Alternative contraception should be used in women with uncontrolled dyslipidemia (see also **CONTRAINDICATIONS**). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

### **Gastrointestinal**

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established. (17-22)

### **Genitourinary**

#### ***Vaginal Bleeding***

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

#### ***Fibroids***

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of oral contraceptives.

### **Hematologic**

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism, and of cerebrovascular accidents. These events occur rarely.

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts (following a 4-week or greater pill-free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months. VTE is life-threatening and is fatal in 1% to 2% of cases. (23)

A large, prospective 3-armed cohort study has shown that the frequency of VTE diagnosis ranges from about 8 to 10 per 10,000 woman-years in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in nonpregnant, non-COC users and ranges from 20 to 30 per 10,000 woman-years in pregnant women or postpartum.

Overall the risk for VTE in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) is 2- to 3-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Several epidemiological studies have examined the risk of VTE with drospirenone-containing COCs versus other COCs. Two prospective cohort studies showed that the risk of VTE with drospirenone-containing COCs is comparable to that of other COCs, including levonorgestrel-containing COCs. (24, 25) One case-control and three retrospective cohort studies suggested that the risk of VTE with drospirenone-containing COCs is higher compared to users of levonorgestrel-containing COCs. (26-29) Two additional nested case-control studies have reported a two-fold and three-fold increased risk of idiopathic VTE in users of drospirenone containing COCs as compared with levonorgestrel-containing COCs. (30, 31) These retrospective studies suggest a potential 1.5-3 times risk of VTE in users of drospirenone containing COCs. Epidemiological studies have inherent methodological issues making the interpretation of their results complex. (26-31) However, prescribers should consider the benefits and risks for specific patients with respect to VTE risk given the current retrospective epidemiological studies suggesting a higher risk of VTE with drospirenone-containing COCs compared to levonorgestrel-containing COCs.

VTE, manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE), may occur during the use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users.

Symptoms of DVT can include: unilateral swelling of the leg 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 discolored skin on the leg.

Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (eg, “shortness of breath”, “coughing”) are nonspecific and might be misinterpreted as more common or less severe events (eg, respiratory tract infections).



The risk for arterial thromboembolism (ATE) in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) ranges from about 1 to 3 cases per 10,000 woman-years. An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion, or myocardial infarction (MI). 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 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. Other signs of vascular occlusion can include: sudden pain, swelling, and slight blue discoloration of an extremity; acute abdomen.

Symptoms of 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; fullness, indigestion or choking feeling; sweating, nausea, vomiting, or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events are life-threatening and may have a fatal outcome.

### ***Other Risk Factors for Venous or Arterial Thromboembolism or of a Cerebrovascular Accident***

Other generalized risk factors for venous or arterial thromboembolism include but are not limited to age, severe obesity (body mass index >30 kg/m<sup>2</sup>), a personal history, a positive family history (the occurrence of VTE/ATE in a direct relative at a relatively early age may indicate genetic predisposition) and systemic lupus erythematosus. If a hereditary or acquired predisposition for venous or arterial thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use. The risk of VTE/ATE may be temporarily increased with prolonged immobilization, major surgery, or trauma. In these situations, it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume COC use until 2 weeks after complete remobilization. Also, patients with varicose veins and leg cast should be closely supervised. Other risk factors may include smoking (with heavier smoking and increasing age, the risk further increases, especially in women over 35 years of age), dyslipoproteinemia, hypertension, migraine, valvular heart disease, and atrial fibrillation.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinyl estradiol).

### **Hepatic/Biliary/Pancreatic**

In some cases of elevated liver enzymes reported during clinical trials with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, a contributory role of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol could not be ruled out. NIKKI is contraindicated in patients with active liver disease (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS - Drug-Laboratory Test Interactions**).

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

### ***Jaundice***

Patients who have had jaundice should be given oral contraceptives with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking hormonal contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

### ***Gallbladder Disease***

Patients taking oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after 4 or 5 years.

### ***Hepatic Nodules***

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

## **Immune**

### ***Angioedema***

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular, in women with hereditary angioedema. (32-34)

## **Neurologic**

### ***Migraine and Headache***

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of hormonal contraceptives and evaluation of the cause. Women with migraine headaches who take oral contraceptives may be at increased risk of stroke (see **CONTRAINDICATIONS**).

## **Ophthalmologic**

### ***Ocular Disease***

Patients who are pregnant or are taking oral contraceptives may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in

tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

### ***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.

### **Peri-operative Considerations**

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least 1 month prior to **MAJOR** elective surgery. Oral contraceptive use should not be resumed until the first menstrual period after hospital discharge following surgery.

### **Psychiatric**

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made, which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

### **Renal**

#### ***Fluid Retention***

Hormonal 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.

### **Sexual Function/Reproduction**

#### ***Return to Fertility***

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least 1 normal spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

#### ***Amenorrhea***

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

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

### ***Reduced Efficacy***

The efficacy of COCs may be reduced in the event of missed tablets, gastrointestinal disturbances or concomitant medication (see **DOSAGE AND ADMINISTRATION** and **DRUG INTERACTIONS**).

### **Skin**

Chloasma may occasionally occur with use of COCs, 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.

### **Special Populations**

#### ***Pregnant Women***

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with NIKKI, further intake must be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. One infant was born with esophageal atresia during treatment with YASMIN, an OC of similar composition but with different dose and regimen. The causal association is unknown.

#### ***Nursing Women***

In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low-dose oral contraceptives are harmful to the nursing infant.

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 YASMIN, an OC of similar composition but with different dose and regimen, 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 µg drospirenone in an infant.

#### ***Pediatrics***

The safety and efficacy of NIKKI has not been established in women under the age of 14 years. Use of this product before menarche is not indicated.

#### ***Geriatrics***

NIKKI is not indicated for use in postmenopausal women.

## **Monitoring and Laboratory Tests**

### ***Physical Examination and Follow-up***

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (eg, deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities, and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

The first follow-up visit should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

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

- arterial and venous thromboembolism
- being diagnosed with breast cancer
- benign and malignant hepatic tumors
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (eg, retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following adverse reactions also have been reported in patients receiving oral contraceptives: nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or fewer of patients during the first cycle. The following other reactions, as a general rule, are seen less frequently or only occasionally:

- abdominal pain
- amenorrhea during and after treatment
- angioedema (exogenous estrogens may induce or exacerbate symptoms of angioedema in women with hereditary angioedema)
- auditory disturbances

- breakthrough bleeding
- breast changes (tenderness, enlargement and secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in libido
- change in menstrual flow
- change in weight (increase or decrease)
- changes in glucose tolerance or effect on peripheral insulin resistance
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- mental depression
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum
- gallstone formation<sup>a</sup>
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome<sup>a</sup>
- hemorrhagic eruption
- herpes gestationis<sup>a</sup>
- hirsutism
- hypersensitivity
- hypertriglyceridemia (increased risk of pancreatitis when using COCs).
- hypertension
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestasis<sup>a</sup>
- liver function disturbances
- loss of scalp hair
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss<sup>a</sup>
- pancreatitis
- porphyria<sup>a</sup>

- possible diminution in lactation when given immediately postpartum
- premenstrual-like syndrome
- pruritus related to cholestasis<sup>a</sup>
- rash (allergic)
- Raynaud’s phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- Sydenham’s chorea<sup>a</sup>
- systemic lupus erythematosus<sup>a</sup>
- temporary infertility after discontinuation of treatment
- urticaria
- ulcerative colitis
- vaginal candidiasis
- vaginal discharge
- vaginitis

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The clinical development programs were conducted independently for each of the 2 indications and utilized indication-specific inclusion criteria, study designs, and settings. Thus, the safety results of the studies are presented separately and are not pooled.

The following adverse drug reactions were reported at a frequency  $\geq 1\%$  in pivotal clinical trials using 3.0 mg drospirenone and 0.020 mg ethinyl estradiol as an oral contraceptive:

**Table 2: Adverse Drug Reactions With Frequency of  $\geq 1\%$  in Pivotal OC Clinical Trials With 3.0 mg Drospirenone and 0.020 mg Ethinyl Estradiol (N=2438)**

<b>HARTS Body System</b>	<b>HARTS Preferred Term</b>	<b>n</b>	<b>%</b>
Digestive System/General	Nausea	48	2.0
Nervous System/General	Headache	118	4.8
Nervous System/Central Nervous System/Brain	Emotional lability	28	1.1
Skin and Appendages/Dermatose/Acneform	Acne	24	1.0
Skin and Appendages/Breast Disorders	Breast pain	106	4.3
Urogenital System/Female Genital Disorders/Menstrual Disorders	Amenorrhea	61	2.5
	Intermenstrual bleeding	110	4.5

Abbreviations: HARTS = Hoechst Adverse Reaction Terminology System, N = total number, n = number of subjects, OC = oral contraception

<sup>a</sup> Occurrence or deterioration of conditions for which association with COC use is not conclusive

The following adverse drug reactions were reported at a frequency  $\geq 1\%$  in pivotal clinical trials using 3.0 mg drospirenone and 0.020 mg ethinyl estradiol in the treatment of moderate acne vulgaris:

**Table 3: Adverse Drug Reactions With Frequency of  $\geq 1\%$  in Pivotal Moderate Acne Vulgaris Clinical Trials With 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (N=536)**

HARTS Body System	HARTS Preferred Term	n	%
Digestive System/General	Nausea	22	4.1
	Vomiting	7	1.3
Nervous System/General	Headache	24	4.5
Nervous System/Central Nervous System/Brain	Emotional lability	12	2.2
	Depression	7	1.3
Skin and Appendages/Breast Disorders	Breast pain	8	1.5
Urogenital System/Female Genital Disorders/Menstrual Disorders	Dysmenorrhea	8	1.5
	Metrorrhagia	53	9.9
	Menorrhagia	14	2.6
	Menstrual Disorder	8	1.5

Abbreviations: HARTS = Hoechst Adverse Reaction Terminology System, N = total number, n = number of subjects

### **Less Common Clinical Trial Adverse Drug Reactions**

The following adverse drug reactions were seen at a frequency of  $< 1\%$  and  $\geq 0.1\%$  in pivotal clinical trials using 3.0 mg drospirenone and 0.020 mg ethinyl estradiol as an oral contraceptive:

**Body as a whole:** abdominal pain, asthenia, back pain, pain in extremity, pelvic pain

**Cardiovascular system:** hypertension, migraine, varicose vein

**Digestive system:** diarrhea, dyspepsia, flatulence, gastritis, vomiting

**Metabolic and nutritional disorders:** weight gain, edema, peripheral edema

**Musculoskeletal system:** muscle cramps

**Nervous system:** dizziness, paresthesia, sweating increased, depression, libido decreased, nervousness, somnolence

**Skin and appendages:** breast enlargement, acne, pruritus, fibrocystic breast, rash

**Urogenital system:** hypomenorrhea, leukorrhea, vaginal dryness, vaginal moniliasis, dysmenorrhea, metrorrhagia, vaginal hemorrhage, menstrual disorder, PAP smear suspicious, vaginitis, menorrhagia

The following adverse drug reactions were seen at a frequency of  $< 1\%$  and  $\geq 0.1\%$  in pivotal clinical trials using 3.0 mg drospirenone and 0.020 mg ethinyl estradiol in the treatment of moderate acne vulgaris:



**Body as a whole:** abdominal pain, asthenia, malaise

**Cardiovascular system:** hypertension, migraine

**Urogenital system:** amenorrhea, leukorrhea, PAP smear suspicious, uterine enlargement, vaginal moniliasis

The following adverse drug reactions were seen at a frequency of <0.1% and ≥0.01% in pivotal clinical trials using 3.0 mg drospirenone and 0.020 mg ethinyl estradiol as an oral contraceptive:

**Body as a whole:** abdomen enlarged, accidental injury, allergic reaction, cyst, face edema, hernia, infection, moniliasis

**Cardiovascular system:** phlebitis, syncope, tachycardia, vascular disorder

**Digestive system:** biliary pain, cholecystitis, constipation, gastrointestinal disorder, gastrointestinal fullness, increased appetite, liver function test abnormal, oral moniliasis

**Endocrine system:** endocrine disorder

**Metabolic and nutritional disorders:** generalized edema, SGPT increased, weight loss,

**Nervous system:** hot flashes, insomnia, vertigo

**Respiratory system:** epistaxis

**Skin and appendages:** alopecia, breast neoplasm, chloasma, dermatitis acneiform, dry skin, eczema, erythema nodosum, hypertrichosis, skin disorder, skin striae

**Special senses:** conjunctivitis, dry eye, eye disorder

**Urogenital system:** anorgasmia, cervix neoplasm, dyspareunia, endometrial disorder, ovarian cyst, vulvovaginitis, withdrawal bleeding

### **Postmarket Adverse Drug Reactions**

The following unexpected adverse events have also been reported very rarely in users of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, but a causal relationship has not been established: hot/cold sensations, muscle spasms, muscle twitching, and erythema multiforme.

