PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrINDAYO®

Levonorgestrel and Ethinyl Estradiol Tablets

Tablets, 0.15 mg and 0.03 mg, Oral

USP

Oral Contraceptive

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indayo® (levonorgestrel and ethinyl estradiol, USP) tablets are indicated for the prevention of pregnancy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available in women under the age of 18 years; therefore, Health Canada has not authorized an indication for pediatric use.

Use of this product before menarche is not indicated.

1.2 Geriatrics

Geriatrics: Indayo is not indicated for use in post-menopausal women.

2 CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- History of or actual thrombophlebitis or thromboembolic disorders.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary artery disease.
- Valvular heart disease with complications.
- Active liver disease or history of or actual benign or malignant liver tumours.
- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- 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.
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - diabetes mellitus with vascular symptoms
  - severe hypertension (persistent values of ≥160/100mm Hg)
  - severe dyslipoproteinemia

- 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, hyperhomocysteinaemia (e.g., due to MTHFR C677 T, A1298 mutations), prothrombin mutation G20210A and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
- major surgery associated with an increased risk of post-operative thromboembolism
- prolonged immobilization
- heavy smoking (>15 cigarettes per day) and over age 35

- Current or history of migraine with focal neurological symptoms.
- History of/or actual pancreatitis if associated with severe hypertriglyceridemia.
- Use of Hepatitis C drug combinations containing, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir due to the potential for ALT elevations.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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. For this reason, Combination Oral Contraceptives, including Indayo are contraindicated in women over 35 years of age and who smoke (see **2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Cardiovascular** sections).

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

Use of Indayo provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of hormonal exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Levonorgestrel and Ethinyl Estradiol Tablets have not suggested, nor can exclude, this additional risk.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B and syphilis.

The patient should be advised to use a non-hormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of ovulation and

conception prior to initiation of medication should be considered.

The tablets should not be removed from the protective blister packaging to avoid damage to the product. The blister pack should be kept in the foil pouch until dispensed to the patient.

4.2 Recommended Dose and Dosage Adjustment

The dosage of Indayo is one pink (active) tablet taken daily for 84 consecutive days followed by 7 days of white (inert) tablets. To achieve maximum contraceptive effectiveness, Indayo must be taken exactly as directed and at intervals not exceeding 24 hours. Ideally, the tablets should be taken at the same time of the day on each day of active treatment.

During the first cycle of medication, the patient is instructed to begin taking Indayo on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (pink) is taken that day. One pink tablet should be taken daily for 84 consecutive days, followed by 7 days on which a white (inert) tablet is taken. Withdrawal bleeding should occur during the 7 days following discontinuation of pink active tablets.

During the first cycle, contraceptive reliance should not be placed on Indayo until a pink (active) tablet has been taken daily for 7 consecutive days and a non-hormonal back-up method of birth control (such as condoms or spermicide) should be used during those 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins her next and all subsequent 91-day course of tablets without interruption on the same day of the week (Sunday) on which she began her first course, following the same schedule: 84 days on which pink tablets are taken followed by 7 days on which white tablets are taken.

If in any cycle the patient starts the tablets later than the proper day, she should protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken a pink tablet daily for 7 consecutive days.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

If spotting or breakthrough bleeding occurs:

Breakthrough bleeding or spotting may occur in women taking combination oral contraceptives (COC). The patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her healthcare provider.

If withdrawal bleeding does not occur:

Correct use of contraceptives can result in lower failure rates. If withdrawal bleeding does not occur while taking white (inactive) tablets, the possibility of pregnancy must be considered. Appropriate diagnostic measures to rule out pregnancy should be taken at the time of any missed menstrual period. Indayo should be discontinued if pregnancy is confirmed.

Use after pregnancy or abortion:

In the non-lactating mother, Indayo may be initiated no earlier than Day 28 of postpartum for contraception due to the increased risk for thromboembolism. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see also 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Indayo may be initiated immediately after a first-trimester abortion; if the patient starts Indayo immediately, additional contraceptive measures are not needed.

