PRODUCT MONOGRAPH

Pr APRI® 21 and Pr APRI® 28

150 mcg desogestrel and 30 mcg ethinyl estradiol tablets,

USP

Oral Contraceptive

Teva Canada Limited
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Toronto, ON M1B 2K9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets / 150 mcg desogestrel and 30 mcg ethinyl estradiol	Lactose monohydrate, anhydrous lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APRI® (desogestrel/ethinyl estradiol tablets, USP) is indicated for:

- Conception control

CONTRAINDICATIONS

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- Presence or history of venous thrombosis (deep vein thrombosis, pulmonary embolism);
- A history of or actual cerebrovascular disorders;
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g., transient ischaemic attack, angina pectoris);
- Valvular heart disease with complications;
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal;
- Use with the Hepatitis C virus combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **WARNINGS AND PRECAUTIONS**).
- Presence or history of liver tumours (benign or malignant);
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or of the breast);
- Undiagnosed abnormal vaginal bleeding;

- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice of 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;
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
- severe hypertension (persistent values of ≥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 (eg, due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
- severe dyslipoproteinemia
- smoking and over age 35
- diabetes mellitus with vascular involvement
- major surgery associated with an increased risk of postoperative thromboembolism (see **WARNINGS AND PRECAUTIONS**)
- prolonged immobilization (see **WARNINGS AND PRECAUTIONS**)
- 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.**

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 oral contraceptive users older than 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including APRI®, should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

Patients should be counseled that birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs) including HIV/AIDS. For protection against STDs, patients should be counseled to use latex condoms **IN COMBINATION WITH** birth control pills.

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 which predispose to venous stasis and to vascular thrombosis (e.g., immobilization after accidents or confinement to bed during long-term illness). Other non-

hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **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

Throughout this section the general term combined hormonal contraceptives (CHC) is used when data exist for oral and non-oral contraceptives. The term, combined oral contraceptives (COC) is used when data exist only for oral contraceptives.

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

The use of COCs 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: jaundice and/or pruritus related to cholestasis; gallstone formation; 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); (hereditary) angioedema.

The information contained in this section is principally from studies carried out in women who used COC with higher formulations of estrogen and progestogens than those in common use today. The effect of long-term use of COCs with lower doses of both estrogen and progestogen remains to be determined.

Carcinogenesis and Mutagenesis

Breast Cancer

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 eight 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 physician should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended, because, if a 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 papilloma virus (HPV) infection. 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 the confounding effects, e.g., cervical screening and sexual behavior 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.

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, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use in women who 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, non-smoking 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.

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 dyslipidemias. (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 shown an association between the use of CHCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of CHC with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 3 to 12 cases per 10,000 women-years, but the risk estimate varies according to the progestogen. This compares with 1 to 5 cases per 10,000 women-years for non-CHC users (59).

The use of CHCs carries an increased risk of VTE compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a CHC. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 5 to 20 cases per 10,000 women-years or the risk in the postpartum period which is estimated as 40-65 cases per 10,000 women-years. The risk is also increased after initially starting a CHC or restarting the same or different CHC after a break in use of 4 weeks or more. VTE is fatal in 1-2% of cases (23) (59).

Several epidemiological studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. These studies indicate an approximate 2-fold difference in

risk, which corresponds to 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this difference in risk.

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

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include: unilateral leg pain and/ or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

Other Risk Factors for Venous Thromboembolism

Other generalized risk factors for venous thromboembolism include but are not limited to:

- a personal history,
- a positive family history (the occurrence of VTE in a direct relative at a relatively early age). If a hereditary or acquired predisposition for venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any CHC use.
- severe obesity (body mass index >30kg/m^2)
- systemic lupus erythematosus.

The risk of VTE also increases with increasing age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, any surgery to the legs or major trauma. In these situations it is advisable to discontinue CHC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization (see **CONTRAINDICATIONS**).

Also, patients with superficial thrombophlebitis and varicose veins and leg cast should be closely supervised. There is no consensus about the possible role of these conditions in the etiology of venous thromboembolism.

Other Risk Factors for Arterial Thromboembolism

The risk of arterial thromboembolic complications increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m^2); hypertension;
- migraine;

- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

Hepatic/Biliary/Pancreatic

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 only 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 four or five 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.

Hepatitis C

During clinical trials with the HCV combination drug regimen ombitasvir /paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. **APRI®** must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see **CONTRAINDICATIONS and DRUG INTERACTIONS**). **APRI®** can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema (24-26).

Neurologic

Migraine and Headache

The onset or exacerbation of migraine or the development of headaches with 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

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.

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 one 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 one 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, which continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Reduced Efficacy
The efficacy of desogestrel/ethinyl estradiol may be reduced in the event of missed tablets, gastro-intestinal disturbances or concomitant medications that decrease the plasma concentration of ethinyl estradiol and/or etonogestrel, the active metabolite of desogestrel (see **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 APRI®, further intake should 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.

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. Published studies have indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel (27) and 0.02% of the daily maternal dose of ethinyl estradiol (28) could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement (29). 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.

Pediatrics
The safety and efficacy of APRI® has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

Geriatrics
APRI® is not indicated 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 (e.g., 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 three 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 combination hormonal contraceptives:
- arterial and venous thromboembolism
- benign and malignant hepatic tumours
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (e.g., retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following other adverse reactions also have been reported in patients receiving combination hormonal 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)[a]
- auditory disturbances
- breakthrough bleeding
- breast changes (tenderness, enlargement, and secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in glucose tolerance or effect on peripheral insulin resistance
- changes in libido
- change in menstrual flow
- change in weight (increase or decrease)
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum
- gallstone formation[a]
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome
- hemorrhagic eruption
- herpes gestationis[a]
- hirsutism
- hypersensitivity
- hypertension [a]
- hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestasis[a]
- liver function disturbances

- loss of scalp hair
- mental depression
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss[a]
- pancreatitis
- porphyria
- possible diminution in lactation when given immediately postpartum
- premenstrual-like syndrome
- pruritus related to cholestasis[a]
- rash (allergic)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- Sydenham's chorea[a]
- Systemic lupus erythematosus[a]
- temporary infertility after discontinuation of treatment
- ulcerative colitis
- urticaria
- vaginal candidiasis
- vaginal discharge
- vaginitis

[a]Occurrence or deterioration of conditions for which association with COC use is not conclusive.

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.

Eighty-six per cent of the 1,195 subjects reported 1 or more adverse experiences. The majority of these (64%) were considered (by the investigators) to be unrelated to desogestrel/ethinyl estradiol (150 mcg/30 mcg) usage. Of the total population, approximately 12% of the subjects discontinued due to an adverse experience.

OVERALL ASSESSMENT OF CLINICAL ADVERSE EXPERIENCES (AES) ALL-PATIENTS-TREATED-GROUP

CLINICAL AE CATEGORIES	STARTERS N (%)[a]		SWITCHERS N (%)		TOTAL N (%)	
Total Patients Entered	549	(100.0)	645	(100.0)	1,194[b]	(100.0)
Patients with a Clinical AE	458	(83.4)	569	(88.2)	1,027	(86.0)
Patients with a Serious Clinical AE	20	(3.6)	18	(2.7)	38	(3.1)
Patients with Clinical AEs Contributing to Discontinuation[c]	76	(13.8)	70	(10.9)	146	(12.2)
Patients with a Reasonably Possibly, Probably or Definitely Drug-Related Clinical AE	197	(35.8)	236	(36.5)	433	(36.2)

[a]Percentages are of total patients entered.
[b]Starter/Switcher status could not be determined in one subject.
[c]A total of 145 patients actually had a clinical AE as the primary reason for discontinuation.

With the exception of menses-related adverse experiences, no significant changes in the incidence of adverse experiences over time were seen. No drug-related adverse effects were observed during general physical or pelvic examination. The breast examination showed a reduction in nodularity. No changes in body mass index or blood pressure were observed. Baseline distribution of abnormalities in cervical cytology was comparable to those at last visit. No patient developed a clinically significant abnormal value for routine laboratory analytes that led to either early discontinuation or hospitalization.

Detailed opthalmologic examinations, including slit-lamp, were performed in a subset of 28 healthy women at baseline and after 12 cycles. No patients were found to have a decrease in visual acuity. Complete opthalmological examination failed to identify possible desogestrel/ethinyl estradiol -related changes.