In addition, venous and arterial thromboembolic events (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction/cerebral infarction and stroke not specified as hemorrhagic) have been identified as Adverse Drug Reactions (ADRs) from postmarketing experience reported in association with the use of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS - Hematologic**). 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.

## DRUG INTERACTIONS

### Overview

The concurrent administration of oral contraceptives with other may lead to breakthrough bleeding and/or may result in an altered response to either agent (see Table 4 and Table 5). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and nonprescription, before oral contraceptives are prescribed.

### Drug-Drug Interactions

**Table 4: Drugs Which May Decrease the Efficacy of Oral Contraceptives**

<b>Class of Compound</b>	<b>Drug</b>	<b>Proposed Mechanism</b>	<b>Suggested Management</b>
Antacids		Decreased intestinal absorption of progestins.	Dose 2 hours apart.
Antibiotics (35)	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another non-hormonal method of contraception.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants (36-38)	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another non-hormonal method of contraception.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another non-hormonal method of contraception.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another non-hormonal method of contraception.

<b>Class of Compound</b>	<b>Drug</b>	<b>Proposed Mechanism</b>	<b>Suggested Management</b>
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed.	Use another drug or another non-hormonal method of contraception.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Non-nucleoside reverse transcriptase inhibitors (39, 40)	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional non-hormonal method of contraception or another drug. For long course, use another non-hormonal method of contraception or higher dose oral contraceptives.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

Several of the anti-HIV/HCV protease inhibitors (eg, ritonavir, telaprevir, boceprevir) and nonnucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem and grapefruit juice, can increase plasma concentrations of the estrogen or the progestin or both. Increase in DRSP may increase serum potassium levels, possibly increasing the risk of hyperkalemia in high-risk patients (see **WARNINGS AND PRECAUTIONS, General**).

Oral contraceptives may also interfere with the metabolism of other drugs (see Table 5). Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine).

**Table 5: Modification of Other Drug Action by Oral Contraceptives**

<b>Class of Compound</b>	<b>Drug</b>	<b>Modification of Drug Action</b>	<b>Suggested Management</b>
Alcohol		Possible increased levels of ethanol or acetaldehyde	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another non-hormonal method of contraception.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another non-hormonal method of contraception.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures.	Use another non-hormonal method of contraception.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another non-hormonal method of contraception. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyl dopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another non-hormonal method of contraception.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.

<b>Class of Compound</b>	<b>Drug</b>	<b>Modification of Drug Action</b>	<b>Suggested Management</b>
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic acid		Oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, depression	Use with caution.
Vitamin B <sub>12</sub>		Oral contraceptives have been reported to reduce serum levels of Vitamin B <sub>12</sub>	May need to increase dietary intake, or supplement.

In clinical studies, administration of a hormonal contraceptive containing ethinyl estradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (eg, midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (eg, theophylline) or moderately (eg, melatonin and tizanidine).

No formal drug-drug interaction studies have been conducted with ethinyl estradiol/drospirenone.

### ***Interactions With Drugs That Have the Potential to Increase Serum Potassium***

There is a potential for an increase in serum potassium in women taking NIKKI with other drugs (see **WARNINGS AND PRECAUTIONS**). Of note, occasional or chronic use of NSAID medication was not restricted in any of the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol clinical trials.

A drug-drug interaction study of DRSP 3 mg/estradiol 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium levels were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium levels in the DRSP/estradiol treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple timepoints over 24 hours at baseline and on day 14. On day 14, the ratios for serum potassium C<sub>max</sub> and AUC in the DRSP/estradiol group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and

1.010 (90% CI: 0.944, 1.080), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations >5.5 mEq/L).

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

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 contraceptive steroids. This may also result in breakthrough bleeding.

### **Drug-Laboratory Test Interactions**

Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive. The following laboratory tests are modified:

#### ***A. Liver Function Tests***

Aspartate serum transaminase (AST) - variously reported elevations  
Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated

#### ***B. Coagulation Tests***

Minimal elevation of test values reported for such parameters as prothrombin and factors VII, VIII, IX, and X.

#### ***C. Thyroid Function Tests***

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T<sub>3</sub> resin uptake.

#### ***D. Lipoproteins***

Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

#### ***E. Gonadotropins***

LH and FSH levels are suppressed by the use of oral contraceptives. Wait 2 weeks after discontinuing the use of oral contraceptives before measurements are made.

#### ***F. Glucose Tolerance***

Oral glucose tolerance remained unchanged or was slightly decreased.

### ***Tissue Specimens***

Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and PAP smears are submitted for examination.

## **Drug-Lifestyle Interactions**

No studies on the effects of drospirenone and ethinyl estradiol tablets, 3 mg/0.02 mg on the ability to drive or use machines have been performed.

## **Metabolic Interactions**

### ***Drospirenone***

Metabolism of drospirenone (DRSP) and potential effects of DRSP on hepatic cytochrome P450 (CYP) enzymes have been investigated in in vitro and in vivo studies (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics: *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. The potential effect of DRSP on CYP2C19 and CYP3A4 activity was investigated in clinical pharmacokinetic studies using omeprazole, simvastatin and midazolam as marker substrates. In a study with 24 postmenopausal women (including 12 women with homozygous [wild type] CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype), the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose). Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day. Based on the available results of in vivo and in vitro studies, it can be concluded that, at clinical dose levels, DRSP shows little propensity to interact to a significant extent with cytochrome P450 enzymes.

### ***Ethinyl estradiol***

In vitro, ethinyl estradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

## **Noncontraceptive Benefits of Oral Contraceptives**

Several health advantages other than contraception have been reported:

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.

6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Oral contraceptives have potential beneficial effects on endometriosis.

## **DOSAGE AND ADMINISTRATION**

Tablets must be taken in the order directed on the package every day at about the same time. The patient may begin using NIKKI (3.0 mg drospirenone and 0.020 mg ethinyl estradiol) on day 1 of her menstrual cycle (ie, the first day of menstrual flow) or on the first Sunday after her period begins. If the patient's period begins on Sunday, she should start that same day. If NIKKI tablets are taken later than day 1 when first starting medication, an additional (barrier) method of birth control is recommended for the first 7 days of use.

One hormone-containing pink tablet is to be taken daily for 24 consecutive days, followed by 1 hormone-free white tablet daily for 4 consecutive days. Withdrawal bleeding usually occurs within 2 to 3 days following administration of the last hormone-containing pink tablet (ie, while the patient is taking the hormone-free white tablets).

The patient begins each subsequent course of NIKKI tablets on the same day of the week that she began her first course. She begins taking her next course immediately after completion of the last course, regardless of whether or not withdrawal bleeding is still in progress.

**Management of missed tablets:** The patient should be instructed to use the following chart if she misses 1 or more of her birth control pills. She should be told to match the number of tablets missed with the appropriate starting time for her dosing regimen. The risk of pregnancy increases with each hormone-containing pink tablet missed.



**Table 6: Management of Missed Hormone-Containing Pink Tablet**

<b>Sunday Start</b>	<b>Other Than Sunday Start</b>
<b>Miss One Pink Tablet at Any Time</b>	<b>Miss One Pink Tablet at Any Time</b>
Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day.	Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day.
<b>Miss Two Pink Tablets in a Row</b>	<b>Miss Two Pink Tablets in a Row</b>
<b>First Two Weeks</b> 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets.	<b>First Two Weeks</b> 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets.
<b>Third and Fourth Weeks</b> 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month.	<b>Third and Fourth Weeks</b> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month.
<b>If you miss two periods in a row, call your doctor or clinic.</b>	<b>If you miss two periods in a row, call your doctor or clinic.</b>
<b>Miss Three or More Pink Tablets in a Row</b>	<b>Miss Three or More Pink Tablets in a Row</b>
<b>Anytime in the Cycle</b> 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month.	<b>Anytime in the Cycle</b> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month.
<b>If you miss two periods in a row, call your doctor or clinic.</b>	<b>If you miss two periods in a row, call your doctor or clinic.</b>

If the patient forgets any of the 4 hormone-free white tablets in week 4, she should be advised to safely dispose of the tablets she missed, and then to keep taking 1 tablet each day until the pack is empty. A back-up method of birth control is not required.

**Special Notes on Administration**

**Switching from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch):** The patient should start NIKKI on the day she would normally start her next pack of combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using NIKKI preferably on the day of removal, but at the latest when the next application would have been due.

**Switching from a progestin-only method (mini-pill, injection) or from a Progestin-releasing Intrauterine System (IUS):** The patient may switch from the mini-pill to NIKKI on any day of her cycle. Patients using a progestin injection should start NIKKI on the day the next injection is due. Patients using an IUS should start NIKKI on the day the IUS is removed. In all cases, the patient should be advised to use an additional (barrier) method for the first 7 days of NIKKI use.

**Following first trimester abortion:** The patient may start using NIKKI immediately. When doing so, she need not take additional contraceptive measures.

**Following delivery or second trimester abortion:** Patients should be advised to start NIKKI on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first 7 days of NIKKI use. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of use, or the woman should be advised to wait for her next menstrual period prior to starting NIKKI. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

**Withdrawal/breakthrough bleeding:** Withdrawal bleeding usually occurs within 3 days following the last hormone-containing pink tablet. If spotting or breakthrough bleeding occurs while taking NIKKI, the patient should be instructed to continue taking NIKKI as prescribed 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 NIKKI 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 1 or more hormone-containing tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

**Advice in case of vomiting:** If vomiting occurs within 3 to 4 hours after a tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed tablets is applicable.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been no reports of overdose with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol. Overdosage may cause nausea and vomiting, and withdrawal bleeding may occur in females. There are no antidotes and further treatment should be symptomatic based on the knowledge of the pharmacological action of the constituents. Drospirenone 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. Liver function tests should be

conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

NIKKI is a monophasic, combination oral contraceptive that contains the progestin drospirenone (3.0 mg) and a low dose of the estrogen ethinyl estradiol (0.020 mg). (41) Combination oral contraceptives 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. (42) 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. (43, 44)

Estrogen-containing combinations such as NIKKI increase the blood level of sex hormone binding globulin (SHBG), which is capable of binding and thus inactivating androgens such as testosterone. Moreover, the antiandrogenic activity of drospirenone partially counteracts the effects of endogenous androgens, blocking the binding of dihydrotestosterone (DHT) at the receptor level, which makes it a suitable option in the treatment of acne. Drospirenone may also help to reduce edema of the wall of the sebaceous follicle during the second half of the menstrual cycle, which is partly responsible for the flare-up of inflammatory lesions at this cycle phase.

### **Pharmacodynamics**

Drospirenone inhibits ovulation and follicular development at an oral threshold dose of 2 mg. (45) Drospirenone 3 mg in combination with ethinyl estradiol was found to be optimal for inhibition of ovulation and cycle control. Administration of 3 extra days of hormone (3.0 mg drospirenone and 0.020 mg ethinyl estradiol 24-day active versus a 21-day active of the same combined oral contraceptive) results in additional suppression of the ovary and of follicular development. This was observed in a study where hormone-containing pills of each regimen were intentionally missed on the first 3 days of the cycle and subsequent follicular development was monitored.

Drospirenone exhibited aldosterone antagonist activity at doses as low as 2 mg/day in healthy volunteers. Plasma renin activity and plasma aldosterone concentrations were increased, as was the excretion of aldosterone metabolites. The excretion of  $\text{Na}^+$  was transiently increased by drospirenone (2 or 3 mg) alone or in combination with ethinyl estradiol. Serum  $\text{Na}^+$  and  $\text{K}^+$  concentrations remained unchanged. The potency of drospirenone was 6.6 times higher on average than that of spironolactone, using the  $\text{Na}^+/\text{K}^+$  urinary ratio as the primary indicator of potency of the aldosterone antagonistic effect.