4.5 Missed Dose

Detailed patient instructions regarding missed pills are presented in the Missed Dose section of Part III in the product monograph. If a patient misses one pink tablet, she should take it as soon as possible, meaning she can take two tablets in one day. If a patient misses two pink tablets, she should take 2 tablets on the day she remembers and 2 tablets on the following day. Should three or more tablets be missed, the regular dosing schedule should be resumed, that is one pink tablet per day. Any time the patient misses two or more pink tablets, she should also use another method of non-hormonal back-up contraception until she has taken a pink tablet daily for seven consecutive days. If the patient misses one or more white tablets, she is still protected against pregnancy provided she begins taking pink tablets again on the appropriate day. The possibility of ovulation increases with each successive day that scheduled pink tablets are missed. The risk of pregnancy increases with each active (pink) tablet missed.

5 OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; and withdrawal bleeding may occur in females. There is no antidote and further treatment should be symptomatic.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol	Each pink active tablet contains the following inactive ingredients: lactose monohydrate, D&C Red No. 27, FD&C Blue No. 2, FD&C Yellow No. 5, magnesium stearate, polacrilin potassium and red iron oxide. Each white inert tablet contains the

		following inactive ingredients: lactose monohydrate, magnesium stearate and polacrilin potassium.

Description

Indayo (levonorgestrel and ethinyl estradiol, USP) tablets are available in Extended-Cycle Tablet Blister Packs. Extended cycle dispenser pack contains two blister packs of 28 tablets and one blister pack of 35 tablets. Two blister packs of 28 round, pink, uncoated tablets each containing 0.15 mg of Levonorgestrel and 0.03 mg of Ethinyl Estradiol and One blister pack of 35 tablets with 28 round, pink, uncoated tablets each containing 0.15 mg of Levonorgestrel and 0.03 mg of Ethinyl Estradiol and 7 round, white, uncoated tablets containing inert ingredients. Three such blisters to be packed in a printed blister card. One such blister card to be packed in Trilaminated pouch along with one patient information leaflet. Three such Trilaminated pouches to be packed in a carton. The active pink tablets are round, uncoated, biconvex tablets with a debossed **409** on one side and plain on the other side. The inert tablets are white, round, biconvex tablets debossed with **473** on one side and plain on the other side.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Discontinue Medication at the Earliest Manifestation of:

A. Thromboembolic and cardiovascular disorders such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

B. Conditions that predispose to venous stasis and 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 **7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations**, below.

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

Indayo Oral Contraceptive

Indayo is a 91-day cyclic dosing regimen (84 days with active oral tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with placebo tablets).

Pregnancy should be ruled out in cases of unanticipated bleeding/spotting, missed withdrawal bleeding/amenorrhea or signs and symptoms of pregnancy.

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

The information contained in this section is principally from studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestogen administered orally 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 healthcare professionals 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 studies suggest that oral contraceptive use has been associated with an increase in risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which the findings may be due to differences in sexual behaviours and other factors.

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.

Also see **16 NON-CLINICAL TOXICOLOGY**.

Cardiovascular

See also 2 CONTRAINDICATIONS, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS – General, Haematologic, Ophthalmologic

Use of Indayo provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of hormonal exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Levonorgestrel and Ethinyl Estradiol Tablets have not suggested, nor can exclude, this additional risk. Two subjects had pulmonary embolism and one subject had myocardial infarction while on Levonorgestrel and Ethinyl Estradiol Tablets in clinical studies. Coagulation profile has not been studied with Levonorgestrel and Ethinyl Estradiol Tablets.

In the post-market period, there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism reported with the use of Levonorgestrel and Ethinyl Estradiol Tablets.

Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism and discuss the risk of thromboembolism with all patients before prescribing Indayo.

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 by 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.

Thromboembolism

See **7 WARNINGS AND PRECAUTIONS, Haematologic** section.

Hypertension

Patients with essential hypertension whose blood pressure is well-controlled may be given oral 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 2 CONTRAINDICATIONS). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Genitourinary

Vaginal Bleeding and Bleeding Irregularities

In the pivotal, controlled clinical study 7.7% of subjects on Levonorgestrel and Ethinyl Estradiol Tablets discontinued medication prematurely due to unacceptable bleeding vs. 1.8% of subjects on the 28-day cycle regimen.