PREVALENCE OF MOST FREQUENT[A] SIDE EFFECTS OVER CYCLES INCIDENCE DURING STUDY WITH N=1,195 TOTAL (PER CENT)

--Body System-- Adverse Experience	Cycle Number						
	1	2	3		12	18	21
	Number of Patients Per Cycle						
	1,095	1,064	1,001	863	465	115	30
--Body as a Whole--							
Abdominal Pain	115 (10.5)	71 (6.7)	58 (5.8)	42 (4.9)	20 (4.3)	4 (3.5)	1 (3.3)
Asthenia	27 (2.5)	18 (1.7)	11 (1.1)	11 (1.3)	2 (0.4)	1 (0.9)	1 (3.3)
Malaise	26 (2.4)	13 (1.2)	10 (1.0)	6 (0.7)	4 (0.9)	2 (1.7)	0 (0.0)
-- Digestive --							
Diarrhea	40 (3.6)	29 (2.7)	23 (2.3)	26 (3.0)	3 (0.6)	2 (1.7)	0 (0.0)
Dyspepsia	13 (1.2)	12 (1.1)	9 (0.9)	10 (1.2)	5 (1.1)	0 (0.0)	0 (0.0)

Nausea	99 (9.0)	66 (6.2)	55 (5.5)	26 (3.0)	8 (1.7)	3 (2.6)	0 (0.0)
Vomiting	25 (2.3)	22 (2.1)	21 (2.1)	16 (1.8)	4 (0.9)	0 (0.0)	1 (3.3)
-- Musculoskeletal --							
Back Pain	78 (7.1)	47 (4.4)	30 (3.0)	27 (3.1)	14 (3.0)	3 (2.6)	1 (3.3)
-- Nervous System / Psychiatric --							
Depression	25 (2.3)	20 (1.9)	18 (1.8)	10 (1.2)	4 (0.9)	1 (0.9)	0 (0.0)
Dizziness	18 (1.6)	16 (1.5)	8 (0.8)	18 (2.1)	3 (0.6)	1 (0.9)	0 (0.0)
Headache	389 (35.5)	286 (26.9)	220 (22.0)	191 (22.1)	87 (18.7)	19 (16.5)	5 (16.7)
Migraine	21 (1.9)	23 (2.2)	13 (1.3)	11 (1.3)	3 (0.6)	0 (0.0)	0 (0.0)
-- Respiratory --							
Allergic Rhinitis	9 (0.8)	11 (1.0)	13 (1.3)	9 (1.0)	12 (2.6)	1 (0.9)	0 (0.0)
Cough	26 (2.4)	17 (1.6)	17 (1.7)	16 (1.8)	5 (1.1)	2 (1.7)	0 (0.0)
Influenza	25 (2.3)	27 (2.5)	11 (1.1)	11 (1.3)	4 (0.9)	1 (0.9)	0 (0.0)
Pharyngitis	65 (5.9)	45 (4.2)	42 (4.2)	27 (3.1)	11 (2.4)	5 (4.4)	0 (0.0)
Upper Respiratory Infection	93 (8.5)	86 (8.1)	63 (6.3)	52 (6.0)	20 (4.3)	7 (6.1)	1 (3.3)
-- Urogenital --							
Breast Pain	75 (6.8)	55 (5.2)	51 (5.1)	15 (1.7)	4 (0.9)	1 (0.9)	0 (0.0)
Dysmenorrhea	323 (29.5)	155 (14.6)	121 (12.1)	88 (10.2)	49 (10.5)	8 (7.0)	5 (16.7)
Vaginal Candidiasis	11 (1.0)	12 (1.1)	7 (0.7)	14 (1.6)	9 (1.9)	3 (2.6)	0 (0.0)
Cystitis	9 (0.8)	11 (1.0)	7 (0.7)	5 (0.6)	4 (0.9)	1 (0.9)	0 (0.0)

[a]Adverse experiences reported by >5% of patients.

Post-Market Adverse Drug Reactions

The most serious undesirable effects associated with the use of COCs are listed in WARNINGS AND PRECAUTIONS. Other side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are:[1]

Body system	Common/Uncommon (more than 1/1000)	Rare (less than 1/1000)
Immune system disorders		Hypersensitivity
Metabolism and nutrition disorders	Weight increased, fluid retention	Weight decreased
Nervous system disorders	Headache, migraine, libido decreased, depressed mood, mood altered	Libido increased
Eye disorders		Contact lens intolerance
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhea	
Skin and subcutaneous tissue disorders	Rash, urticaria	Erythema nodosum, erythema multiforme
Reproductive system and breast disorders	Breast pain, breast tenderness, breast hypertrophy	Vaginal discharge, breast discharge

[1] The most appropriate MedDRA term (version 6.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

DRUG INTERACTIONS

Overview

Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

The concurrent administration of oral contraceptives with other medicinal products may lead to breakthrough bleeding and/or may result in an altered response to either agent (see table 1 and 2). 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 non-prescription, before oral contraceptives are prescribed.

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including APRI®. These products are identified in Drug-Drug Interactions and Drug-Herb Interactions with an (*). Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days. For women on long-term therapy with enzyme-inducing medicinal products, an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Drug-Drug Interactions

Table 1: Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics (30)	Rifabutin Rifampicin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method. For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
	Chloramphenicol Neomycin Nitrofurantoin Sulfonamides	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants (31-33)	Carbamazepine 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.	For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.

Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method. For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another method.
HCV Protease Inhibitors HIV protease inhibitors (34) Non-nucleoside reverse transcriptase inhibitors (29, 35)	Boceprevir Telaprevir Nelfinavir Ritonavir Nevirapine Efavirenz	HCV and HIV combination therapy may alter clearance of the sex hormones; decreased, increased or no change in the plasma concentrations of the progestin or estrogen component.	For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction.
Sedatives and Hypnotics	Barbiturates Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drugs, use another method of contraception unaffected by enzyme induction..

Pulmonary arterial hypertension Drugs	Bosentan	Induction of hepatic microsomal enzymes	For short course, use a barrier contraceptive method in addition to APRI® during administration and for 28 days after discontinuation of the enzyme inducing drug. For long course of enzyme inducing drug, use another method of contraception unaffected by enzyme induction.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

Oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue may either increase (e.g., cyclosporine) or decrease (e.g. lamotrigine).

If concomitant drug administration runs beyond the end of the tablets in the current COC pack, the next COC pack should be started right away without the usual tablet-free interval.

Table 2: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
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 s may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures.	Use another method.
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 method. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low estrogen oral contraceptive or use another method.
	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.
	Antipyridine	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.
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.
Meperedine		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 method.
Sedatives and hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	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; i.e. depression.	Use with caution.

Vitamin B_{12}		Oral contraceptives have been reported to reduce serum levels of Vitamin $B_{12.}$	May need to increase dietary intake, or supplement.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g., nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g., boceprevir, telaprevir) can increase or decrease plasma concentrations of progestins, including etonogestrel, the active metabolite of desogestrel, or estrogens. The net effect of these changes may be clinically relevant in some cases.

During clinical trials with the HCV combination drug regimen ombitasvir /paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as CHCs. APRI® must be discontinued prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS). APRI® can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP 3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

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. For short course, a barrier contraceptive method should be used in addition to APRI® during administration and for 28 days after discontinuation of the herbal product. For long course, use another method of contraception.
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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.

Liver Function Tests
Aspartate serum transaminase (AST) - variously reported elevations

Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated.

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

Thyroid Function Tests
Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake.

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

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

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.

Non-Contraceptive 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

Patients should be instructed to read the package insert prior to starting APRI® and any time they are unsure of administration. If they have additional question they should call their doctor or clinic.

APRI® tablets may be prescribed as a 21-day or a 28-day regimen. APRI® tablets must be taken at approximately the same time every day until the pack is empty. The patient may begin taking APRI® on Day 1 of her menstrual cycle (i.e., the first day of menstrual flow) or on the first Sunday after her period begins. If the patient's period starts on Sunday, she should start that same day.

Dosage

APRI® 21 (21-Day Regimen): One rose tablet is to be taken for 21 consecutive days (three weeks). Tablets are then discontinued for one week. The patient must not be off the pill for more than seven consecutive days. A new pack will be started on the eighth day. The patient will have a period during the seven days off the pill (bleeding may be lighter and shorter than their usual period.)