Drospirenone (2, 3, or 4 mg) in combination with ethinyl estradiol (0.020 mg) displayed a favourable effect on the lipid profile with an increase in HDL and a slight decrease in LDL. Total cholesterol remained unchanged. In addition, oral glucose tolerance was slightly increased, but

remained within the reference range.

Drospirenone had no effect on the biosynthesis of SHBG, and when administered in conjunction with ethinyl estradiol (0.020 mg), resulted in SHBG and corticosteroid binding globulin increases consistent with the dosage of ethinyl estradiol.

In vitro, drospirenone bound with low affinity to SHBG and did not bind at all to corticosteroid binding globulin (CBG).

## **Pharmacokinetics**

**Table 7: Summary of Pharmacokinetic Parameters<sup>a</sup> (Drospirenone 3 mg and Ethinyl Estradiol 0.020 mg) in Healthy Young Women**

Cycle/Day	No. of Subjects	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (h)	AUC <sub>(0-24h)</sub> (ng·h/mL)	t <sub>1/2</sub> (h)
<b>Drospirenone</b>					
1/1	23	38.4 (25.2%)	1.5 (1-2)	268 (18.9%)	nd
1/21	23	70.3 (14.5%)	1.5 (1-2)	763 (17.4%)	30.8 (21.9%)
<b>Ethinyl Estradiol</b>					
1/1	23	32.8 (44.9%)	1.5 (1-2.2)	108 (51.8%)	nd
1/21	23	45.1 (34.7%)	1.5 (1-2)	220 (57.4%)	nd

Abbreviations: AUC = area under the curve, C<sub>max</sub> = maximum concentration, h = hour, mL = millilitre, nd = not determined, ng = nanogram, t<sub>1/2</sub> = elimination half life, t<sub>max</sub> = time of maximum concentration  
 a The geometric mean is given for all parameters except t<sub>max</sub>, with the geometric coefficient of variation in parentheses. For t<sub>max</sub>, the median is given, with the range in parentheses.

## ***Absorption***

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol which is a combination tablet of drospirenone and ethinyl estradiol stabilized by betadex as a clathrate (molecular inclusion complex) has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1 to 2 hours after administration of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol. After single dose administration of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, the relative bioavailability compared to a suspension was 107% and 97% for DRSP and EE, respectively.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, steady-state DRSP concentrations were observed after 8 days. There was about 2- to 3-fold accumulation in serum C<sub>max</sub> and AUC<sub>(0-24h)</sub> values of DRSP following multiple-dose administration of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol.

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, serum C<sub>max</sub> and AUC<sub>(0-24h)</sub> values of EE accumulate by a factor of about 1.5 to 2.0 (see Table 7 above).

## **Effect of Food**

The rate of absorption of DRSP and EE following single administration of 2 tablets, each containing 3 mg DRSP and 0.030 mg EE was slower under fed 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 levels decline in 2 phases. The apparent volume of distribution of DRSP is approximately 4 L/kg, and that of EE is reported to be approximately 4 to 5 L/kg.

DRSP does not bind to SHBG or 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 nonspecifically 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 2 main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. DRSP is also subject to oxidative metabolism catalyzed by CYP3A4.

EE is subject to significant gut and hepatic first-pass metabolism. EE and its oxidative metabolites are primarily conjugated with glucuronides or sulfate. CYP3A4 in the liver are 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 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 10 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% to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17% to 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.

## **Special Populations and Conditions**

### ***Pediatrics***

The safety and efficacy of NIKKI has not been established in women under the age of 14 years. Use of this product before menarche is not indicated.

### ***Geriatrics***

NIKKI is not indicated for use in postmenopausal women.

### ***Race***

No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (aged 20-35 years) when 3.0 mg drospirenone and 0.020 mg ethinyl estradiol was administered daily for 21 days. The effect of race on the disposition of NIKKI has not been evaluated.

### ***Hepatic Insufficiency***

NIKKI is contraindicated in patients with hepatic dysfunction (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**). The mean exposure to DRSP in women with moderate hepatic impairment is approximately 3 times higher than the exposure in women with normal hepatic function. The mean terminal half-life of DRSP for women with moderate hepatic impairment was 1.8 times greater than for women with normal hepatic function. NIKKI has not been studied in women with severe hepatic impairment.

### ***Renal Insufficiency***

NIKKI is contraindicated in patients with renal insufficiency (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The effect of renal insufficiency on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium levels were investigated in female subjects (n=28, age 30-65) with normal renal function and mild and moderate renal impairment. All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of the underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP levels in the group with mild renal impairment (creatinine clearance CL<sub>cr</sub>, 50-80 mL/min) were comparable to those in the group with normal renal function (CL<sub>cr</sub>, >80 mL/min). The serum DRSP levels were on average 37% higher in the group with moderate renal impairment (CL<sub>cr</sub>, 30-50 mL/min) compared to those in the group with normal renal function. DRSP treatment was well tolerated by all groups. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in 5 of the 7 subjects who continued use of potassium-sparing drugs during the study, mean serum potassium levels increased by up to 0.33 mEq/L. Therefore, potential exists for hyperkalemia to occur in subjects with renal impairment whose serum potassium is in the upper reference range and who are concomitantly using potassium sparing drugs.

## **STORAGE AND STABILITY**

Store in original packaging between 15°C and 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## **SPECIAL HANDLING INSTRUCTIONS**

There are no special handling instructions.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

NIKKI (3.0 mg drospirenone and 0.020 mg ethinyl estradiol) tablets are available in a 28-day regimen.

Each blister pack contains 24 hormone-containing tablets that are pink round, biconvex, film coated tablets, plain on one side and 'DR1' on the other side and 4 hormone-free tablets that are white to off-white, round, biconvex film-coated debossed with 'K33' on one side and 'LU' on the other side.

Each hormone-containing, pink, film-coated tablet contains 3.0 mg drospirenone and 0.020 mg ethinyl estradiol.

Nonmedicinal ingredients for hormone-containing tablets: corn starch, hypromellose, lactose monohydrate, magnesium stearate, pregelatinised starch, red iron oxide, talc and titanium dioxide.

Nonmedicinal ingredients for hormone-free tablets: corn starch, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, pregelatinised starch and titanium dioxide.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

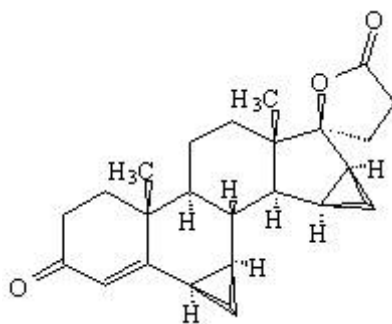
#### Drug Substance

#### *Drospirenone:*

**Proper Name:** drospirenone

**Chemical Name:** 6 $\beta$ , 7 $\beta$ ; 15 $\beta$ , 16 $\beta$ -dimethylene-3-oxo-17 $\alpha$ -pregn-4-ene-21, 17-carbolactone (IUPAC) [6R-(6 $\alpha$ , 7 $\alpha$ , 8 $\beta$ , 9 $\alpha$ , 10 $\beta$ , 13 $\beta$ , 14 $\alpha$ , 15 $\alpha$ , 16 $\alpha$ , 17 $\beta$ )-1,3',4',6,7,8,9,10,11,12,13,14,15,16,20,21-hexadecahydro-10,13-dimethylspiro[17H-dicyclopropa[6,7:15,16]cyclopenta[ $\alpha$ ]phenanthrene-17,2'(5'H)-furan]-3,5'(2H)-dione (USAN)

#### **Structural Formula:**



**Molecular Formula:** C<sub>24</sub>H<sub>30</sub>O<sub>3</sub>

**Molecular Weight:** 366.50 g/mol

**Description:** White to off-white crystalline powder. Freely soluble in dichloromethane; soluble in acetone, methanol, ethyl acetate, dimethoxyethane and toluene; sparingly soluble in ethanol; and practically insoluble in water, n-hexane and diisopropyl ether. Melting range is 199°C to 201°C.

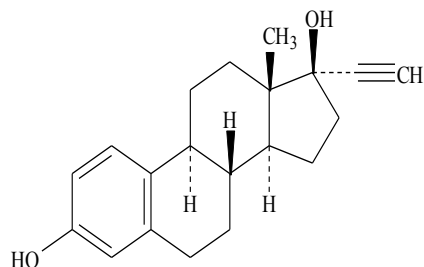
**pKa:** Neutral molecule without any acid-base properties in aqueous solutions (pH 1 to 12)



**Ethinyl estradiol:**

**Proper Name:** ethinyl estradiol

**Chemical Name:** 19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol



**Structural Formula:**

**Molecular Formula:** C<sub>20</sub>H<sub>24</sub>O<sub>2</sub>

**Molecular Weight:** 296.40 g/mol

**Description:** White to slightly yellowish- white, crystalline powder.

**pKa:** 10.5 (phenol)

## CLINICAL TRIALS

### Comparative Bioavailability Study

A double blind, balanced randomized, two-treatment, two-sequence, two-period crossover, single-dose comparative bioavailability study of NIKKI (3.0 mg drospirenone and 0.02 mg ethinyl estradiol, Lupin Limited, India) and 'YAZ<sup>®</sup>' (3.0 mg drospirenone 0.02 mg ethinyl estradiol, Bayer Inc., Canada) tablets in 32 healthy, adult, female subjects under fasting conditions was conducted. Bioavailability data were measured and the results are summarized in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Drospirenone (2 tablets x 3.0 mg, administered as 3.0 mg/0.02 mg (drospirenone/ethinyl estradiol) tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-72</sub> (units)	1044.673	1064.466	98.14	95.81 to 100.53
C <sub>max</sub> (ng/mL)	60.776	73.096	83.15	78.73 to 87.81
T <sub>max</sub> <sup>§</sup> (h)	2.25 (1.25-6.05)	1.75 (0.75-6.00)		
T <sub>1/2</sub> <sup>ε</sup> (h)	44.43 (32.44)	45.05 (43.66)		

\* NIKKI (drospirenone and ethinyl estradiol tablets, 3 mg/0.02 mg, Lupin Limited)

† <sup>Pr</sup>YAZ<sup>®</sup> (Drospirenone/Ethinyl Estradiol) 3.0 mg/0.02 mg tablets (Bayer Inc.)

§ Expressed as the median (range) only

ε Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ethinyl Estradiol (2 tablets x 0.02 mg, administered as 3.0 mg/0.02 mg (drospirenone/ethinyl estradiol) tablet) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval
AUC <sub>0-72</sub> (pg*h / mL)	890.172	897.047	99.23	93.89 to 104.88
C <sub>max</sub> (pg/mL)	64.933	77.360	83.94	78.25 to 90.03
T <sub>max</sub> <sup>§</sup> (h)	2.00 (1.25-6.05)	1.75 (1.00-6.00)		
T <sub>1/2</sub> <sup>ε</sup> (h)	14.36 (40.81)	14.94 (41.39)		

\* NIKKI (drospirenone and ethinyl estradiol tablets, 3 mg/0.02 mg, Lupin Limited)

† <sup>Pr</sup>YAZ<sup>®</sup> (Drospirenone/Ethinyl Estradiol) 3.0 mg/0.02 mg tablets (Bayer Inc.)

§ Expressed as the median (range) only

ε Expressed as the arithmetic mean (CV%) only

## **Contraception**

### ***General Information***

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in 1 year.

**Table 8: Reported Pregnancies per 100 Women per Year**

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

### ***Study Demographics and Trial Design***

The contraceptive efficacy of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol/EE/DRSP was evaluated in 2 pivotal phase III clinical trials. These studies (Studies 303740 and 308021) were large, open-label studies with the Pearl Index (PI) as primary criterion for the assessment of the contraceptive reliability.

Study 308020 was a comparison study with the following efficacy variables: cycle control, bleeding parameters, and the pregnancy rate expressed as PI.

An additional, single-center, controlled study (Study 301888) was conducted to investigate the impact of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol on plasma lipids, hemostatic variables and carbohydrate metabolism. Bleeding patterns were also assessed.