The following table shows the percentage of subjects with inter-menstrual bleeding and /or spotting.

Table 2 - Percentage of Subjects with Inter-menstrual Bleeding and/or Spotting

Days of inter-menstrual bleeding and/or spotting	Percentage of Subjects*	
Levonorgestrel and Ethinyl Estradiol Tablets	Cycle 1 (N=385)	Cycle 4 (N=261)
≥ 7 days	65%	42%
≥ 20 days	35%	15%
28-day regimen	Cycles 1-4 (N=194)	Cycles 10-13 (N=158)
≥ 7 days	38%	39%
≥ 20 days	6%	4%

* Based on spotting and/or bleeding on days 1-84 of a 91-day cycle in the Levonorgestrel and Ethinyl Estradiol Tablets subjects and days 1-21 of a 28-day cycle over 4 cycles in the 28-day dosing regimen.

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 that the incidence of VTE in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 20 to 40 cases per

100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users.

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases.

Other risk factors for venous thromboembolism

Other generalized risk factors for venous thromboembolism include, but are not limited to, a personal history, obesity, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index >30 kg/m^2), systemic lupus erythematosus, hemolytic uremic syndrome, inflammatory bowel disease such as Crohn's disease or ulcerative colitis, and sickle cell disease. The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. Also patients with varicose veins and leg cast should be closely supervised.

If a hereditary or acquired predisposition to venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use.

Hepatic/Biliary/Pancreatic

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 oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

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.

Risk of ALT Elevations with Concomitant Hepatitis C Treatment

Discontinue Indayo prior to starting therapy with the hepatitis C combination drug regimen glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir due to the potential for ALT elevations (see 2 CONTRAINDICATIONS).

Indayo can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary and acquired angioedema.

Chloasma

Chloasma may occur with combination oral contraceptives use including Indayo, especially in women with a history of chloasma gravidarum. Women who tend to develop chloasma should avoid exposure to the sun or ultraviolet radiation while taking Indayo.

Gallbladder disease

Users of 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 of use.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before hormonal contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after the initiation of hormonal contraceptive therapy. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. At each annual visit, examination should include those procedures that were done at the initial visit, as outlined above or as per the recommendations of the Canadian Task Force on the Periodic Health Examination.

Neurologic

Migraine and headache

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke (see **2 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

Emotional Disorders/Depression

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 case of a serious recurrence, Indayo should be discontinued and 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.

Reproductive Health: Female Potential

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 alternative contraceptive method should be used during this time.

Amenorrhea

Indayo is a 91-day cyclic dosing regimen (84 days with active oral tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with placebo tablets). In the case of unanticipated bleeding/spotting, missed withdrawal bleeding or amenorrhea, the possibility of pregnancy must be considered.

Women with 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.

7.1 Special Populations

7.1.1 Pregnant Women

Oral contraceptive use should be discontinued if pregnancy is confirmed. Oral contraceptives should not be taken by pregnant women. 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.

7.1.2 Breast-feeding

In breast-feeding women, the use of hormonal contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk.

A few adverse effects on the child have been reported, including jaundice and breast enlargement. The nursing mother should be advised not to use combination oral contraceptives, but to use other forms of contraception until she has completely weaned her child.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available in women under the age of 18 years; therefore, Health Canada has not authorized an indication for pediatric use.

Use of this product before menarche is not indicated.

7.1.4 Geriatrics

Indayo is not indicated for use in post-menopausal women.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

- thrombophlebitis
- pulmonary embolism
- mesenteric thrombosis
- neuro-ocular lesions (e.g., retinal thrombosis)

- myocardial infarction
- cerebral thrombosis
- cerebral hemorrhage
- hypertension
- benign hepatic tumours
- gallbladder disease
- congenital anomalies

The following adverse reactions also have been reported in patients receiving oral contraceptives:

Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 % or fewer of patients during the first cycle.