APRI® 28 (28-Day Regimen): One rose tablet is to be taken for 21 consecutive days (three weeks), followed by a white tablet for seven consecutive days (one week). A new pack (rose tablet) will be started on the eighth day, following the completion of the white tablets. The patient will have a period while they are on the white tablet. On this regimen the patient must not go a day without taking a pill.

Management of Missed Tablets:
The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills missed with the appropriate starting time for her dosing regimen.

Sunday Start	Day One Start
Miss One Pill	**Miss One Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 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 2 pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**

First Two Weeks 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.	**First Two Weeks** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.
Third Week 1. Keep taking 1 pill 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 method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the Cycle 1. Keep taking 1 pill 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 method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the Cycle** 1. Safely dispose of the rest of the rest of pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

Missing pills can cause spotting or light bleeding, even if the missed pills are made up. The woman may also feel a little sick to her stomach on the days she takes two pills to make up for missed pills.

If a woman misses pills at any time, she could get pregnant. The greatest risks for pregnancy are starting a pack late or missing a pill(s) at the beginning or at the very end of the pack.

The patient should be counselled to always have another kind of birth control (such as latex condoms and spermicidal foam or gel) to use as a back-up in case they miss pills, and an extra, full pack of pills available.

If the patient forgets more than one pill, two months in a row, they should be instructed to talk to their doctor or clinic. The patient may require further counselling about ways to make pill-taking easier or about using another method of birth control.

NOTE to Patients on the 28 day regimen (APRI® 28): If the patient forgets any of the seven white pills (without hormones) in Week 4, she should be advised to safely dispose of the pills she missed and then keep taking one pill each day until the pack is empty. A back-up method of birth control is not needed.

Administration

It is recommended that APRI® be taken at the same time each day. The patient should be counselled to associate taking the pill with some regular activity like eating a meal or going to bed.

The first-time user may wish to use a second method of birth control (e.g. latex 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 they are getting used to taking them.

If spotting, light bleeding, or feeling sick to their stomach occurs during the first three months the women should be counselled to not stop taking the pill. The problem will usually go away. If it does not subside, the patient should consult her doctor or clinic.

The dosage regimen should not be altered (i.e., the pill should not be stopped) even if the women does not have sex very often.

When receiving any medical treatment, patients should tell their doctor that they are using birth control pills.

Advice in case of vomiting

In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning the Management of missed tablets is outlined above. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

Special Notes on Administration

When to start APRI®

No hormonal contraceptive use in the preceding cycle: Tablet taking should start on Day 1 of the woman's menstrual cycle or on the first Sunday after her period begins.

Switching from another combination hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch): The woman should start APRI® preferably on the day after the last active tablet of her previous COC, but at the latest, on the day following the usual tablet-free or inactive tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using APRI® preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a progestogen-only-method (mini-pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS): The woman may switch from the mini-pill to APRI® on any day of her cycle. Patients using a progestogen injection should start APRI® on the day the next injection is due. Patients using an implant or an IUS should start APRI® on the day it is removed. In all cases, the woman should be advised to use an additional barrier method for the first 7 days of APRI® use.

Following complete first-trimester abortion: The woman may start using APRI® immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion: Women should be advised to start APRI® on Day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the woman should be advised to use an additional barrier method for the first seven days of tablet-taking. 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 first menstrual period prior to starting APRI®.

The increased risk of VTE during the postpartum period should be considered when restarting **APRI®** (see **WARNINGS AND PRECAUTIONS**).

For breastfeeding women, see **WARNINGS AND PRECAUTIONS - Nursing Women**.

OVERDOSAGE

Treatment of Overdosage or Accidental Ingestion

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

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. There are no antidotes and further treatment should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Combination hormonal contraceptives act by the suppression of gonadotropins. The primary mechanism of action is inhibition of ovulation, but other alterations include impaired sperm penetration and "spinnbarkeit" of the cervical mucus, and changes to the endometrium to reduce the likelihood of implantation. Receptor binding studies, as well as studies in animals and humans, have shown etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity. Desogestrel (DSG) in combination with ethinyl estradiol (EE) does not counteract the estrogen-induced increase in SHBG resulting in lower serum levels of free testosterone.

Pharmacodynamics

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Desogestrel, the progestogen component of APRI®, displays low androgenic activity in relation to its progestogenic effects and may increase the HDL/LDL ratio and apoprotein A-1/B ratio without affecting HDL_2. Like other oral contraceptives, these changes in lipid profile can be associated with an increase in triglycerides.

Pharmacokinetics

Desogestrel (DSG) is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, (3-K-DSG), its biologically active metabolite. After a single dose of desogestrel/ethinyl estradiol, maximum concentrations of 3-K-DSG of approximately 6 pmol/mL are reached at 1.6 hours. The area under the curve ($AUC_{0-\infty}$) is approximately 59 pmol/mL.hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of approximately 18 pmol/mL are reached at 1.4 hours. The minimum plasma levels of 3-K-DSG at steady state are approximately 4 pmol/mL. The AUC_{0-24} at steady state is approximately 161 pmol/mL▪hr. The relative bioavailability of 3-K-DSG is approximately 84%. The elimination half-life for 3-K-DSG is approximately 38 hours at steady state.

Major phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-, 5α-OH-desogestrel. These degradation products are in part further converted by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides. Approximately 48% of 3-K-DSG is recovered unchanged in urine within 24 hours.

Ethinyl estradiol (EE) is rapidly and almost completely absorbed. After a single dose of desogestrel/ethinyl estradiol, maximum concentrations of EE of approximately 0.3 pmol/mL are reached at 1.6 hours. The $AUC_{0-\infty}$ is about 4.9 pmol/mL.hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of approximately 0.5 pmol/mL are reached at about 1.4 hours. The minimum serum levels of ethinyl estradiol at steady state are about 0.08 pmol/mL. The AUC_{0-24}, at steady state is approximately 4.6 pmol/mL·hr. The relative bioavailability is approximately 83% and the elimination half-life about 26 hr at steady state.

Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both EE and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

Absorption

Desogestrel (DSG) is rapidly and almost completely absorbed and converted into etonogestrel, (ENG), its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, compared to solution, as measured by serum levels of etonogestrel,

is approximately 100%. Ethinyl estradiol is rapidly and almost completely absorbed. When the lowest and highest tablet strengths, 0.100 mg desogestrel/0.025 ethinyl estradiol and 0.150 mg desogestrel/0.025 mg ethinyl estradiol, were compared to solution, the relative bioavailability of ethinyl estradiol was 92% and 98% respectively. The effect of food on the bioavailability of APRI® tablets following oral administration has not been evaluated.

Distribution
Etonogestrel, the active metabolite of desogestrel, was found to be 98% protein bound, primarily to sex hormone-binding globulin (SHBG). Ethinyl estradiol is primarily bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone.

Metabolism
Desogestrel: Desogestrel is rapidly and completely metabolized by hydroxylation in the intestinal mucosa and on first pass through the liver to etonogestrel. *In vitro* data suggest an important role for the cytochrome P450 CYP2C9 in the bioactivation of desogestrel. Further metabolism of etonogestrel into 6ß-hydroxy, etonogestrel and 6ß-13ethyl-dihydroxylated as major metabolites is catalyzed by CYP3A4. Other metabolites (i.e., 3α-OH-desogestrel, 3ß-OHdesogrestrel, and 3α-OH-5-H-desogestrel) also have been identified and these metabolites may undergo glucuronide and sulfate conjugation.

Ethinyl estradiol: Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol, escaping gut wall conjugation, undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

Excretion
Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces. At steady state, on Day 21, the elimination half-lives of etonogestrel and ethinyl estradiol are 37.1±14.8 hours and 28.2±10.5 hours, respectively.

Special Populations and Conditions

Race
There is no information to determine the effect of race on the pharmacokinetics of APRI® (desogestrel/ethinyl estradiol tablets).

Hepatic Insufficiency
No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of APRI®. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see WARNINGS & PRECAUTIONS – Hepatic/Biliary/Pancreatic).

Renal Insufficiency
No formal studies were conducted to evaluate the effect of renal disease on the disposition of APRI®.