**Table 9: Overview of Studies Evaluating the Efficacy of 3.0 mg Drospirenone and 0.020 mg Ethinyl Estradiol for Conception Control**

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects <sup>a</sup>	Mean Age (Range) [Years]	Mean BMI [kg/m <sup>2</sup> ]
303740 (46)	Pearl Index Multicenter, open, uncontrolled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 13 cycles	Test product: DRSP 3 mg + EE 0.02 mg  Placebo	1027	24.7 (18-35)	22.4±3.3

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects <sup>a</sup>	Mean Age (Range) [Years]	Mean BMI [kg/m <sup>2</sup> ]
308021	Pearl Index Multicenter, open, uncontrolled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 13 cycles	Test product: DRSP 3 mg + EE 0.02 mg  Placebo	1101	24.7 (18-35)	21.7±2.8
308020	Bleeding pattern and cycle control Multicenter, open, randomized, parallel comparison	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 7 cycles  One medicated tablet daily for 21 days followed by a 7-day tablet-free interval for 7 cycles	Test product: DRSP 3 mg + EE 0.02 mg	229	25.2 (18-35)	22.3±2.7
			Comparator <sup>b</sup> : DSG 0.150 mg + EE 0.02 mg	220	24.5 (18-35)	22.0±2.9
301888 (47)	Effect on lipid, hemostatic and carbohydrate profile Single center, open-label, randomized, controlled	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 7 cycles  One medicated tablet daily for 21 days followed by a 7-day tablet-free interval for 7 cycles	Test product: -DRSP 3 mg + EE 0.02 mg	29	23.8 (18-35)	21.8±2.9
			Comparator <sup>b</sup> : DSG 0.150 mg + EE 0.02 mg	30	23.7 (18-35)	21.7±1.8

Abbreviations: BMI = Body Mass Index, DSG = desogestrel, DRSP = drospirenone, EE = ethinyl estradiol, kg = kilogram, m = meter, mg = milligram

- a Full analysis set (FAS)  
b Not available in Canada

### Study Results

The total number of cycles under 3.0 mg drospirenone and 0.020 mg ethinyl estradiol treatment in the two 13-cycle pivotal oral contraception studies was 24,818 (11,421 in Study 303740 and 13,397 in Study 308021). For Pearl Index (PI) calculations, 13/28-day cycles constitute 1 woman-year (wy). The pooled PI was calculated to be 0.85 with an upper one-sided 97.5% confidence limit of 1.39, and this is equal to the upper limit of the corresponding two-sided 95% confidence interval (CI). The PI was calculated based on the 16 pregnancies observed during 3.0 mg drospirenone and 0.020 mg ethinyl estradiol treatment (Study 303740 with 11 pregnancies, PI=1.29 and Study 308021 with 5 pregnancies, PI=0.49) and a treatment exposure of 682,892 days (corresponding to 1,876.1 wy).

The adjusted Pearl Index (PI<sub>c</sub>) in the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol studies was calculated on the basis of 7 pregnancies rated as method failure (5 in Study 303740 and 2 in Study 308021) and a treatment exposure of 581,408 days (corresponding to 1,597.2 wy). The PI was calculated to be 0.44 with an upper 2-sided 95% confidence limit of 0.90 (see Table 10). The individual study PI<sub>c</sub> and upper 2-sided 95% confidence limit values were 0.72 and 1.69 for Study 303740, and 0.22 and 0.80 for Study 308021, respectively.

**Table 10: Pearl Index (PI) and Adjusted Pearl Index (PI<sub>c</sub>) – Data of Studies 303740 and 308021**

	Pooled		Study 303740		Study 308021	
	PI	PI <sub>c</sub>	PI	PI <sub>c</sub>	PI	PI <sub>c</sub>
Total time of exposure (days/cycles/wy)	694,903/ 24,818/ 1,909		319,785/ 11,421/ 878.5		375,118/ 13,397/ 1,030.5	
Backup contraception (days)	12,011		7,842		4,169	
Noncompliant and/or backup contraceptive cycles (days)		113,495		67,504		45,991 <sup>a</sup>
Relevant exposure time (days/cycles/wy)	682,892/ 24,389/ 1,876.1	581,408/ 20,765/ 1,597.2	311,943/ 11,141/ 856.9	252,281/ 9,010/ 693	370,949/ 13,248/ 1,019.1	329,127/ 11,755/ 904.2 <sup>b</sup>
Number of pregnancies	16	7	11	5	5	2
PI and PI <sub>c</sub>	<b>0.85</b>	<b>0.44</b>	<b>1.29</b>	<b>0.72</b>	<b>0.49</b>	<b>0.22</b>
Upper two-sided 95% confidence limit of PI and PI <sub>c</sub>	1.39	0.90	2.30	1.69	1.14	0.80

Abbreviations: PI = Pearl Index; PI<sub>c</sub> = adjusted Pearl Index; wy = woman-years

a For PI<sub>c</sub>: days on back-up contraception and noncompliant days

b For PI<sub>c</sub>: relevant treatment exposure time = time treatment exposure time minus days on cycles with back-up contraception and noncompliant days

In addition to the calculation of the PI, a life table analysis was performed for the time to the occurrence of a pregnancy in the two 13-cycle pivotal studies. The cumulative failure rate, ie, the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of unintended pregnancies considered to have occurred “during treatment.”

The pooled Kaplan-Meier estimation after the last conception date after up to 1 year of treatment was 0.0085 with a 95% CI of 0.0052 to 0.0138, ie, the probability of contraceptive protection was estimated to be 0.9915 (99.15%). The estimation of the 1-year pregnancy rate for Study 303740 was 1.26% with a 95% CI of 0.0052 to 0.0201, and for Study 308021 this was 0.5% with a 95% CI of 0.0021 to 0.0119.

### Bleeding Pattern

A multicenter, randomized, open, parallel-group study (Study 308020) was conducted to evaluate the bleeding pattern, cycle control, and contraceptive reliability of 0.02 mg EE/3 mg DRSP (EE/DRSP) versus 0.02 mg EE/150 mg DSG (EE/DSG). Female subjects were randomized to EE/DRSP (n=230) or EE/DSG (n=223) for 7 cycles.

The bleeding pattern was also evaluated in a multicenter, uncontrolled study (Study 303740) in which women were treated with EE/DRSP (n=890) for 13 cycles.

The bleeding episodes were described using the Reference Period method recommended by the World Health Organization (WHO). The length of the Reference Period is 90 days.

A bleeding/spotting episode was defined as a number of days with bleeding/spotting preceded and followed by at least 2 bleeding-free days; correspondingly, a spotting-only episode was defined as a number of days with spotting preceded and followed by at least 2 bleeding-free days. A bleeding-free interval consisted of at least 2 days without bleeding/spotting preceded and followed by at least 1 day of bleeding/spotting. Bleeding pattern evaluations are presented for the FAS using means and standard deviations (SD).

An overview of the bleeding pattern parameters for both treatment groups in Study 308020 is presented in Table 11 for Reference Period 1 and Reference Period 2. The mean values for all the parameters studied were very similar in both treatment groups.

The results were similar for the per protocol set (PPS).

**Table 11: Bleeding Pattern Parameters in Reference Period 1 and Reference Period 2 – FAS (Study 308020)**

	<b>n</b>	<b>Mean</b>	<b>SD</b>
<b>Reference Period 1</b>			
3.0 mg drospirenone and 0.020 mg ethinyl estradiol			
Number of bleeding/spotting days	196	23.6	10.1
Number of bleeding/spotting episodes	196	4.4	1.0
Mean length of bleeding/spotting episodes (days)	196	5.6	3.3
Maximum length of bleeding/spotting episodes (days)	196	8.8	6.8
Number of spotting only days	196	9.5	7.1
Number of spotting only episodes	196	0.6	0.9
Mean length of spotting only episodes (days)	78 <sup>a</sup>	2.6	1.6
Maximum length of spotting only episodes (days)	78 <sup>a</sup>	3.0	2.4
<b>Comparator<sup>b</sup></b>			
Number of bleeding/spotting days	165	24.0	8.5
Number of bleeding/spotting episodes	165	4.3	0.9
Mean length of bleeding/spotting episodes (days)	165	5.7	2.3
Maximum length of bleeding/spotting episodes (days)	165	8.6	5.5
Number of spotting only days	165	8.9	7.1
Number of spotting only episodes	165	0.5	0.8
Mean length of spotting only episodes (days)	54 <sup>a</sup>	2.8	2.6
Maximum length of spotting only episodes (days)	54 <sup>a</sup>	3.0	2.7
<b>Reference Period 2</b>			
3.0 mg drospirenone and 0.020 mg ethinyl estradiol			
Number of bleeding/spotting days	182	16.1	6.4
Number of bleeding/spotting episodes	182	3.4	1.1
Mean length of bleeding/spotting episodes (days)	180	4.8	1.5
Maximum length of bleeding/spotting episodes (days)	180	6.0	2.6
Number of spotting only days	182	6.2	4.8
Number of spotting only episodes	182	0.5	0.9
Mean length of spotting only episodes (days)	48 <sup>a</sup>	3.0	2.2
Maximum length of spotting only episodes (days)	48 <sup>a</sup>	3.6	2.8
<b>Comparator<sup>b</sup></b>			
Number of bleeding/spotting days	153	16.6	8.5
Number of bleeding/spotting episodes	153	3.3	0.9
Mean length of bleeding/spotting episodes (days)	153	5.1	2.3
Maximum length of bleeding/spotting episodes (days)	153	6.3	5.5
Number of spotting only days	153	5.6	7.1
Number of spotting only episodes	153	0.3	0.8
Mean length of spotting only episodes (days)	32 <sup>a</sup>	3.1	2.6
Maximum length of spotting only episodes (days)	32 <sup>a</sup>	3.6	2.7

Abbreviations: FAS = full analysis set, n = number of subjects, SD = standard deviation

a n = number of volunteers with at least 1 spotting-only episode

b Not available in Canada

Bleeding pattern parameters for Study 303740 for Reference Periods 1 to 4 are presented in Table 12.

**Table 12: Bleeding Pattern Parameters by Reference Period – 3.0 mg drospirenone and 0.020 mg ethinyl estradiol Treatment Group - FAS (Study 303740)**

	<b>n</b>	<b>Mean</b>	<b>SD</b>
<b>Reference Period 1</b>			
Number of bleeding/spotting days	890	22.49	10.34
Number of bleeding/spotting episodes	890	4.28	1.14
Mean length of bleeding/spotting episodes (days)	889	5.43	2.74
Max. length of bleeding/spotting episodes (days)	889	8.45	5.96
Number of spotting only days	890	7.72	7.67
Number of spotting only episodes	890	0.63	1.01
Mean length of spotting only episodes (days)	340	3.22	2.40
Maximum length of spotting only episodes (days)	340	3.80	3.02
<b>Reference Period 2</b>			
Number of bleeding/spotting days	853	15.09	7.36
Number of bleeding/spotting episodes	853	3.25	1.09
Mean length of bleeding/spotting episodes (days)	837	4.71	1.94
Max. length of bleeding/spotting episodes (days)	837	6.18	3.42
Number of spotting only days	853	5.16	5.31
Number of spotting only episodes	853	0.56	1.02
Mean length of spotting only episodes (days)	285	2.85	2.00
Maximum length of spotting only episodes (days)	287	3.20	2.25
<b>Reference Period 3</b>			
Number of bleeding/spotting days	792	14.48	6.98
Number of bleeding/spotting episodes	792	3.18	1.00
Mean length of bleeding/spotting episodes (days)	774	4.54	1.79
Max. length of bleeding/spotting episodes (days)	774	5.87	3.24
Number of spotting only days	792	5.04	5.64
Number of spotting only episodes	792	0.52	0.99
Mean length of spotting only episodes (days)	234	2.93	1.79
Maximum length of spotting only episodes (days)	236	3.42	2.45
<b>Reference Period 4</b>			
Number of bleeding/spotting days	719	14.56	7.23
Number of bleeding/spotting episodes	719	3.20	1.04
Mean length of bleeding/spotting episodes (days)	706	4.57	1.93
Max. length of bleeding/spotting episodes (days)	706	5.74	3.38
Number of spotting only days	719	5.16	5.82
Number of spotting only episodes	719	0.56	1.00
Mean length of spotting only episodes (days)	215	2.89	1.63
Maximum length of spotting only episodes (days)	234	3.25	2.23

Abbreviations: FAS = full analysis set, n = number of subjects, SD = standard deviation

The bleeding parameters (number of bleeding/spotting days, length of bleeding/spotting episodes and maximum length of bleeding/spotting episodes) decreased from Reference Period 1 to 2. After further treatment with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol, in Reference Periods 3 and 4, these bleeding parameters remained relatively stable at around the level of Reference Period 2. A similar pattern was observed in the analysis of spotting-only days and episodes.