The following other reactions, as a general rule, are seen less frequently or only occasionally:

Blood and lymphatic system disorders: hemolytic uremic syndrome.

Ear and labyrinth disorders: auditory disturbances.

Eye disorders: cataracts, change in corneal curvature (steepening), retinal thrombosis, intolerance to contact lenses.

Gastrointestinal disorders: gastrointestinal symptoms (such as abdominal cramps and bloating), pancreatitis.

General disorders and administrative site conditions: edema.

Hepatobiliary disorders: cholestatic jaundice.

Infections and infestations: rhinitis, vaginal candidiasis, vaginitis.

Investigations: change in weight (increase or decrease), reduced tolerance to carbohydrates.

Metabolism and nutritional disorders: changes in appetite, porphyria.

Neoplasm benign, malignant and unspecified (including cysts and polyps): increase in size of uterine leiomyomata.

Nervous system disorders: chorea, dizziness, headache, migraine, optic neuritis.

Psychiatric disorders: changes in libido, mental depression, nervousness.

Renal and urinary disorders: cystitis-like syndrome, impaired renal function.

Reproductive system and breast disorders: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, amenorrhea during and after treatment, temporary infertility after discontinuation of treatment, breast changes (tenderness, enlargement, secretion), endocervical hyperplasia, possible diminution in lactation when given immediately postpartum, premenstrual like syndrome.

Skin and subcutaneous tissue disorders: chloasma or melasma which may persist, loss of scalp hair, hirsutism, erythema multiforme, erythema nodosum, hemorrhagic eruption, rash (allergic).

Vascular disorder: Raynaud's phenomenon.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Levonorgestrel and Ethinyl Estradiol Tablets included 15,027 28-day equivalent cycles for the safety ITT data; 609 subjects completed 1 year treatment, 123 subjects completed 18 months treatment and 108 subjects completed 2 years treatment.

Two subjects had pulmonary embolism and one subject had myocardial infarction while on Levonorgestrel and Ethinyl Estradiol Tablets in clinical studies.

The comparative safety data with a conventional monthly oral contraceptive containing similar strength synthetic estrogens and progestins on lipids profile were used as controls; liver functions and endometrial biopsies (50 subjects only) is available for one year only.

Study SEA-301 (A Phase III, Parallel, Randomized, Multicenter, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Levonorgestrel and Ethinyl Estradiol Tablets Extended Oral Contraceptive Therapy - 84-Day Active Cycle)

Table 3 shows the incidence rates for the most frequently reported adverse events for all treated patients with 1 year of treatment. The table displays results where the 5% or greater criterion was observed within any treatment group.

Table 3: Study SEA 301: Incidence of Most Frequently Reported Adverse Events Occurring in 5% or More Patients - All Treated Patients (ITT)

MedDRA System Organ Class	Levonorgestrel and Ethinyl Estradiol Tablets (N=456)		Control* (N=226)	
	N	%	N	%
INFECTIONS AND INFESTATIONS				
NASOPHARYNGITIS	100	21.93	67	29.65
SINUSITIS NOS	45	9.87	25	11.06
INFLUENZA	32	7.02	15	6.64
FUNGAL INFECTION NOS	27	5.92	11	4.87
UPPER RESPIRATORY TRACT INFECTION NOS	25	5.48	22	9.73
URINARY TRACT INFECTION NOS	20	4.39	14	6.19

NERVOUS SYSTEM DISORDERS				
HEADACHE NOS	94	20.61	64	28.32
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
MENORRHAGIA	53	11.62	6	2.65
DYSMENORRHOEA	26	5.70	9	3.98
GASTROINTESTINAL DISORDERS				
PHARYNGOLARYNGEAL PAIN	37	8.11	12	5.31
NAUSEA	34	7.46	20	8.85
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BACK PAIN	29	6.36	19	8.41
PSYCHIATRIC DISORDERS				
DEPRESSION NOS	10	2.19	13	5.75

* Control: a conventional monthly oral contraceptive containing similar strength synthetic estrogens and progestins