STORAGE AND STABILITY

Store between 15-30 ^{o}C.
Keep in a safe place out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS
APRI 21 and APRI 28 should be protected from light once opened using the protective covering provided. Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms and Packaging
- **APRI® 21:** Each sachet contains an Aclar blister dispenser with 21 round rose active tablets. Each rose colored tablet (debossed with "dp" on one side and "575" on the other side) contains 150 mcg desogestrel and 30 mcg ethinyl estradiol.
- **APRI® 28:** Each sachet contains an Aclar blister dispenser with 21 round rose active tablets and 7 round white inert tablets. Each rose colored tablet (debossed with "dp" on one side and "575" on the other side) contains 150 mcg desogestrel and 30 mcg ethinyl estradiol. Each white tablet (debossed with "dp" on one side and "570" on the other side) contains inert ingredients.

Composition
APRI 21 and APRI 28 tablets have 21 rose active tablets each containing 150 mcg desogestrel and 30 mcg ethinyl estradiol. Inactive ingredients include Lactose monohydrate; Pregelatinized starch; Vitamin E; Povidone; Colloidal silicon dioxide; Stearic acid; Opadry Maroon YS-1-16002 containing: hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol. FD&C red no. 40 aluminum lake, polysorbate 80, FD&C blue no. 2 aluminum lake; Opadry Clear YS-1-7472 containing: hydroypropyl methylcellulose and polyethylene glycol. APRI 28 also contains the following inactive ingredients: Anhydrous lactose; Pregelatinized starch; Microcrystalline cellulose; Magnesium Stearate.

PART II: SCIENTIFIC INFORMATION PHARMACEUTICAL INFORMATION

Drug Substance

I. Progestogen

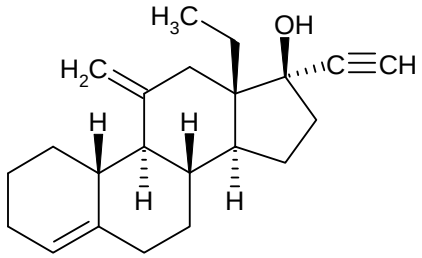
Common Name: Desogestrel

Chemical Name: 17 (α)- 13- Ethyl-11-methylene 18, 19-dinor-pregn-4-en-20-yn-17-ol

Molecular Formula: $C_{22}H_{30}O$

Molecular Weight: 310.48 g/mole

Structural Formula:



Physical Form: White, crystalline powder

Solubility: Solubility at 20°C: n-Hexane: 40 mg/mL
Ethanol (96%): > 200 mg/mL
Ethyl acetate: > 150 mg/mL
Water: practically insoluble

Melting Point: 110-112^{0}C

II. Estrogen

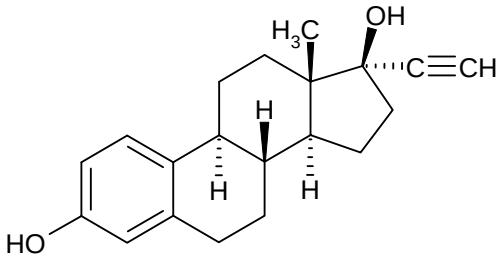
Common Name: Ethinyl Estradiol

Chemical Name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.4 g/mole

Structural Formula:



Physical Form: White, crystalline powder

Solubility: Soluble in ethanol, ether, acetone, chloroform, Practically insoluble in water.

Melting Point: 182-184°C

CLINICAL TRIALS

Comparative Bioavailability Studies

A single bioequivalence study of 25 women was conducted. It was a randomized, fasting, single dose, two-treatment crossover study with a washout period of 28 days between treatments. The objective of the study was to compare the rate and extent of absorption of APRI (test) to Marvelon® (Canadian Reference Product) administered as 2 x 0.15 / 0.03 mg tablets under fasting conditions.

Comparative Bioavailability of APRI® vs Marvelon®				
3-Keto-desogestrel Following the administration of Desogestrel/Ethinyl Estradiol (2 x 0.15/0.03 mg tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	APRI®	Marvelon®‡	% Ratio of Geometric Means$^{\epsilon}$	90% Confidence Interval$^{\epsilon}$
AUC_{0-72} (ng·hr/mL)	24.45 25.15 (23.20)	24.64 25.56 (28.14)	99.23	95.42 - 103.18
AUC_I (ng·hr/mL)	32.14 33.03 (23.57)	32.68 34.22 (32.10)	97.00	93.15 - 101.01
C_{max} (ng/mL)	3.23 3.41 (33.51)	2.71 2.93 (36.99)	118.70	105.98 - 132.95
T_{max}[§] (h)	1.50 (0.67 – 2.25)	1.52 (1.00 - 5.00)		
$T_{½}$[†](h)	40.73 (35.48)	39.72 (37.80)		

‡ Marvelon® (desogestrel/ethinyl estradiol) 0.15/0.03 mg tablets by Merck Canada Inc. were purchased in Canada.
$^{\epsilon}$ Based on the least-squares mean estimates.
§ Expressed as the median (range) only.
† Expressed as the mean (CV%) only.

Ethinyl Estradiol Following the administration of Desogestrel/Ethinyl Estradiol (2 x 0.15/0.03 mg tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	APRI®	Marvelon®‡	% Ratio of Geometric Means$^{\epsilon}$	90% Confidence Interval$^{\epsilon}$
AUC_T (pg·hr/mL)	1274.11 1331.65 (29.11)	1325.57 1384.81 (28.97)	96.24	92.29 - 100.35
AUC_I (pg·hr/mL)	1340.37 1396.61 (28.23)	1398.00 1455.40 (27.69)	96.02	91.99 - 100.21
C_{max} (pg/mL)	120.01 125.63 (28.49)	119.49 126.24 (31.55)	100.89	94.17 - 108.10
T_{max}[§] (h)	1.50 (1.00 – 2.50)	1.50 (1.00 - 3.00)		
$T_{½}$[†] (h)	16.66 (30.61)	15.95 (25.58)		

‡ Marvelon® (desogestrel/ethinyl estradiol) 0.15/0.03 mg tablets by Merck Canada Inc. were purchased in Canada.
$^{\epsilon}$ Based on the least-squares mean estimates.
§ Expressed as the median (range) only.
† Expressed as the mean (CV%) only.

Extensive clinical experience, in excess of 125,000 cycles in published reports alone, has documented the efficacy of desogestrel/ethinyl estradiol.

NUMBER OF STUDIES, NUMBER OF SUBJECTS EXPOSED, ESTIMATED MINIMUM EXPOSURE AND NUMBER OF PREGNANCIES BY STUDY SIZE

STUDY SIZE	NUMBER OF STUDIES	TOTAL ENROLLED	CALCULATED MINIMUM EXPOSURE (#CYCLES)[a]	TOTAL NUMBER OF PREGNANCIES
>500	6	53,773	106,399	5
201-500	8	2,514	11,380	2
101-200	4	437	689	0
51-100	9	704	2,174	1
26-50	27	970	1,762	0
1-25	80	1,058	2,804	0
Total	134	59,456	125,208	8

[a] For the purpose of estimation of extent of exposure, it is assumed that dropouts were evenly distributed over the interval of observation (if 60 subjects discontinued over 6 months, it is assumed that 10 discontinued each month). Several studies provided inadequate information on the number of subjects at subsequent visits. Therefore, the actual number of cycles is likely to be substantially larger.

In addition, several well controlled studies were designed to determine the efficacy and safety of desogestrel/ethinyl estradiol. One of these involved 1,195 patients who completed a total of 11,426 cycles.

(a) Pearl Index

The observed Pearl Index among desogestrel/ethinyl estradiol users compares favourably to what has been reported for other low dose oral contraceptives. Nine patients participating in this study became pregnant. User failure accounted for all of these in-treatment pregnancies. Consequently, the Pearl Index for method failure is 0.00.

N	CYCLES	PEARL INDEX	
		METHOD	TOTAL
1,195	11,656	0.00	0.92

(b) Life Table estimates

The annual cumulative life-table pregnancy rate is estimated as 1.0/100 women years.