The results were similar for the PPS.

## Cycle Control

A summary of withdrawal and intracyclic bleeding data is presented in Table 13 for the 3 pivotal studies, based on the FAS population.

**Table 13: Frequency of Withdrawal and Intracyclic Bleeding – FAS**

Cycle	Parameter No. of Women With:	Study									
		303740		308020				301888			
		EE/DRSP n/N (%)		EE/DRSP n/N (%)		Comparator EE/DSG <sup>a</sup> n/N (%)		EE/DRSP n/N (%)		Comparator EE/DSG <sup>a</sup> n/N (%)	
1	WB	838/935	(89.6)	178/207	(86.0)	148/170	(87.1)	27/29	(93.1)	22/29	(75.9)
	IB	231/935	(24.7)	200/207	(96.6)	165/170	(97.1)	7/29	(24.1)	7/29	(24.1)
3	WB	821/874	(93.9)	187/196	(95.4)	156/166	(94.0)	26/27	(96.3)	27/28	(96.4)
	IB	121/874	(13.8)	34/196	(17.3)	27	(16.3)	7/27	(25.9)	4/28	(14.3)
6	WB	773/843	(91.7)	171/182	(94.0)	149/153	(97.4)	24/26	(92.3)	25/25	(100)
	IB	116/843	(13.8)	16/182	(8.8)	17/153	(11.1)	5/26	(19.2)	3/25	(12.0)
9	WB	709/763	(92.9)	-		-		-		-	
	IB	76/763	(10.0)	-		-		-		-	
13	WB	482/523	(92.2)	-		-		-		-	
	IB	81/523	(15.5)	-		-		-		-	

Abbreviations: DSG=desogestrel, DRSP=drospirenone, EE=ethinyl estradiol, FAS=full analysis set,  
IB=intracyclic bleeding; N=total number, n=number of subjects; WB=withdrawal bleeding

a Not available in Canada

### Withdrawal Bleeding

Across all 3 studies, the majority of women had withdrawal bleeding. The percentage of volunteers with withdrawal bleeding was somewhat lower in cycle 1 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 86.0% to 93.1% vs comparator: 75.9% to 87.1%) than in subsequent cycles, when at least 91.7% of subjects treated with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol and 92.3% of women in the comparator group experienced withdrawal bleeding.

The mean length of withdrawal bleeding decreased for both treatment groups from cycle 1 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 5.2 to 7.3 days; comparator: 5.4 to 6.7 days) to cycle 6 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 4.7 to 4.8 days; comparator: 5.2 to 5.3 days) with a slightly more pronounced decrease in the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol group. In the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol group, the mean length of withdrawal bleeding remained similar in cycle 9 (4.8 days), but further decreased to 2.6 days in cycle 13.

### Intracyclic Bleeding

About one-quarter of the women in both the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol and comparator treatment groups of Studies 303740 and 301888 experienced intracyclic bleeding during cycle 1. In Study 308020, the withdrawal bleeding at study entry, on the first day of which the subjects had to take the first dose of study medication, was counted as intracyclic bleeding. Therefore, in this study the majority of women in both treatment groups had intermenstrual bleeding reported for cycle 1 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 96.6%; comparator: 97.1%). However, across all studies and in both treatment groups the proportion of



volunteers with intracyclic bleeding decreased to below one-fifth by cycle 6 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 8.8% to 19.2%; comparator: 11.1% to 12.0%). With continued treatment, in the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol group the number of subjects who had intracyclic bleeding remained in the same range (cycle 9: 10.0%; cycle 13: 15.5%).

The mean length of intracyclic bleeding was similar between treatment groups and in general decreased from cycle 1 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 4.7 to 8.4 days; comparator: 8.1 to 10.6 days) to cycle 6 (3.0 mg drospirenone and 0.020 mg ethinyl estradiol: 0.3 to 4.5 days; comparator: 0.5 to 5 days). In 1 study with longer 3.0 mg drospirenone and 0.020 mg ethinyl estradiol treatment, the mean duration of intracyclic bleeding remained stable up to cycle 13 (4.5 to 4.8 days).

The mean number of intracyclic bleeding episodes per cycle was very low and varied between 0.1 and 1.4 for the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol -treated subjects and between 0.1 and 1.3 for the women in the comparator treatment group throughout the treatment period.

While more than one-half of women in both treatment groups experienced intracyclic bleeding of normal intensity in cycle 1, the predominant mean maximum intensity of intracyclic bleeding from cycle 2 onwards was spotting in both treatment groups. Intracyclic bleeding of normal and light intensity was equally distributed in most treatment cycles for both groups. Intracyclic bleeding of heavy intensity was only recorded for a few women.

From cycle 1 onwards, a decrease in the mean maximum length of intracyclic bleeding episodes was noted for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol and comparator-treated women. The mean maximum length of intracyclic bleeding episodes ranged from approximately 5 to 6 days from cycles 2 to 12 in the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol group and from 5 to 7 days in the comparator group from cycles 2 to 6.

The results were similar for the PPS.

## **Acne Therapy**

### ***Study Demographics and Trial Design***

The efficacy of 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (EE/DRSP) in treating moderate acne vulgaris was evaluated in 2 pivotal, multicentre, double-blind, randomized clinical trials carried out in North America. An overview of the 2 studies is presented below in Table 14:

**Table 14: Overview of Studies Evaluating the Efficacy of 3.0 mg Drospirenone and 0.020 mg Ethinyl Estradiol in the Treatment of Moderate Acne Vulgaris**

Study	Study Objective/ Design	Route of Administration/ Duration	Study Drug	No. of Subjects <sup>a</sup>	Mean Age (Range) [Years] <sup>b</sup>	Mean BMI [kg/m <sup>2</sup> ] <sup>b</sup>
306820	Efficacy/Safety  Multicentre, double-blind, randomized	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 6 cycles	Test product: (DRSP 3 mg + EE 0.02 mg)	229	25.2 (14-44)	24.0 ± 4.0
			Placebo	227	25.4 (14-45)	25.1 ± 4.9
306996	Efficacy/Safety  Multi-centre, double-blind, randomized	Oral/ One medicated tablet daily for 24 days followed by 1 placebo tablet daily for 4 days for 6 cycles	Test product: (DRSP 3 mg + EE 0.02 mg)	222	25.2 (14-44)	23.8 ± 4.6
			Placebo	215	25.1 (14-44)	23.8 ± 4.4

Abbreviations: BMI = Body Mass Index, DRSP = drospirenone, EE = ethinyl estradiol, kg = kilogram, m = meter, mg = milligram

a Amended full analysis set (Amended FAS)

b Full analysis set (FAS)

In the early course of the studies, the original diagnosis, “mild to moderate acne vulgaris”, was amended to “moderate acne vulgaris.” The amended FAS was considered the primary efficacy analysis. Table 15 provides an overview of the primary efficacy variable results based on the amended FAS. 3.0 mg drospirenone and 0.020 mg ethinyl estradiol produced clinically and statistically significant anti-acne effects in all primary efficacy variables. These results are presented in detail below.

The primary efficacy variables were the percentage change from baseline to endpoint (ie, cycle 6 data with missing values replaced in accordance with the last observation carried forward [LOCF] procedure) in inflammatory lesion counts (including papules, pustules, and nodules), noninflammatory lesion counts (including open and closed comedones), and total lesion counts, as well as the percentage of women classified as “0” (clear skin) or “1” (almost clear skin) on the 6-point Investigator Static Global Assessment (ISGA) scale.

## **Study Results**

### **Study 306820**

Female subjects were randomized to 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (n=266) or placebo (n=268) for 6 treatment cycles. The reduction from baseline to endpoint in mean percentage inflammatory lesion count was 47.8% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 32.7% for placebo. The adjusted mean difference was -14.932% ( $P < 0.0001$  for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage noninflammatory lesion count was 38.4% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 18.2% for placebo. The adjusted mean difference was -20.085% ( $P < 0.0001$  for 3.0 mg drospirenone

and 0.020 mg ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage total lesion count was 42.6% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 25.4% for placebo. The adjusted mean difference was -17.063% ( $P < 0.0001$  for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus placebo). The reductions in inflammatory lesion count, noninflammatory lesion count, and total lesion count over time (from baseline to each visit) were statistically significant within both the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol and placebo groups.

For the investigator's global assessment, improvement of facial acne (eg, subjects rated as "clear" or "almost clear") was observed in subjects treated with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (16.2%) and placebo (4.4%). The resulting odds ratio was 4.447 (confidence interval [CI]: 2.184, 9.880;  $P < 0.0001$ ).

The results for the PPS and FAS were consistent with those for the amended FAS.

### **Study 306996**

A total of 538 women (270 in the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol group and 268 in the placebo group) were randomized and dispensed study medication. After 6 treatment cycles, the reduction from baseline to endpoint in mean percentage inflammatory lesion count was 50.9% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 34.7% for placebo. The adjusted mean difference was -15.752% ( $P < 0.0001$  for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage noninflammatory lesion count was 42.8% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 26.3% for placebo. The adjusted mean difference was -16.010% ( $P < 0.0001$  for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus placebo). The reduction from baseline to endpoint in mean percentage total lesion count was 46.5% for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus 30.9% for placebo. The adjusted mean difference was -15.194% ( $P < 0.0001$  for 3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus placebo). The reductions in inflammatory lesion count, noninflammatory lesion count, and total lesion count over time (from baseline to each visit) were statistically significant within both the 3.0 mg drospirenone and 0.020 mg ethinyl estradiol and placebo groups.

For the investigator's global assessment, improvement of facial acne (eg, subjects rated as "clear" or "almost clear") was observed in subjects treated with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol (21.2%) and placebo (9.3%). The resulting odds ratio was 2.921 (CI: 1.598, 5.341;  $P = 0.0004$ ).

The results for the PPS and FAS were consistent with those for the amended FAS.

**Table 15: Overview of Primary Efficacy Variable Results - Amended FAS (Pooled Data of Studies 306820 and 306996)**

Amended FAS 3.0 mg drospirenone and 0.020 mg ethinyl estradiol: N= 451 Placebo: N=442	Percent Change from Baseline to Endpoint			ISGA
	Inflammatory Lesions	Noninflammatory Lesions	Total Lesions	
	3.0 mg drospirenone and 0.020 mg ethinyl estradiol: n=450 Placebo: n=442	3.0 mg drospirenone and 0.020 mg ethinyl estradiol: n=450 Placebo: n=442	3.0 mg drospirenone and 0.020 mg ethinyl estradiol: n=450 Placebo: n=442	3.0 mg drospirenone and 0.020 mg ethinyl estradiol: n=451 Placebo: n=442
3.0 mg drospirenone and 0.020 mg ethinyl estradiol versus	-15.348%	-18.091%	-16.148%	3.413 <sup>b</sup>
95% CI	-20.427%, -10.268%	-23.553%, -12.629%	-20.685%, -11.612%	2.146, 5.426
P value	<i>P</i> <0.0001	<i>P</i> <0.0001	<i>P</i> <0.0001	<i>P</i> <0.0001

Abbreviations: CI = confidence interval, FAS = full analysis set, ISGA = Investigator Static Global Assessment, N = total number, n = number of subjects

- a Difference in adjusted treatment means (ie, 3.0 mg drospirenone and 0.020 mg ethinyl estradiol minus placebo)
- b *P* value, odds ratio, and confidence limits computed from Cochran Mantel-Haenszel statistic stratified by pooled center, since the logistic regression model did not converge.

## DETAILED PHARMACOLOGY

### Animal Pharmacology

#### *Drospirenone*

Drospirenone exhibits potent progestational activity in a variety of animal models. In ovariectomized pregnant rats treated with drospirenone 3 mg/day sc in combination with ethinyl estradiol 0.1 µg/day sc, maintenance of pregnancy was comparable to intact control animals. Drospirenone effectively inhibited ovulation in mice and rats with half-maximal effects observed at subcutaneous doses of approximately 0.1 and 1 mg/day, respectively, and an oral dose of 1 mg/day (rats). Following subcutaneous administration of drospirenone, a marked transformation of the endometrium was detected in castrated, infantile female rabbits, with a threshold dose of 100 to 300 µg/day. In vitro, drospirenone bound with high affinity to the progesterone receptor, and the binding affinity was not affected by the presence of ethinyl estradiol.