Study SEA-301A (A Phase IIIb, Parallel, Multicenter, Open-Label Clinical Study To Evaluate The Safety Of Levonorgestrel and Ethinyl Estradiol Tablets Extended Oral Contraceptive Therapy – 84-Day Active Cycle), is an extension study to Study SEA-301 providing an additional 2 years of safety data (n=189) for Levonorgestrel and Ethinyl Estradiol Tablets. The adverse reactions most commonly reported in Study SEA-301A were similar to those observed in Study SEA-301.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (≥1% to <5%)

Study SEA-301

Infections and Infestations: Urinary Tract Infection, Bronchitis, Pharyngitis Streptococcal, Ear Infection, Vaginitis Bacterial, Vaginosis Fungal, Bladder Infection, Pharyngitis, Vaginal Candidiasis.

Gastrointestinal Disorders: Abdominal Pain Upper, Vomiting, Dyspepsia, Toothache, Abdominal Pain, Diarrhoea, Abdominal Distension, Constipation.

Nervous System: Migraine, Dizziness (Excl. Vertigo), Sinus Headache.

Musculoskeletal and Connective Tissue Disorders: Muscle Cramps, Arthralgia, Pain in Limb, Myalgia, Neck Pain, Muscle Spasms, Tendonitis.

Reproductive System and Breast Disorders: Breast Tenderness.

Skin and Subcutaneous Tissue Disorders: Acne, Acne Aggravated, Rash.

General Disorders and Administration Site Conditions: Influenza Like Illness, Fatigue, Pain, Pyrexia, Chest Pain.

Respiratory, Thoracic and Mediastinal Disorder: Sinus Congestion, Cough, Nasal Congestion, Asthma.

Psychiatric Disorders: Depression, Insomnia, Mood Swings, Libido Decreased.

Injury, Poisoning and Procedural Complications: Muscle Strain, Post Procedural Pain, Accident, Road Traffic Accident.

Investigations: Weight Increased.

Immune System Disorders: Hypersensitivity, Seasonal Allergy.

Ear and Labyrinth Disorders: Ear Pain.

Less Common Clinical Trial Adverse Drug Reactions (< 1 %)

Study SEA-301

Infections and Infestations: Tonsillitis, Tooth Abscess, Cervicitis, Gastroenteritis Viral, Cystitis, Gastroenteritis, Herpes Simplex, Herpes Viral Infection, Herpes Zoster, Lice Infestation, Lower Respiratory Tract Infection, Meningitis Viral, Pneumonia, Staphylococcal Infection, Tooth Infection, Upper Respiratory Tract Infection Viral, Bacterial Infection, Eye Infection, Furuncle (Excl Genital), Genital Warts, Gingival Abscess, Kidney Infection, Laryngitis, Localised Infection, Lyme Disease, Malaria, Nail Fungal Infection, Oral Candidiasis, Otitis Media, Pertussis, Respiratory Tract Infection, Sinusitis Acute, Skin Bacterial Infection, Stye, Upper Respiratory Tract Infection, Vaginal Infection, Vaginitis, Viral Infection, Vulvitis, Wound Infection.

Gastrointestinal Disorders: Flatulence, Gastro-Oesophageal Reflux Disease, Abdominal Pain Lower, Gastric Ulcer, Tooth Disorder, Abdominal Discomfort, Colitis, Colon Spastic, Constipation Aggravated, Dry Mouth, Gastrointestinal Upset, Hemorrhoidal Bleeding, Hiatus Hernia, Inguinal Hernia, Irritable Bowel Syndrome, Oral Pain, Rectal Haemorrhage, Salivary Gland Calculus.

Nervous System: Tension Headaches, Hypoaesthesia, Headache Aggravated, Migraine Aggravated, Cluster Headaches, Disturbance in Attention, Facial Palsy, Paraesthesia, Sciatica, Syncope, Vasovagal Attack.

Musculoskeletal and Connective Tissue Disorders: Bursitis, Joint Swelling, Arthritis, Bone Disorder, Plantar Fasciitis, Bone Spur, Intervertebral Disc Herniation, Musculoskeletal Chest Pain, Neck Stiffness, Rotator Cuff Syndrome, Swelling, Temporomandibular Joint Disorder.