CYCLE	PATIENTS	NO OF PREGNANCIES	CUMULATIVE PREG RATE/100 WOMEN
3	1037	4	0.39
6	904	4	0.82
9	734	0	0.82
12	525	1	1.00
15	307	0	1.00
18	139	0	1.00
23	9	0	1.00

(c) Cycle control

During the course of the study, 18 subjects (1.5%) discontinued due to menstrual problems. Absence of withdrawal bleeding (AWB) occurred in 1.7% of the cycles, while intermenstrual bleeding (IM) occurred in 8.0% of the total cycles. Both AWB and IM occurred more frequently during the first cycles of usage when compared to subsequent cycles. Spotting was more common than breakthrough bleeding (5.6% versus 2.5% of the cycles).

INCIDENCE BY CYCLE OF INTERMENSTRUAL BLEEDING AND ABSENCE OF WITHDRAWAL BLEEDING

	STARTERS			SWITCHERS		
Cycle	N	IM (%)	AWB (%)	N	IM (%)	AWB (%)
1	467	19.3	3.4	578	12.3	3.1
2	446	8.1	1.4	561	10.7	1.8
3	420	9.3	2.6	532	10.3	2.3
6	350	8.6	0.6	479	6.9	1.2
12	164	6.7	3.7	276	6.5	0.4

- intermenstrual bleeding (IM) was defined as any bleeding and/or spotting that started during the pill-taking interval that was not early or continued withdrawal bleed;
- absence of withdrawal bleeding (AWB) was defined as no bleeding and/or spotting episode that began during or continued into the pill-free interval;

INCIDENCE BY CYCLE OF BREAKTHROUGH BLEEDING (BTB) AND SPOTTING (BTS)

	STARTERS			SWITCHERS		
Cycle	N	BTB (%)	BTS (%)	N	BTB (%)	BTS (%)
1	467	1.5	17.8	578	1.4	11.1
2	446	2.2	5.8	561	3.4	7.5
3	420	4.0	5.5	532	3.2	7.5
6	350	3.4	5.4	479	2.5	4.6
12	164	2.4	4.3	276	2.2	4.7

- breakthrough bleeding (BTB) was defined as any bleeding episode that occurred during the pill-taking interval that was not early or continued withdrawal bleed;
- breakthrough spotting (BTS) was defined as any spotting episode that occurred during the pill-taking interval that was not early or continued withdrawal bleed;

The results indicate that cycle control with desogestrel/ethinyl estradiol is generally excellent, resulting in very few dropouts due to irregular bleeding or to absence of withdrawal bleeding, these results are very similar to those obtained with other oral contraceptives.

(d) Lipid Metabolism

A causal relationship between ischemic heart disease and unfavourable plasma lipid/lipoprotein profiles, specifically, a high LDL/HDL ratio, is now widely accepted on the basis of epidemiologic, biochemical and other evidence. It has also been demonstrated that androgens influence the lipid/lipoprotein ratio unfavourably, while estrogens have a beneficial effect, largely by increasing HDL_2 and, to a lesser extent, by reducing LDL levels. Major adverse or counteractive effects on the beneficial action of estrogen are therefore of fundamental importance in any long-term medication.

Desogestrel/ethinyl estradiol increased HDL-C levels, decreased LDL-C, but left HDL_2 and Apo B unchanged. Thus there was no significant effect on the HDL_2/LDL-C ratio. Like other oral contraceptives, desogestrel/ethinyl estradiol can be associated with an increase in triglyceride plasma levels.

NUMBER OF STUDIES DEMONSTRATING A PARTICULAR EFFECT ON LIPOPROTEIN METABOLISM AFTER 2 TO 4 MONTHS OF USE

		desogestrel/ethinyl estradiol (150 mcg/30 mcg)
Total Cholesterol	No Change	12
	Increase	0
Triglycerides	No Change	4
	Increase	5
LDL-C	No Change	5
	Increase	0
HDL-C	Decrease	0
	No Change	5
	Increase	7

DETAILED PHARMACOLOGY

Animal and <u>in vitro</u> pharmacology

Animal pharmacology and *<u>in vitro</u>* receptor binding studies indicate that 3-k-desogestrel, the biologically active metabolite, is a highly selective progestational agent (see table below) with no estrogenic effects, and only residual androgenicity.

COMPARISON OF RELATIVE BINDING AFFINITY OF DESOGESTREL, 3-k-DESOGESTREL AND PROGESTERONE FOR THE PROGESTERONE RECEPTOR IN UTERINE CYTOSOL.*

	RABBIT MYOMETRIUM	HUMAN MYOMETRIUM
Desogestrel	5	2
3-K-desogestrel	111	113
Progesterone	32	18

*Binding affinities were determined at 4NC using the reference standard 16α-ethyl-21-hydroxy-9-nor-pregn-4-ene-3,20-dione.

Desogestrel and its metabolites, other than 3-k-desogestrel and 3-keto-5α-H-desogestrel, display minimal binding affinity for the androgen receptor with respect to dihydrotestosterone, as studied in intact MCF-7 cells. The binding affinity of both 3-k-desogestrel and 3-keto-5α-H-desogestrel is approximately 1/10 of 5α-dihydrotestosterone; suggesting a low androgenic activity. The binding affinity for the androgen receptor in intact MCF-7 cells as displayed by 3-k-desogestrel was also significantly lower than that of other progestogens.

The "selectivity index" (progestogen/androgen receptor binding affinity ratio) for 3-k-desogestrel in intact MCF-7 cells is higher than any other progestogen.

Oral desogestrel displays weak androgenic activity, approximately 0.05 the activity of 17α-methyl-testosterone, in orchidectomized rats, using the Herschberger test.

Human pharmacology
After oral administration of desogestrel, typical anti-gonadotropic and progestational effects are observed; these include suppression of the hypothalamic-pituitary-gonadal axis; secretory transformation of an estrogen primed endometrium; impaired sperm penetration and "spinnbarkeit" of the cervical mucus. Endometrial morphology in chronic users of desogestrel/ethinyl estradiol show a homogeneous picture with findings typical of the luteal phase of the menstrual cycle.

TOXICOLOGY

Acute Toxicity Studies
Acute single dose studies were conducted in both rats and mice, with desogestrel + ethinyl estradiol and desogestrel alone, to determine the upper limits of tolerance and to assess specific signs of toxicity. Both compounds were dosed orally by gavage or intraperitoneal as aqueous suspensions. The oral dosage level of 2000 mg/kg was about 6×10^5 times the projected human clinical dose. The intraperitoneal dosage was 500 mg/kg. Groups of 10 males and 10 females were tested with desogestrel + ethinyl estradiol and groups of 6 males and 6 females with desogestrel alone. The animals were observed for 7 days and then necropsied.

None of the test animals died during the oral or intraperitoneal studies. The oral dosed mice and rats had temporary signs of reduced activity, some motor incoordination, diminished food consumption, and other nonspecific signs related to the large dose of the test material. Likewise, mice and rats dosed intraperitoneal showed similar signs. Some evidence of serositis (localized peritoneal irritation) was associated with the test substances.

These data are consistent with published information on other contraceptive steroids which indicate that steroids in general have a low level of toxicity in single dose acute animal studies.

Multidose Toxicity Studies
The objective of the multidose toxicity studies was to determine whether the chronic oral administration of either desogestrel + ethinyl estradiol or desogestrel alone to mice, rats, dogs, and monkeys would induce either reversible or irreversible systemic adverse effects or cause the development of benign or malignant neoplasms. Desogestrel + ethinyl estradiol, in a ratio of 2.5:1, was employed in most multidose toxicity and multidose tumorigenicity toxicity studies and in a ratio of 5:1 in 52-, 104-week and 3-year studies in dogs and monkeys. The test compounds were administered orally by gavage to mice and rats, orally by tablet or capsule to dogs, and orally by soft drink or by intubation to monkeys.

The protocol for each of these studies was typical of that used for multidose toxicity tests in general. The doses were multiples of the human dose and generally calculated to be 2, 20, and 200 times the expected human usage levels in most multidose and tumorigenicity studies in mouse, rat and dog. In shorter studies, the duration of treatment was 26 or 52 weeks with a 4 to 13 week recovery period incorporated into the study design. In the 52-, 104-week and 3-year dog and monkey studies dose levels were 1, 10, 25 and 2, 10, and 50 times the human dose respectively.