In addition to its progestational activity, drospirenone also has antiandrogenic activity. Oral or subcutaneous administration of drospirenone (0.3 to 10 mg/day for 7 days) dose-dependently inhibited testosterone-induced growth of the seminal vesicle and prostate in castrated, testosterone-substituted rats. This activity does not appear to be centrally mediated in rats because decreases in the relative weights of male accessory sex organs occur in the absence of significant changes in testes weights or serum luteinizing hormone levels. Oral or subcutaneous administration of drospirenone (10 mg/day) to pregnant rats during the final trimester of pregnancy resulted in the feminization of male fetuses, characterized by a significant shortening of the anogenital distance and the length of the urethra.

Significant antimineralocorticoid activity, characterized by increased sodium excretion and an increase of the urinary Na<sup>+</sup>/K<sup>+</sup> ratio, was observed following single oral or subcutaneous

administration of drospirenone to adrenalectomized, aldosterone-substituted rats. Drospirenone was 5 to 10 times more potent than spironolactone, and its aldosterone antagonist activity was not affected by concomitant administration of ethinyl estradiol. (48) When administered for 21 days to ovariectomized female rats, drospirenone (10 mg/day) stimulated the Na<sup>+</sup>/K<sup>+</sup> excretion ratio over the entire treatment period, while spironolactone (10 mg/day) became ineffective after the initial treatment phase due to counter-regulation. Drospirenone also exhibited significant antimineralocorticoid activity in vitro, inhibiting aldosterone-stimulated electrogenic sodium transport 10 times more effectively than either spironolactone or progesterone. In vitro, drospirenone binds with high affinity to the mineralocorticoid receptor.

Drospirenone has no androgenic activity. This was demonstrated in vitro by the lack of stimulation of androgen receptor-driven gene transcription. In vivo in castrated male rats, drospirenone (10 mg/day) did not stimulate the growth of accessory sex organs above castration level. The same dose had no virilizing effect on the process of sexual differentiation of female rat fetuses.

Drospirenone is devoid of estrogenic, gluco- and antigluco-corticoid activity, as concluded from the absence of an influence on vaginal epithelial cornification in rats, adrenal weight changes in rats, and thymus regression in adrenalectomized, glucocorticoid-substituted rats, respectively.

Drospirenone did not affect smooth muscle organs (ileum, trachea, uterus) in vivo (rabbit) or in vitro (guinea pigs). In female mice, drospirenone did not affect central nervous system function at single oral doses up to 100 mg/kg.

Drospirenone in subcutaneous doses of 1 or 10 mg/animal/day did not prevent hormone deficiency-induced trabecular bone loss in ovariectomized rats after treatment for 24 weeks. In addition, drospirenone in both tested doses did neither impair nor enhance the bone protective effect of ethinyl estradiol on trabecular bone after 24 weeks of treatment.

When drospirenone (30 mg/kg/day) was subcutaneously administered to ovariectomized telemetered normotensive rats, only a slight increase in heart rate was found. However, this finding was not accompanied by any changes in systolic or diastolic blood pressure. The effects produced by 0.01 mg/kg/day ethinyl estradiol (increased systolic blood pressure and lowered heart rate) were reduced when ethinyl estradiol was coadministered with drospirenone. Drospirenone in subcutaneous doses of 1 or 10 mg/animal/day had no effect on liver-derived parameters (serum angiotensinogen and IGF-I) in ovariectomized rats after 11 treatment days.

In safety pharmacology studies, oral administration of drospirenone or drospirenone in combination with ethinyl estradiol had no effect on pentylenetetrazole- or maximal electroshock-induced seizure activity in mice. When drospirenone was administered to rats as a single oral dose in combination with ethinyl estradiol (100:1), a dose-dependent increase in urine volume and Na<sup>+</sup> excretion, coupled with a dose-dependent decrease in urinary creatinine clearance, K<sup>+</sup> and Cl<sup>-</sup> excretion and BUN was observed. These effects on renal function were attributed to the antimineralocorticoid activity of drospirenone.

### ***Ethinyl estradiol***

Ethinyl estradiol is a potent estrogen with qualities similar to estradiol. In contrast to estradiol, it

is highly effective after oral administration. The relative oral potency of ethinyl estradiol's antigonadotropic and antifertility effects (eg, inhibition of ovulation, inhibition of implantation) is 3-30 times higher than that of orally administered estradiol.

Ethinyl estradiol also exhibits effects on carbohydrate, protein, and lipid metabolism similar to those of other estrogens: in rats, hepatic glycogen content and serum triglycerides are significantly increased, whereas serum cholesterol is decreased. In addition, a small but significant increase in the liver weight can be seen. Phospholipids were also raised after treatment for 1 month. The effects on lipid and carbohydrate metabolism may be attributed to an indirect glucocorticoid activity of estrogens. It is well established that estrogens in the rat cause a stimulation of the adrenals and a depletion of corticoids. The increased glucocorticoid level may be responsible for an induction of gluconeogenesis concomitant with high fasting blood glucose levels.

Following administration of ethinyl estradiol alone in ovariectomized rats, observations included dose-dependently higher uterine weights. Partial reversal of the stimulatory effect of ethinyl estradiol on uterine weight was observed following administration of drospirenone (10 mg/animal/day) in combination with ethinyl estradiol (0.0001, 0.001 mg/animal/day).

## TOXICOLOGY

### Acute Toxicity

#### *Drospirenone*

Table 16 below summarizes the median lethal doses (LD<sub>50</sub>) determined in acute toxicity studies with drospirenone.

**Table 16: LD<sub>50</sub> Values for Drospirenone**

Species	Doses Tested (mg/kg/day)	Route of Administration	LD <sub>50</sub> (mg/kg)
Mouse	0, 250, 500, 1250, 2500	intragastric	500 - 2500
	0, 250, 500, 1250, 2500	intraperitoneal	250 - 500
Rat	0, 250, 500, 1250, 2000	intragastric	500 - 1250
	0, 100, 250, 500, 1250, 2000	intraperitoneal	100 - 250
Dog	0, 250	oral (capsules)	> 250
	0, 0.165	intravenous	> 0.165

The principle clinical signs observed in mice and rats were similar in all studies, including apathy, gait, and posture disturbances and at higher doses, twitching, spasms, and/or unconsciousness. Deaths generally occurred within 3 to 4 days of dosing.

Single high doses of drospirenone to female Beagle dogs were generally well tolerated, with compound-related effects limited to vomiting, transient changes in food/water consumption, and slight changes in serum biochemistry and coagulation parameters. No deaths occurred.

### Long-term Toxicity

The long-term toxicity of drospirenone, alone and in combination with ethinyl estradiol, was investigated after daily intragastric administration of the following doses.

**Table 17: Long-term Toxicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)**

Species	No./Group	Dose (mg/kg/day)			Treatment Period
		DRSP+EE	DRSP Alone	EE Alone	
Mouse	25-30F	0+0, 3+0.03, 10+0.1, 30+0.3	3, 10, 30	0.03, 0.1, 0.3	14-15 weeks
Rat	6F	--	0, 10, 50, 100	--	7 days
Rat	20F	0+0, 1+0.01, 3+0.03, 10+0.1	1, 3, 10	0.01, 0.03, 0.1	14 weeks
Rat	25F	--	0, 0.6, 3, 15	--	27 weeks
Rat	20F	0+0, 0.3+0.003, 3+0.03, 10+0.1	--	--	52-53 weeks
Monkey	4F	--	0, 0.2, 2, 10	--	27 weeks
Monkey	4-5F	0+0, 0.3+0.03, 3+0.3, 10+1	3, 1.0	0.03, 0.1	53-54 weeks

Compound related findings were generally limited to pharmacologic and exaggerated pharmacologic effects expected following administration of an exogenous progestogen or estrogen/progestogen combination. No organ toxicity was observed.

Changes observed following administration of drospirenone alone included:

- alterations in lipid, carbohydrate and protein metabolism (rats:  $\geq 1$  mg/kg/day)
- increased body weight gain and food consumption (rats:  $\geq 3$  mg/kg/day)
- decreased liver weights accompanied by decreased hepatic glycogen content (monkeys:  $\geq 2$  mg/kg/day)
- increased liver weights accompanied by increased hepatic DNA and protein content (rats:  $\geq 50$  mg/kg/day)
- changes in electrolyte excretion (rats:  $\geq 10$  mg/kg/day; monkeys: 10 mg/kg/day)
- decreased ovarian weights (mice: 30 mg/kg/day)
- decreased (mice: 30 mg/kg/day) or slightly increased (monkeys: 10 mg/kg/day) adrenal gland weights
- microscopic changes in endocrine target organs (mice:  $\geq 3$  mg/kg/day; rats:  $\geq 3$  mg/kg/day; monkeys:  $\geq 0.2$  mg/kg/day)

A spectrum of compound-related estrogenic, progestogenic, and antimineralocorticoid effects was observed following administration of the combination to female mice, rats, and monkeys. In addition, the antagonism of some estrogenic effects (decreased body weight and food consumption [rats]; hematologic changes [rats, monkeys], and increased uterine weights [mice]), and antagonism of some progestogenic effects (increased body weight and food consumption [rats]) were observed.

Synergism of other effects was observed in mice and rats and included atrophy of ovarian interstitial glands, decreased luteal mass and sexual cycles in mice, and decreased ovarian weights and increased hepatic N-demethylase activity in rats. In comparison with administration of either substance alone, administration of the combination to rats and cynomolgus monkeys eliminated some single substance effects (alterations in hepatic cytochrome P450 content). Overt toxicity was limited to 1 possible compound-related death in cynomolgus monkeys administered the combination at a dose of 3 mg/kg drospirenone + 0.03 mg/kg ethinyl estradiol for 11 weeks.

Toxicokinetic monitoring showed that on the basis of AUC<sub>0-24h</sub> values, the highest doses used in mice (30 mg/kg/day), rats (15 mg/kg/day), and monkeys (10 mg/kg/day) which did not produce

overt signs of toxicity led to roughly 10.6 times (mice), >12 times (rats), and ca 22 times (monkeys) higher systemic exposure as compared to human exposure at the therapeutic dose.

### **Carcinogenicity**

The carcinogenic potential of drospirenone, alone and in combination with ethinyl estradiol, was investigated in female mice and rats after daily intragastric administration of the following doses.

**Table 18: Carcinogenicity Studies Conducted With Drospirenone (DRSP) and Ethinyl Estradiol (EE)**

Species	No./Group	Dose (mg/kg/day)			Treatment Period
		DRSP+EE	DRSP Alone	EE Alone	
Mouse	55F or 110F	0+0, 1+0.01, 3+0.03, 10+0.1	1, 3, 10	0.01, 0.03, 0.1	104 weeks
Rat	55F or 110F	0+0, 0.3+0.003, 3+0.03, 10+1	0.3, 3, 10	0.003, 0.03, 1	106-110 weeks

No carcinogenicity was observed after 2 years of treatment with drospirenone as a single compound in mice or rats. Mortality was increased in rats at the highest dose of drospirenone. The increased food intake of the rats with a resultant increase in body weight was considered as the reason for the reduction in their life span. In the mouse study, there were no effects on the survival of the animals observed after treatment with drospirenone.

Tumorigenic effects of the drug combination in mice were manifested by an increased incidence of pituitary adenomas at all doses, overall mammary tumors at the mid and low doses, and uterine adenocarcinomas at the mid and high doses in comparison with controls. The same qualitative tumor pattern (however, quantitatively more pronounced, especially in the pituitary) was seen in groups treated with ethinyl estradiol alone. As drospirenone alone elicited no tumorigenic response, the tumorigenic potential of the combination was attributed to ethinyl estradiol.

Treatment of rats with the drug combination resulted in an increased incidence of hepatic adenomas at the high dose and of total liver tumors from the mid dose onwards. A similar effect on liver tumor induction was seen in groups receiving ethinyl estradiol alone. Therefore, this effect on the liver could be attributed to the activity of ethinyl estradiol.