Reproductive System and Breast Disorders: Breast Enlargement, Dyspareunia, Premenstrual Syndrome, Oligomenorrhoea, Pelvic Pain, Uterine Cervix Ulcer, Vaginal Discharge, Vulvovaginal Dryness, Breast Discharge, Breast Fibrosis, Cervical Cyst, Genital Rash, Ovarian Cyst, Ovarian Pain, Post-Coital Bleeding, Uterine Cervical Disorder, Uterine Cyst, Vaginal Irritation, Vaginal Odour, Vulval Disorder.

Skin and Subcutaneous Tissue Disorders: Genital Pruritus Female, Night Sweats, Pruritus, Contusion, Dermatitis Atopic, Skin Cysts, Urticaria, Alopecia, Dermatitis Contact, Eczema, Erythema, Onychoclasis, Rash Papular, Skin Disorder, Skin Lesion, Skin Ulcer, Solar Urticaria, Sweating Increased.

General Disorders and Administration Site Conditions: Facial Pain, Analgesic Effect, Fatigue Aggravated, Feeling Hot, Groin Pain, Injection Site Pain, Limb Discomfort, Oedema Lower Limb, Thirst.

Respiratory, Thoracic and Mediastinal Disorder: Rhinitis, Upper Respiratory Tract Congestion, Asthma Aggravated, Nasal Sinus Drainage, Pulmonary Congestion, Rhinitis Allergic, Sinus Pain, Chest Wall Pain, Dyspnoea, Postnasal Drip, Rhinitis Atrophic, Rhinitis Seasonal, Sinus Disorder.

Psychiatric Disorders: Anxiety, Irritability, Mood Alteration, Attention Deficit/Hyperactivity Disorder, Bipolar I Disorder, Emotional Disturbance, Loss of Libido, Nervousness, Obsessive-Compulsive Disorder, Panic Attack, Sleep Disorder, Stammering.

Injury, Poisoning and Procedural Complications: Arthropod Bite, Joint Sprain, Back Injury, Limb Injury, Animal Bite, Bite, Burns, Burns Second Degree, Caustic Injury, Concussion, Ear Canal Abrasion, Facial Bones Fracture, Foot Fracture, Gun Shot Wound, Hand Fracture, Laceration, Ligament Injury, Ligament Sprain, Nerve Injury, Post-Traumatic Wound, Infection, Sunburn, Whiplash Injury.

Investigations: Smear Cervix Abnormal, Weight Decreased, Blood Cholesterol Increased, Blood Pressure Increased, Blood Urine Present, Colonoscopy, Heart Rate Increased, Helicobacter Pylori, Antibody Positive, Lipids Increased, Liver Function Tests Abnormal, White Blood Cell Count Increase.

Immune System Disorders: Allergy Aggravated, Drug Hypersensitivity, Allergy to Insect Sting, Food Allergy.

Ear and Labyrinth Disorders: Motion Sickness, Ear Congestion, Eustachian Tube Disorder, Labyrinthitis, Sensation of Block in Ear, Vertigo.

Surgical and Medical Procedures: Tooth Extraction, Eye Operation, Breast Operation, Cervical Cautery, Cholecystectomy, Dental Operation, Knee Operation, Ligament Repair.

Blood and Lymphatic System Disorders: ABO Haemolytic Disease of Newborn, Anaemia, Lymphadenopathy, Iron Deficiency Anaemia, Mononucleosis Syndrome.

Vascular Disorders: Carotid Artery Occlusion, Hot Flushes, Hypertension.

Eye Disorders: Conjunctivitis, Vision Blurred, Conjunctival Hyperaemia, Corneal Ulcer, Eye Irritation, Lacrimal Disorder, Pterygium, Retinal Detachment.

Metabolism and Nutrition Disorders: Appetite Increased, Fluid Retention, Hunger.

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast Lump, Basal Cell Carcinoma, Fibrocystic Breast Disease.

Renal and Urinary Disorders: Loin Pain, Urinary Frequency, Urine Odour Foul.

Cardiac Disorders: Palpitations, Palpitations Aggravated.

Endocrine Disorders: Goitre.