The following table lists the study duration, species tested, and the test compounds:

Multidose Toxicity Studies				
Duration	Species	Drugs	Dose(mg/kg)	n
52 weeks	rat, dog	DSG + EE*	0.005 + 0.002[a] 0.05 + 0.02 0.5 + 0.2	70,14
	dog	DSG + EE	0.003 + 0.0006[b] 0.03 + 0.006 0.075 + 0.015	20
	monkey	DSG + EE	0.006+0.0012[c] 0.03 +0.006 0.15 +0.03	20
80 weeks	mouse	DSG + EE	see [a]	112
104 weeks	rat dog	DSG + EE	see [a]	110
	monkey	DSG + EE	see [b]	20
		DSG + EE	see [c]	20
3 years	dog	DSG + EE	see [b]	20
	monkey	DSG + EE	see [c]	20
26 weeks	rat, dog	DSG	0.00625 0.0625 0.625	64,14
52 weeks	rat, dog	DSG	0.005[d] 0.05 0.5	60,12
81 weeks	mouse	DSG	see [d]	112
104 weeks	rat	DSG	see [d]	110

*DSG = desogestrel EE = ethinyl estradiol

The 52-week study with desogestrel + ethinyl estradiol in rats revealed no direct treatment-associated effect on mortality. Clinical signs of treatment included alopecia and reduction of testicle size, primarily in high dose animals, which were reversible on treatment cessation. Depressed weight gain and/or decreased food consumption was present in both sexes of the intermediate and high dose animals. There was an alteration in APTT, Hb, and PCV were noted along with lowered neutrophil and lymphocyte counts. These changes are known to occur in

these type of studies and were found to be reversible upon treatment cessation. No unusual changes were found in blood chemistry or urinalysis. Dose-related lower protein content of the urine in males may be attributed to the atrophic change in secondary sex organs.

Organ weight changes were consistent with those noted with other combination oral contraceptives. The liver weight was increased at 26 and 52 weeks in primarily ID and high dose animals; testes, epididymides, prostate, seminal vesicles, ovaries, uterus, adrenals, and the pituitary gland were also affected by treatment.

Microscopic tissue changes included the following: hepatocytic vacuolation and occasional foci of hepatocellular hyperplasia, especially in high dose animals; a dose-related increase in yellowish pigment in the kidney cortical tubule epithelium, and increased mineralized concretions in high dose males; atrophy of the testes, epididymides, prostate, and seminal vesicles; reduction or absence of corpora lutea in the ovaries; hyalinization or endometrial hyperplasia of the uterus; increased keratinization of the vagina in high dose females; hypertrophy and hyperplasia of the adrenal cortex with sinusoidal telangiectasis; and hypertrophy/hyperplasia of the anterior lobe of the pituitary, especially at 52 weeks in high dose animals.

The 8-week withdrawal period used in this study resulted in a partial reversal of the prior changes. All would have probably reverted to normal with a longer recovery period. There was an increased incidence of benign mammary neoplasms in all drug-treated groups.

The 52-week dog study was conducted with oral dosed desogestrel + ethinyl estradiol tablets in a ratio of 2.5:1. Three high dose mortalities occurred during the study. Two females died and the other was killed in extremis. The cause of death or morbidity was peritonitis, secondary to perforating pyometra. Clinical signs included typical skin thickening and folding with alopecia, interruption of the estrous cycle with swelling of external genitalia in females, vaginal discharge in high dose females, pendulous penile sheath in males with reduction in testicle size, enlarged and/or secretory mammary tissue in females, and 2 transient (1, intermediate dose) and 1 transient and 1 persistent nodule (1, high dose) of the mammary gland. The persistent nodule was an area of hyperplasia.

Changes in certain hematological, coagulation, blood chemistry and urinalysis parameters were neither unusual nor unexpected for this type of compound. Changes either in weight or histomorphological characteristics were noted in the primary and secondary sex organs and liver, primarily in high dose animals. All were associated with the hormonal attributes of the drug.

The multidose toxicity study in the monkey was performed at a 5:1 ratio of desogestrel to ethinyl estradiol with dosing for 21 days followed by a 7-day drug-free period. The 12-month data revealed no unexpected clinical, clinicopathological, or histomorphological findings. Typical hormonally dose-related changes occurred, such as decreased corpora lutea, secretory mammary glands, increased endocervical mucus, decreased thickness of the endometrium with secretory changes, a dose-related decrease in the thickness of the vaginal epithelium and increased pituitary weight.

The multidose studies in rats and dogs with desogestrel alone resulted in fewer alterations in the primary and secondary sex organs and other peripheral hormonally sensitive tissues.

In rats, the absence of ethinyl estradiol in the test compound resulted in expected progestational changes at 26 and 52 weeks, such as secretory changes in the uterine endometrium, mucification of the vaginal epithelium, mild glandular hyperplasia of the mammary glands, and reduced pituitary weights. In the 52-week portion of the study, a small number of benign or malignant neoplasms were observed, but none of these were causally related to the test compound.

The toxicity of multidoses of desogestrel alone in dogs resulted in no unusual or unexpected changes at 26 weeks. The liver weight in high dose animals was increased but this was due primarily to the progestogenic effect of increased glycogen storage. The uterus was increased in both size and weight due to hormonal stimulation of the endometrium and the ovaries had a lack of mature follicles and an absence of corpora lutea. The prostate weight was slightly reduced in high dose males. Lobular development of the mammary glands was increased in intermediate and high dose females.

The 52-week segment of the dog study with desogestrel alone resulted in changes similar to those seen at 26 weeks; however, occasional small mammary nodules (5 mm or less) were present in 1 control (C), 1 low dose (LD), 1 ID, and 4 high dose animals. They disappeared in the 1 C and 2 high dose animals. The remaining nodules were found to be nonneoplastic and proved to be either smaller superficial lymph nodes or dilated ducts. The uterine stimulation was increased at 52 weeks but did not result in the death of any animal.

Four multidose toxicity studies of up to 2 years in duration were conducted in rats, dogs, and monkeys. Desogestrel + ethinyl estradiol was studied in rats, monkeys, and dogs, and desogestrel alone was studied in rats.

In rats, there was no evidence of a neoplastic response when desogestrel was administered alone, however, increased evidence of benign mammary neoplasms were evident in all desogestrel + ethinyl estradiol treated groups. Other clinical, clinicopathological, and histopathological changes were attributable to the hormonal influences of either desogestrel or its combination with ethinyl estradiol.

The 2-year dog study utilized a 5:1 desogestrel + ethinyl estradiol ratio. The test compound was dosed at 1, 10 and 25 times the human dosage levels for 21 days with a 7-day drug-free period. There was evidence of the following: suppression of the estrous cycle in intermediate and high dose animals, an increased incidence of mammary gland development and secretory activity similar to those observed in the normal metestrous phase of the cycle; decreased AP in high dose dogs, and a single focus of ductal epithelial hyperplasia in 1 low dose dog. No tumorigenic effect was present.

The 2-year study of desogestrel + ethinyl estradiol in monkeys caused the expected pattern of hormonally-mediated changes. Menstrual and ovarian activity were reduced in high dose

animals. Secretory activity of the mammary glands was increased in a dose-related manner in intermediate and high dose animals. Other hormonally-associated changes included: an increased fibrinogen and APTT; decreased PPT; reduced AP; increased triglycerides and cholesterol levels; and lowered albumen in intermediate and high dose animals; endometrium which was either stimulated (ID and HD) or lacked activity (some high dose animals); and increased acidophils and decreased basophils in the pituitary in intermediate and high dose animals. All of these findings are consistent with contraceptive steroid effects in the monkey.

Multidose tumorigenicity studies were conducted in the mouse (80-81 months) and rat (2 years) with either desogestrel + ethinyl estradiol or desogestrel alone, respectively. Desogestrel + ethinyl estradiol in mice resulted in a higher mortality rate; this was primarily due to the increased incidence of pituitary tumors in treated mice, especially high dose animals. Other nonneoplastic alterations occurred, but were within expected limits for a compound of this type. Desogestrel alone in mice did not remarkedly affect the mortality rate and had no influence on tumorigenicity.

Desogestrel + ethinyl estradiol in the rat, resulted in slightly increased mortality at the high dose level and contributed to a dose-dependent increase in the number of pituitary and mammary neoplasms; this increase was largely attributable to the ethinyl estradiol component.

Desogestrel alone in the rat had no influence on mortality and possibly was responsible for a slight lowering effect. Incidences of mammary and pituitary tumors were slightly lessened at the high dose level. This is in contrast to the 104-week rat study with desogestrel + ethinyl estradiol, where the differences noted were considered to have been attributable to the ethinyl estradiol component.