Compared to the control group, a tendency towards an increased rate of endometrial adenoma with a concomitant decrease in the rate of adenocarcinoma was seen in the uteri from the animals of the low-dose combination group. In the mid- and high-dose combination groups, no endometrial adenomas or adenocarcinomas were noted, ie, there was a reduction in the rate of uterine tumors below the control level. A clear-cut increase in these uterine tumor incidences was induced by ethinyl estradiol when given alone from the mid dose onwards. Thus, the presence of drospirenone in the drug combination apparently led to a suppression of the deleterious estrogenic effect on the uterus. Treatment with ethinyl estradiol at the high dose led to an increased incidence of adenocarcinoma in the mammary glands. This effect was also completely counteracted by drospirenone in the drug combination group.

Evaluation of concomitant drug plasma concentrations revealed that exposure to drospirenone on the basis of AUC<sub>0-24h</sub> values amounted to roughly 0.1-, 0.5-, and 3-fold multiples of human exposure after the low, mid, and high doses, respectively. The corresponding exposure multiples for drospirenone in the rat were approximately 0.5, 3.5, and 10 to 12 times human steady-state exposure.



## **Mutagenicity**

No mutagenic effect of drospirenone was demonstrated in vitro in bacterial (*Salmonella typhimurium*, *Escherichia coli*) or mammalian (human lymphocyte, Chinese hamster) cells in the presence or absence of extrinsic metabolic activation. Drospirenone did not increase the occurrence of micronucleated red blood cells in vivo following single intragastric administration of 1000 mg/kg to mice.

Drospirenone increased unscheduled DNA synthesis in primary hepatocytes of female rats in vitro in a dose-dependent manner at a concentration of 10 to 60 µg/mL. Intragastric administration of drospirenone 10 mg/kg/day to rats for 14 consecutive days generated 2 forms of DNA adducts in male and female rat livers. Low levels of 3 compound-related DNA adducts were also observed in the livers of female mice given drospirenone 10 mg/kg/day, alone or in combination with 0.1 mg/kg/day ethinyl estradiol, in the carcinogenicity study. In contrast to these findings observed in rodent livers, results from an in vitro study conducted with drospirenone 5 µg/mL in human liver slices did not indicate a DNA adduct-forming potential of drospirenone in human tissue. Given the lack of any drospirenone-related liver tumor formation in mice and rats, the biological relevance of this interaction with DNA in the rodent liver with regard to risk assessment in humans is questionable.

Drospirenone did not demonstrate clastogenic potential in human lymphocytes in vitro at concentrations that were cytotoxic or precipitating in the presence or absence of extrinsic metabolic activation. No DNA adducts were detected in primary hepatocytes isolated from female rats incubated with 3.62 µM tritiated-drospirenone in vitro.

Based on the highest dose given in the mouse micronucleus study, the specification level of 0.1% and the expected maximum human intake of the impurity contained in a daily (3 mg) dose of drospirenone, the results of the mouse micronucleus test support a safety margin of  $5 \times 10^5$ .

Following oral administration of drospirenone to juvenile rats for 5 days in a dose range-finding study, serum liver enzymes (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) were not altered at doses up to 500 mg/kg/day. Therefore, the high dose of 500 mg/kg/day was considered an adequate, nonhepatotoxic dose for a rat liver foci bioassay (which was subsequently cancelled for drospirenone when long-term data became available for drospirenone).

## **Reproduction and Teratology**

The reproductive toxicity of drospirenone, alone and in combination with ethinyl estradiol, was investigated in rats, rabbits, and monkeys following intragastric administration at the following doses:

**Table 19: Reproductive Toxicity Studies Conducted With Drospirenone (DRSP) + Ethinyl Estradiol (EE)**

Segment	Species	No./Group	Dose (mg/kg/day) DRSP + EE	Treatment Period
I: Fertility and General Reproductive Performance	Rat	25F	0 + 0; 5 + 0.05; 15 + 0.15; 45 + 0.45	42 days prior to mating
	Rat	25F	0 + 0; 1 + 0.01; 3 + 0.03; 10 + 0.1	Days 0 to 6 of gestation
II: Embryotoxicity/ Teratogenicity	Rat	36F	0 + 0; 5 + 0; 15 + 0; 45 + 0	Days 6 to 15 of gestation
	Rat	16F	0 + 0; 5 + 0.05; 15 + 0.15; 45 + 0.45	Days 14 to 21 of gestation
	Rabbit	20F	0 + 0; 10 + 0; 30 + 0; 100 + 0	Days 6 to 18 of gestation
	Rabbit	164F-182F	0 + 0; 30 + 0	Days 6 to 18 of gestation
	Monkey	12F	0 + 0; 1 + 0.01; 3 + 0.03; 10 + 0.1	Days 20 to 90 of gestation
III: Perinatal/ Postnatal Toxicity	Rat	10F	15 + 0.15; 45 + 0.45	Day 15 of gestation to day 3 postpartum
	Rat	35F	0 + 0; 5 + 0.05; 15 + 0.15; 45 + 0.45	Days 15 to 18 of gestation and days 1 to 22 postpartum

As expected from the pharmacological activity of an estrogen/progestogen combination, estrous cycle disturbances and a transient impairment of fertility were observed in rats when treated for 6 weeks prior to mating with doses of 5 mg/kg/day drospirenone + 0.05 mg/kg/day ethinyl estradiol and higher. Pre- and postimplantation losses were significantly increased when 10 mg/kg/day drospirenone + 0.1 mg/kg/day ethinyl estradiol were administered during the preimplantation phase of gestation in rats.

No teratogenicity was observed following intragastric administration of drospirenone, alone or in combination with ethinyl estradiol, to female rats, rabbits and/or monkeys prior to mating or during gestation. Compound-related maternal toxicity characterized by decreased body weight gain (rats) and occasional vomiting (monkeys) was observed. The incidence of abortions was increased following administration of high doses of drospirenone (100 mg/kg/day) to pregnant rabbits, and a dose-dependent increase in abortions occurred following the administration of all doses to monkeys. Embryotoxicity and slight retardations of fetal development (eg, delayed ossification of feet bones, sternbrae, vertebrae; incomplete ossification of skull; slight increase in visceral abnormalities) were observed in the rat and rabbit at drospirenone doses of 15 mg/kg/day and 100 mg/kg/day, respectively.

Virilization of female fetuses (attributed to ethinyl estradiol) and feminization of male fetuses (attributed to drospirenone) were observed following administration of the drug combination to pregnant rats on days 14 through 21 of pregnancy, beginning at doses of 5 + 0.05 mg/kg and 15 + 0.15 mg/kg, respectively. If exposure estimates from nonpregnant rats are extrapolated to pregnant animals, the administration of 15 mg/kg/day drospirenone would result in plasma exposure levels which are at least 10 times higher than the steady-state human exposure after intake of the drug product.

Prolonged or incomplete parturition or inability to deliver was observed when the drug combination was administered to rats from day 15 of gestation through day 3 postpartum. In the rat peri-/postnatal study, treatment from days 15 to 18 of gestation and days 1 to 22 postpartum caused a dose-dependent delay in postnatal development (body weight, physical, and functional

parameters) and a dose-dependent increased mortality of the F1 offspring. These observations were attributed to the negative effects of drospirenone and/or ethinyl estradiol on lactogenesis and milk secretion.

A reduced reproductive performance of the F<sub>1</sub> animals was observed at the dose of 45 mg/kg/day drospirenone + 0.45 mg/kg/day ethinyl estradiol. This was attributed to an impairment of sex organ development in the male offspring due to the antiandrogenic activity of drospirenone.

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## PART III: CONSUMER INFORMATION

Pr **NIKKI**

**3.0 mg drospirenone and 0.020 mg ethinyl estradiol tablets**

*This leaflet is Part III of a three-part “Product Monograph” published when NIKKI was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NIKKI. Contact your doctor or pharmacist if you have any questions about the drug.*

### ABOUT THIS MEDICATION

#### What the medication is used for:

- To prevent pregnancy
- To treat moderate acne vulgaris in women 14 years of age and older who are able to use birth control pills and have achieved menarche. Your first menstrual period is referred to as menarche.

#### What it does:

NIKKI is a birth control pill (oral contraceptive) that contains two female sex hormones, the progestin drospirenone (3.0 mg) and a low dose of the estrogen ethinyl estradiol (0.020 mg). Both hormones are synthetic and similar to those that occur naturally in your body. The NIKKI pill pack has 24 hormone-containing pink “active” pills to be taken for 24 days, followed by 4 hormone-free white “reminder” pills to be taken for four days. It has also been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

Drospirenone in NIKKI helps with androgen- (male sex hormone) related skin problems. Androgen circulates naturally within the female body. Androgens can cause glands in the skin to over-produce oil. This results in acne. NIKKI works by lowering androgen levels in the body and by blocking the effects of androgens at the gland. As a

result, a reduction in the number of acne breakouts is associated with 3.0 mg drospirenone and 0.020 mg ethinyl estradiol treatment.

#### Effectiveness of Birth Control Pills

Combination birth control pills are more than 99 percent effective in preventing pregnancy when:

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

A 99 percent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The chance of becoming pregnant increases with incorrect use.

#### Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

#### Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus.). Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth



control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully.

**When it should not be used:**

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of the birth control pill always should be supervised by your doctor.

**You should not use NIKKI** if you have or have had any of the following conditions:

- blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation or swelling of the veins)
- stroke, heart attack, or coronary artery disease (eg, angina pectoris), or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- severe high blood pressure
- diabetes with complications
- very high blood cholesterol or triglyceride levels
- you smoke and are over age 35
- migraine headache
- you are scheduled for major surgery
- prolonged bed rest
- jaundice (yellowing of the eyes or skin), liver disease, or liver tumor
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- allergy (hypersensitivity) to ethinyl estradiol, drospirenone or to any of the other ingredients in NIKKI (see **What the medicinal ingredients are** and **What the nonmedicinal ingredients are**)

In addition, you should not use NIKKI if you have any of the following conditions:

- Kidney disease
- Liver disease
- Adrenal disease

Tell your doctor if you have ever had any of the above conditions (your doctor can recommend another method of birth control).

**What the medicinal ingredients are:**

drospirenone and ethinyl estradiol

**What the nonmedicinal ingredients are:**

corn starch, hypromellose, lactose monohydrate, polyethylene glycol, magnesium stearate, pregelatinized starch, red iron oxide, talc, titanium dioxide.

**What dosage forms it comes in:**

NIKKI (3.0 mg drospirenone and 0.020 mg ethinyl estradiol) tablets are available in a 28-day regimen.

Each blister pack contains 24 hormone-containing tablets that are pink round, biconvex, film coated tablets, plain on one side and ‘DR1’ on the other side and 4 hormone-free tablets that are white to off-white, round, biconvex film-coated debossed with ‘K33’ on one side and ‘LU’ on the other side. Each hormone-containing pink, film-coated tablet contains 3.0 mg drospirenone and 0.020 mg ethinyl estradiol.

**WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions**

**Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including NIKKI, should not be used by women who are over 35 years of age and smoke. Women should not smoke.**

**Birth control pills DO NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS.**

**For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH birth control pills.**

**NIKKI is a birth control pill containing estrogen and progestin. The progestin in NIKKI is known as drospirenone and it may increase the levels of potassium in your blood. Therefore, you should not take NIKKI if you have kidney, liver, or adrenal disease (a disease that may alter the body’s fluid and mineral balance) because this could cause serious heart and health problems. Other drugs may also increase potassium (see Before you use NIKKI, talk to your doctor or pharmacist if you:). During the first month that you take NIKKI, you should have a blood test to check your potassium level.**

**It has been reported that drospirenone, the progestin in NIKKI, may carry a higher risk of blood clots than some other progestins (including levonorgestrel). You should talk to your doctor about the available options.**

**BEFORE you use NIKKI, talk to your doctor or pharmacist if you:**

- smoke
- are overweight
- have a history of breast disease (eg, breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumors of the uterus)
- may be pregnant or are breastfeeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have haemolytic uremic syndrome
- have sickle cell disease
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- **you are currently on daily, long-term treatment for a chronic condition with any of the medications listed below:**
  - **Non steroidal anti-inflammatory drugs (NSAIDs) when taken long-term and for treatment of arthritis or other problems (eg, ibuprofen, naproxen, or others)**
  - **Potassium-sparing diuretics (spironolactone and others)**
  - **Potassium supplements**
  - **ACE inhibitors and Angiotensin-II receptor antagonists for the treatment of high blood pressure (eg, captopril, enalapril, lisinopril, losartan, valsartan, irbesartan, or others)**
  - **Heparin**

You should also inform your doctor about a family history of blood clots, heart attacks, or strokes.