Three year studies were conducted in both Beagle dogs and Rhesus monkeys with desogestrel + ethinyl estradiol with a 1- and 2-year interim sacrifice in monkey and a 2-year interim sacrifice in dogs. No tumorigenic response was noted. Mammary glands of dogs had lobulo-alveolar development with limited secretory change, an expected hormonal effect. Other tissue changes as described under the 2-year interim report, limited to the primary and secondary sex organs, were associated with the hormonal activities of the combination OC.

The monkey study conducted for 3 years, with a 1- and 2- year interim sacrifice, revealed no evidence of a tumorigenic effect. The changes observed, as described at the 2-year interim studies, were typical of the hormonal activities of the combination OC and included effects on the menstrual cycle, cervical mucus and endometrial morphology.

Reproductive Toxicity Studies

Nonclinical reproductive toxicity studies included 11 studies conducted in rats and 2 studies conducted in rabbits. Desogestrel, both alone and in combination with ethinyl estradiol, was tested. These studies were conducted to assess what effect, if any, the test substance might have on the reproductive process, including; fertility and reproductive performance, teratogenicity and embryotoxicity, and perinatal and postnatal effects in the offspring.

Four segment I reproductive toxicity studies were conducted in rats; 1 study with desogestrel + ethinyl estradiol and 3 studies with desogestrel alone. The desogestrel + ethinyl estradiol study, conducted using doses of 0.5 mg desogestrel + 0.2 mg ethinyl estradiol/kg/day, demonstrated that the test compound had no adverse effect on mating and pregnancy performance in F_0 females or on the number, anatomical features, development and fertility of the offspring.

Desogestrel alone was studied in both Sprague Dawley and CFY rats. An additional study in Sprague Dawley rats was conducted after microphthalmia was increased in CFY offspring of the desogestrel -treated dams. No increase in microphthalmia was seen in the second Sprague Dawley study. The defect was thus thought to be strain-related. In all 3 studies the contraceptive effect of desogestrel was reversible. Treatment at contraceptive and subcontraceptive dose levels did not cause any serious after effects on the dams or their offspring.

A fertility and embryotoxicity study with desogestrel + ethinyl estradiol at levels causing complete infertility, slight infertility, and no infertility, were conducted in rats. Uninterrupted daily administration of desogestrel + ethinyl estradiol, at subcontraceptive doses before and during pregnancy, reduced the number of offspring but had no effect on the quality of the F_1 generation.

Segment II embryotoxicity studies following the classical design with dosage exclusively during pregnancy and organogenesis were performed in both the rat and rabbit. A total of 5 embryotoxicity studies were conducted; 3 studies with desogestrel alone and 2 studies with desogestrel + ethinyl estradiol.

Desogestrel + ethinyl estradiol tested at high dose levels in rats and rabbits caused maternal toxicity and embryolethality, but at lower doses had no untoward reaction in the dams and no detectable effect on the course of pregnancy, embryonic mortality, or fetal morphology.

Desogestrel alone was tested in both Sprague Dawley and CFY rats and in rabbits. High dosages of desogestrel caused maternal toxicity (2-8 mg/kg) in rats, while doses of 2 to 4 mg/kg caused abortion in rabbits. Lower dosages in rats and rabbits caused no discernible effect on the course of pregnancy, embryonic mortality, or on fetal morphology.

The effects of desogestrel alone, when dosed during late pregnancy, was assessed in rats. Dose levels up to 4 mg/kg/day from days 14-20 of pregnancy caused neither masculinization of female fetuses nor feminization of male fetuses.

Segment III studies, to evaluate the possible effects on peri- and postnatal development due to transfer of drug through the milk, were conducted with desogestrel , either alone or in combination with ethinyl estradiol. Desogestrel + ethinyl estradiol caused reduced food consumption in intermediate and high dose dams. Retarded pup growth persisted until weaning in the high dose group, but there was no effect on the pre- or post-weaning physical development. Fertility of the F_1 offspring was not affected. Desogestrel alone had no effect on the treated dams, weight gain in the pups, or physical development of the pups. Fertility of the

F_1 treated animals was comparable to that of the F_1 control females.

Mutagenicity Studies

The Ames test and the rat Micronucleus test were conducted on desogestrel, either alone or in combination with ethinyl estradiol. Both assays demonstrated that neither desogestrel alone nor in combination with ethinyl estradiol exert any mutagenic effect.

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PART III: CONSUMER INFORMATION

Pr APRI® 21 and Pr APRI® 28
(150 mcg desogestrel and 30 mcg ethinyl estradiol tablets, USP)

This leaflet is part III of a three-part "Product Monograph" published when APRI® 21 and APRI® 28 was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APRI® 21 and APRI® 28. 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.

What it does:

APRI® is a combination hormonal contraceptive because it contains two female sex hormones (desogestrel and ethinyl estradiol). It is in the form of a tablet, therefore it is known as a birth control pill or oral contraceptive. It has 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 over 35.

Combination hormonal contraceptives work in two ways:

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

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:

Combination hormonal contraceptives are 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 APRI® if you have or have had any of the following conditions:

- blood clot in the legs, lungs, eyes or elsewhere, or thrombophlebitis (inflammation of the veins)
- stroke, heart attack or coronary artery disease (e.g. Angina pectoris) or a condition that may be a first sign of stroke (such as transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- severe high blood pressure
- diabetes with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- very high blood cholesterol or triglyceride levels
- you smoke
- migraine headaches
- you are scheduled for major surgery

- prolonged bed rest
- jaundice (yellowing of the eyes or skin), severe liver disease and your liver is not yet working normally
- Hepatitis C and are taking the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see "**INTERACTIONS WITH THIS MEDICATION**").
- liver tumor(s)
- known 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 substance in your blood
- allergy (hypersensitivity) to ethinyl estradiol, desogestrel, or to any of the other ingredients in APRI® (see **What the medicinal ingredients are** and **What the non-medicinal ingredients are**).

What the medicinal ingredients are:
desogestrel and ethinyl estradiol.

What the nonmedicinal ingredients are:
Inactive ingredients include Lactose monohydrate; Pregelatinized starch; Vitamin E; Povidone; Colloidal silicon dioxide; Stearic acid; Opadry Maroon YS-1-16002 containing: hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol. FD&C red no. 40 aluminum lake, polysorbate 80, FD&C blue no. 2 aluminum lake; Opadry Clear YS-1-7472 containing: hydroypropyl methylcellulose and polyethylene glycol.

APRI 28 also contains the following inactive ingredients: Anhydrous lactose; Pregelatinized starch; Microcrystalline cellulose; Magnesium Stearate.

What dosage forms it comes in:
APRI® 21: Each sachet contains an Aclar blister dispenser with 21 round rose active tablets. Each rose colored tablet (debossed with "dp" on one side and "575" on the other side) contains 150 mcg desogestrel and 30 mcg ethinyl estradiol.

APRI® 28: Each sachet contains an Aclar blister dispenser with 21 round rose active tablets and 7 round white inert tablets. Each rose colored tablet (debossed with "dp" on one side and "575" on the other side) contains 150 mcg desogestrel and 30 mcg ethinyl estradiol. Each white tablet (debossed with "dp" on one side and "570" on the other side) contains inert ingredients.

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 APRI® should not be used by women who are over 35 years of age and smoke.

Combination hormonal contraceptives **DO NOT PROTECT** against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

BEFORE you use APRI® talk to your doctor or pharmacist if you:

- smoke
- are overweight
- have a history of breast disease (e.g., 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 tumours of the uterus)
- may be pregnant or are breast feeding
- 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 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
- have recently given birth

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

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

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 or if your ability to move around is limited for a long period of time. You should consult your doctor about stopping the use of APRI® four weeks before surgery and not using APRI® for a time period after surgery or during bed rest.

APRI® 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 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 APRI® 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 APRI® outweigh the risks, you should be aware of the following:

THE RISKS OF USING COMBINATION HORMONAL CONTRACEPTIVES

1. Circulatory disorders (including blood clot in legs, lungs, heart, eyes or brain)
Blood clots are the most common serious side effects of birth control pills. The risk of developing clots is high during the first year a woman uses a hormonal contraceptive. The risk is also higher if you restart a hormonal contraceptive (the same product or a different product) after a break of 4 weeks or more. Clots may occur in many areas 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, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- **P**ain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- Crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- Sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye.

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.

Women who use hormonal contraceptives have a higher risk of developing blood clots, but not as high as the risk during pregnancy. 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.**

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 birth control pills 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 is recommended for all women.

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS OF 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.

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. In women who use combination oral contraceptives (COCs) for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be

caused by the Pill itself but may be related to sexual behavior and other factors.

4. Liver tumors
The short and long-term use of birth control pills also has been linked with the growth of liver tumors or liver injury (e.g., hepatitis, hepatic function abnormal). Such tumors are **extremely** rare.

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

5. Gallbladder disease
Users of hormonal contraceptives 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. They will not prevent the pregnancy from continuing. 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
You will be at increased risk for blood clots. Your doctor will advise you of the appropriate time to start the use of APRI® after childbirth, miscarriage or therapeutic abortion.

8. Pregnancy after stopping APRI®
You will have a menstrual period when you stop using APRI®. 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 breast feeding
If you are breast-feeding, consult your doctor before starting the birth control pill. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception. The use of oral contraceptives is generally not recommended until the nursing mother has completely weaned her child.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with combination hormonal contraceptives **and prevent them from working properly making them less effective in preventing pregnancy or causing unexpected bleeding (spotting or breakthrough bleeding).** Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines or herbal products, even those without a prescription. Also tell any other doctor or dentist (or the dispensing pharmacist) who prescribes another medicine that you use APRI®.

Drugs that may interact with APRI® include:

- drugs used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates (e.g. phenobarbital, carbamazepine, oxcarbazepine, topiramate, felbamate)
- drugs used for the treatment of tuberculosis (e.g., rifampicin, rifabutin)
- drugs used for the treatment of HIV infections or AIDS (e.g., ritonavir, nelfinavir, nevirapine, efavirenz) and Hepatitis C Virus (e.g. boceprevir, telaprevir)
- antibiotics (e.g., nitrofurantoin) for infectious diseases
- antifungals (e.g. griseofulvin)
- cholesterol lowering agents (e.g. clofibrate)
- anti-coagulants (blood thinners)
- the herbal remedy St. John's wort
- antihypertensive drugs (for high blood pressure)
- drugs used for high blood pressure in the blood vessels of the lungs (bosentan)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (e.g. barbiturates, glutethimide, meprobamate)
- antidepressants (e.g. clomipramine)
- other drugs such as phenylbutazone, antihistamines, pain medications, anti-migraine preprations,
- some nutritional supplements (e.g. Vitamin E and Vitamin B12)
- cyclosporine
- Antacids (use 2 hours before or after taking APRI®)

If you are taking medicines or herbal products that might make APRI® less effective, a barrier contraceptive method should also be used. Since the effect of another medicine on APRI® may last up to 28 days after stopping the medicine, it is necessary to use the additional barrier contraceptive method for that long.

APRI® may also interfere with the working of other drugs, causing either an increase in effect (e.g., cyclosporin) or a decrease in effect (e.g., lamotrigine).

Do not use APRI® if you have Hepatitis C and are being treated with ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Using these drugs at the same time as APRI® may cause problems with your liver, such as an increase in the ALT liver enzyme. You can usually start APRI® about 2 weeks after finishing treatment with this

combination of drugs used for Hepatitis C, but always consult with your doctor or pharmacist (See **ABOUT THIS MEDICATION - When it should not be used**")

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

PROPER USE OF THIS MEDICATION

Usual dose:

INFORMATION TO PATIENT ON HOW TO TAKE APRI®:

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** to see if it has 21 or 28 pills:
- 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then take no pills for one week. or
- 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK the pill pack for instructions on 1) where to start and 2) direction to take pills.

3. You may wish to use a second method of birth control (e.g. latex 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.

4. When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.

5. **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.

6. **MISSING PILLS ALSO 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.

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
- when you start a pack late
- when you miss pills at the beginning or at the very end of the pack.

8. **ALWAYS BE SURE YOU HAVE READY:**
- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS.**

9. **IF YOU HAVE VOMITING OR DIARRHEA, OR IF YOU TAKE SOME MEDICINES,** such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

11. **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. Your pills may be either a 21-day or a 28-day type.

A. APRI® 21-DAY COMBINATION
With this type of birth control pill, you are 21 days on pills with seven days off pills. You must not be off the pills for more than seven days in a row.

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 21 days; **THEN TAKE NO PILLS FOR SEVEN DAYS**. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

B. APRI® 28-DAY COMBINATION
With this type of birth control pill, you take 21 pills which contain hormones and seven pills which contain no hormones.

No preceding hormonal contraceptive use (in the past month)
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 ON THE PILLS**. Your period should occur during the last seven days of using that pill pack.

Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch)
The woman should start with APRI® preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free interval or following thelast placebo tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using **APRI®** preferably on the day of removal, but at the latest when the next application would have been due.

Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)
The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

Following first-trimester abortion
The woman may start immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion
For breastfeeding women see WARNINGS AND PRECAUTIONS - Nursing Women.

Women should be advised to start at day 21 to 28 after delivery or second trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

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 like 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**
- **21 PILLS**

WAIT SEVEN DAYS to start the next pack. You will have your period during that week.

- **28 PILLS**

Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

Overdose:
Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain and fatigue/drowsiness. Withdrawal bleeding may occur in females.

If you think you have taken too much APRI®, contact your healthcare professional hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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

SUNDAY START	DAY 1 START
MISS 1 PILL	**MISS 1 PILL**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 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 2 pills in one day.

IMPORTANT: PLEASE READ

SUNDAY START	DAY 1 START
MISS 2 PILLS IN A ROW	**MISS 2 PILLS IN A ROW**
First 2 Weeks: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.	**First 2 Weeks:** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.
Third Week: 1. Keep taking 1 pill 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 method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**Third Week**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC**.
MISS 3 OR MORE PILLS IN A ROW	**MISS 3 OR MORE PILLS IN A ROW**
Anytime in the Cycle: 1. Keep taking 1 pill 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 method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**Anytime in the Cycle**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**

NOTE: 28-DAY PACK: If you forget any of the seven "reminder" pills (without hormones) 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 back-up method of birth control (such as latex 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. Talk about ways to make pill-taking easier or about using another method of birth control.

Non-contraceptive benefits of Combined H**ormonal Contraceptives**

Several health advantages have been linked to the use of hormonal contraceptives.

- Reduction in the incidence of cancer of the uterus and ovaries
- Reduction in the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and

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 women taking Combination hormonal contraceptives in general, including APRI®:
- headache
- dysmenorrhea (painful menstrual cramps)
- abdominal (stomach) pain
- nausea
- upper respiratory tract infections (bronchitis, runny or stuffy nose, sore throat, etc.)
- back pain
- breast tenderness
- pharyngitis (sore throat)
- diarrhea
- vomiting
- asthenia (loss of strength, weakness, fatigue)
- malaise (feeling of physical discomfort or uneasiness)
- cough
- influenza (flu-like symptoms, fever)
- depression
- migraine, severe headaches
- dizziness
- dyspepsia (indigestion)
- vaginal irritation or infections
- cystitis (urinary tract infections or inflammation)
- amenorrhea (lack of a period or breakthrough bleeding, bleeding between menstrual periods)
- weight gain
- difficulty wearing contact lenses
- acne
- insomnia, nervousness
- allergy

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
sharp pain in the chest, coughing blood, or sudden shortness of breath/blood clot in the lung			√
Pain in the calf/blood clot in the leg			√
Crushing chest pain or heaviness/heart attack			√
Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in the arm or leg/stroke			√
Sudden partial or complete loss of vision or double vision/blood clot in the eye			√
abnormal liver test and/or nausea, vomiting, severe pain or lump in the abdomen/liver tumour			√
persistent sad mood			√
Yellowing of the skin/jaundice			√
Unusual swelling of the extremities		√	
Breast lumps/breast cancer		√	
unexpected (abnormal) vaginal bleeding		√	

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

HOW TO STORE IT

Store between 15-30°C. Keep in a safe place out of the reach and sight of children and pets.

IMPORTANT: PLEASE READ

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

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

If you want more information about APRI®:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited,
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