If you see a different doctor, inform him or her that you are using NIKKI.

Tell your doctor if you are scheduled for any laboratory tests since certain blood tests may be affected by hormonal contraceptives.

Also tell your doctor if you are scheduled for **MAJOR** surgery. You should consult your doctor about stopping the use of NIKKI four weeks before surgery and not using NIKKI for a time period after surgery or during bed rest.

NIKKI should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use NIKKI only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of NIKKI outweigh the risks, you should be aware of the following:

### **THE RISKS OF USING NIKKI**

#### **1. Circulatory disorders (including blood clot in legs, lungs, heart, eyes, or brain)**

Women who use hormonal contraceptives have a higher incidence of blood clots. Blood clots are the most common serious side effects of birth control pills. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive or restarts the same or a different hormonal contraceptive. Clots can occur in many parts of the body.

Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest which may increase with deep breathing; coughing blood; sudden shortness of breath or rapid breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf 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. These symptoms could indicate a possible blood clot in the leg.
- crushing chest 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; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats. These symptoms could indicate a possible heart attack.

- sudden severe or worsening headache or vomiting; sudden trouble walking, dizziness, loss of balance or coordination; loss of consciousness or fainting with or without seizure; sudden confusion, disturbances of vision, speech or understanding; sudden weakness or numbness of the face, arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.
- other signs of a blood clot can include sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

The risk of clotting seems to increase with higher estrogen doses. It is important, therefore, to use as low a dosage of estrogen as possible.

**Cancer of the breast, cervix, or liver may be life-threatening or may result in death.**

## 2. Breast cancer

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however. A yearly breast examination by a health care professional is recommended for all women.

**ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF EXAMINATION OF YOUR BREASTS.**

## 3. Cervical cancer

Some studies have found an increase of cancer of the cervix in women who use hormonal contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

## 4. Liver tumors

The short and long-term use of birth control pills have also been linked with the growth of liver tumors. Such tumors are **extremely rare**.

Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

## 5. Gallbladder disease

Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

## 6. Use in pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

## 7. Use after pregnancy, miscarriage or an abortion

Your doctor will advise you of the appropriate time to start the use of NIKKI after childbirth, miscarriage, or therapeutic abortion.

## 8. Pregnancy after stopping NIKKI

You will have a menstrual period when you stop using NIKKI. You should delay pregnancy until another menstrual period occurs within four to six weeks. In this way the pregnancy can be more accurately dated. Contact your doctor for recommendations on alternate methods of contraception during this time.

## 9. Use while breastfeeding

If you are breastfeeding, consult your doctor before starting the birth control pill. The hormones in birth

control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception and only consider starting the birth control pill once you have weaned your child completely.

- the treatment of depressive moods)
- grapefruit juice

*This is not a complete list of possible drug interactions with NIKKI. Talk to your doctor for more information about drug interactions.*

**INTERACTIONS WITH THIS MEDICATION**

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist (or the dispensing pharmacist) who prescribes another drug that you use NIKKI. They can tell you if you need to use an additional method of contraception and if so, for how long.

**Drugs that may interact with NIKKI include:**

- drugs used for the treatment of epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (eg, rifampin, rifabutin), HIV infections (eg, ritonavir, nevirapine), and Hepatitis C Virus infections (eg, boceprevir, telaprevir)
- antibiotics (eg, penicillins, tetracyclines, clarithromycin, erythromycin) for infectious diseases
- cyclosporine
- antifungals (eg, griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- cholesterol-lowering drugs (eg, clofibrate)
- drugs used for the treatment of certain heart diseases or high blood pressure (eg, diltiazem, verapamil)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (eg, clomipramine)
- tizanidine (drug used for multiple sclerosis [MS])
- theophylline (drug used for asthma)
- some nutritional supplements (eg, Vit. B<sub>12</sub>, folic acid)
- antacids (use 2 hours before or after taking NIKKI)

NIKKI may also interfere with the working of other drugs.

**Herbal or food products that may interfere with NIKKI include:**

- the herbal remedy St. John’s wort (primarily used for

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

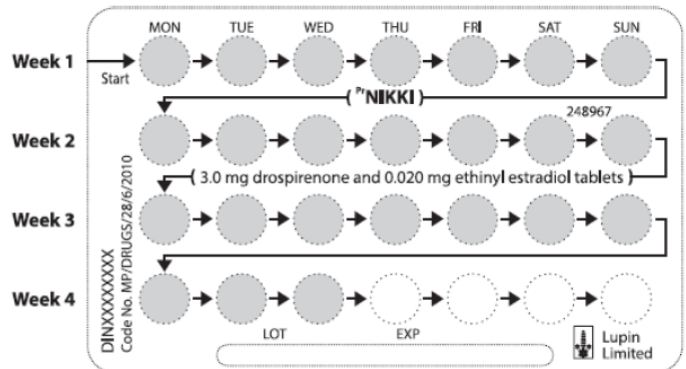
**HOW TO TAKE NIKKI**

**1. READ THESE DIRECTIONS**

- before you start taking your pills, and
- any time you are not sure what to do.

**2. LOOK AT YOUR PILL PACK, it has 28 pills.**

**The NIKKI pill pack has 24 hormone-containing pink “active” pills to be taken for 24 days, followed by 4 hormone-free white “reminder” pills to be taken for four days.**



**ALSO CHECK** the pill pack for: 1) where to start, and 2) direction to take pills in (follow the arrows).

- You should use a second method of birth control (eg, latex or polyurethane condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.
- When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**
- IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN**

**MEDICINES**, such as antibiotics, your pills may not work as well. Use a back-up method, such as latex or polyurethane condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

6. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.
7. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.
8. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.
9. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**
10. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

**WHEN TO START THE *FIRST* PACK OF PILLS**

**BE SURE TO READ THESE INSTRUCTIONS:**

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Pick a time of day which will be easy to remember.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS.** Your period should occur during the last four days of using that pill pack.

**WHAT TO DO DURING THE MONTH**

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**

- Try to associate taking your pill with some regular activity, such as eating a meal or going to bed.
- Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
- Do not skip pills even if you do not have sex very often

**2. WHEN YOU FINISH A PACK**

Start the next pack **on** the day after your last hormone-free white “reminder” pill. Take one pill every day. Do not wait any days between packs.

**Overdose:**

Symptoms of overdose may include nausea, vomiting, or vaginal bleeding. Available information from cases of accidental ingestion of oral contraceptives by children indicates no serious effects.

In case of drug overdose, contact a health care practitioner, hospital emergency department, or regional Poison Control Center immediately, even if there are no symptoms.

**Missed Dose:**

**MISSING PILLS CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

**IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**

- when you start a pack late, or
- when you miss pills at the beginning or at the very end of the pack.

**WHAT TO DO IF YOU MISS PILLS**

The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack

<b>Sunday Start</b>	<b>Other than Sunday Start</b>
<b>Miss One Pink Pill at Any Time</b>	<b>Miss One Pink Pill at Any Time</b>
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
<b>Miss Two Pink Pills in a Row</b>	<b>Miss Two Pink Pills in a Row</b>
<b>First Two Weeks:</b>	<b>First Two Weeks:</b>
<ol style="list-style-type: none"> <li>1. Take two pills the day you remember and two pills the next day.</li> <li>2. Then take one pill a day until you finish the pack.</li> <li>3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> </ol>	<ol style="list-style-type: none"> <li>1. Take two pills the day you remember and two pills the next day.</li> <li>2. Then take one pill a day until you finish the pack.</li> <li>3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> </ol>
<b>Third and Fourth Weeks</b>	<b>Third and Fourth Weeks</b>
<ol style="list-style-type: none"> <li>1. Keep taking one pill a day until Sunday.</li> <li>2. On Sunday, safely discard the rest of the pack and start a new pack that day.</li> <li>3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> <li>4. You may not have a period this month.</li> </ol> <p><b>If you miss two periods in a row, call your doctor or clinic.</b></p>	<ol style="list-style-type: none"> <li>1. Safely dispose of the rest of the pill pack and start a new pack that same day.</li> <li>2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> <li>3. You may not have a period this month.</li> </ol> <p><b>If you miss two periods in a row, call your doctor or clinic.</b></p>
<b>Miss Three or More Pink Pills in a Row</b>	<b>Miss Three or More Pink Pills in a Row</b>
<b>Anytime in the Cycle</b>	<b>Anytime in the cycle</b>
<ol style="list-style-type: none"> <li>1. Keep taking one pill a day until Sunday.</li> </ol>	<ol style="list-style-type: none"> <li>1. Safely dispose of the rest of the pill pack and start a new pack that same</li> </ol>

<ol style="list-style-type: none"> <li>2. On Sunday, safely discard the rest of the pack and start a new pack that day.</li> <li>3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> <li>4. You may not have a period this month.</li> </ol> <p><b>If you miss two periods in a row, call your doctor or clinic</b></p>	<p>day.</p> <ol style="list-style-type: none"> <li>2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</li> <li>3. You may not have a period this month.</li> </ol> <p><b>If you miss two periods in a row, call your doctor or clinic</b></p>
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**NOTE:** If you forget any of the four hormone-free white “reminder” pills in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand

- a backup method of birth control (such as latex or polyurethane condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

**IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC** about ways to make pill-taking easier or about using another method of birth control.

**Noncontraceptive Benefits of Birth Control Pills**

Several health advantages have been linked to the use of birth control pills:

- Combination estrogen and progestin birth control pills reduce the incidence of cancer of the uterus and ovaries.
- Birth control pills reduce the likelihood of developing benign (noncancerous) breast disease and ovarian cysts.
- Users of birth control pills lose less menstrual blood and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and in premenstrual syndrome (PMS).
- Acne, excessive hair growth, and male hormone-related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The following side effects have been observed in studies of women taking 3.0 mg drospirenone and 0.020 mg ethinyl estradiol which may or may not be drug related:

Most side effects when using the birth control pill are not serious. The most common side effects are nausea, vomiting, bleeding or spotting between menstrual periods, breast pain, acne, itching, migraine, dizziness, emotional lability (sudden changes in emotional state without a reason), dysmenorrhea (painful menstrual cramps), headache, vaginal yeast infection, depression, back pain, abdominal pain, nervousness, rash.

Other side effects can occur such as gastrointestinal symptoms (abdominal cramps and bloating), darkening of the skin (particularly on the face), change in appetite, change in libido (sex drive), hair loss, change in weight (increase or decrease), swelling, breast changes (tenderness, enlargement, discharge), temporary infertility after discontinuation of treatment.

If you experience new onset of high blood pressure or worsening of high blood pressure, contact your doctor or pharmacist.

The following additional symptoms have been reported in women taking hormonal contraceptives in general:

- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc)
- severe headaches
- depression, insomnia, nervousness
- amenorrhea (lack of a period or breakthrough bleeding)
- back pain
- abdominal pain
- flu-like symptoms
- allergy, fatigue, fever
- diarrhea, flatulence
- rash

Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months on the pill. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / Possible Side Effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
<b>Uncommon</b>			
Abdominal pain, nausea or vomiting or lump in the abdomen		✓	
Breast lump		✓	
Crushing chest pain or heaviness			✓
Pain or swelling in the leg			✓
Persistent sad mood			✓
Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
Sudden partial or complete loss of vision or double vision			✓
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg			✓
Unexpected vaginal bleeding		✓	
Unusual swelling of the extremities		✓	
Yellowing of the skin or eyes (jaundice)			✓

*This is not a complete list of side effects. For any unexpected effects while taking NIKKI, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store in original packaging between 15°C and 30°C. Keep out of reach of children and pets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Date of Revision: December 20, 2016

**REPORTING SIDE EFFECTS**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**

- Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to:       Canada Vigilance Program  
                  Health Canada, Postal Locator  
                  1908C  
                  Ottawa ON  
                  K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available on the MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

For more information, please contact your health professional or pharmacist first, or Lupin Pharma Canada Ltd. at: 514.866.3863 or at [www.lupinpharma.ca](http://www.lupinpharma.ca).

This document plus the full Product Monograph, prepared for health professionals can be found at: <http://www.lupinworld.com> or by contacting the sponsor at the above-mentioned phone number and website.

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