Hepatobiliary Disorders: Cholecystitis.

Less common adverse reactions reported in Study SEA-301A (2-year duration) were similar to those observed in Study SEA-301 (1-year duration).

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In study SEA-301 (1-year trial), for triglycerides, the percentage of patients on Levonorgestrel and Ethinyl Estradiol Tablets going from normal to high was 6.2% compared to that of 1.9% for patients on control (median increase of 136 (43.6%) for Levonorgestrel and Ethinyl Estradiol Tablets patients compared to 206 (63.1%) for control patients). For LDL, 17.9% of patients on Levonorgestrel and Ethinyl Estradiol Tablets shifted from normal to high values, compared to that of 14.6% for patients on control (median increase in LDL of 40 (27.2%) for Levonorgestrel and Ethinyl Estradiol Tablets patients compared to an increase of 37 (22.8%) for control patients). The percentage of Levonorgestrel and Ethinyl Estradiol Tablets patients who went from normal to high for total cholesterol was 22.1% compared to that of 23.4% for patients on control (median increase of 37 (17.2%) for Levonorgestrel and Ethinyl Estradiol Tablets patients compared to 29 (13.3%) for control patients).

In study SEA-301A (2-year extension trial of SEA-301 with no control), 5 subjects had increase in cholesterol/LDL or triglycerides above the normal ranges among 173 tested Levonorgestrel and Ethinyl Estradiol Tablets subjects. Seven subjects had increase in liver enzymes above the normal range excluding the subject with large common bile duct stone.

The coagulation profile was not studied with this Levonorgestrel and Ethinyl Estradiol Tablets regimen.

8.5 Post-Market Adverse Reactions

The following other serious and unexpected adverse events have been reported in users of Levonorgestrel and Ethinyl Estradiol Tablets in the post marketing period. These adverse events are compiled from spontaneous reports and are listed regardless of frequency and whether or not a causal relationship with Levonorgestrel and Ethinyl Estradiol Tablets has been established.

Blood and Lymphatic System Disorders: Anaemia.

Cardiac Disorders: Cardiac Arrest, Myocardial Infarction, Supraventricular Tachycardia.

Congenital, Familial and Genetic Disorders: Arnold-Chiari Malformation, Bicuspid Aortic Valve, Brain Malformation, Patent Ductus Arteriosus, Spina Bifida, Talipes.

Endocrine Disorders: Hyperprolactinaemia.

Gastrointestinal Disorders: Colitis Ischemic.

Musculoskeletal and Connective Tissue Disorders: Acquired Macrocephaly, Muscle Mass.

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Renal Neoplasm.

Nervous System Disorders: Brain Damage, Convulsion, Epilepsy, Hydrocephalus, Hypotonia, Stroke.

Pregnancy, Puerperium and Perinatal Conditions: Abortion Spontaneous, Intra-Uterine Death.

Psychiatric Disorders: Suicidal Ideation.

Renal and Urinary Disorders: Neurogenic Bladder.

Reproductive System and Breast Disorders: Cervical Polyp, Dysfunctional Uterine Bleeding, Pelvic Pain, Vaginal Haemorrhage.

Skin and Subcutaneous Tissue Disorders: Acute Febrile Neutrophilic Dermatosis, Leukocytoclastic Vasculitis, Skin Lesion.

Vascular Disorders: Deep Vein Thrombosis, Pulmonary Embolism.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.3 Drug-Behavioural Interactions

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

9.4 Drug-Drug Interactions

The drugs listed in Tables 4 and 5 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for possible drug interactions with hormonal contraceptives.

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

Class of Compound	Drug	Effect	Clinical comment
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone Lamotrigine	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For

Table 4: Drugs Which May Decrease the Efficacy of Oral Contraceptives			
Class of Compound	**Drug**	**Effect**	**Clinical comment**
			long course, use another method.
	Rifampin	Increased metabolism of progestin. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose oral contraceptives.
Antacids		Decreased intestinal absorption of progestin.	Dose two hours apart.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

Table 5: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Effect**	**Clinical comment**
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.

Table 5: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Effect**	**Clinical comment**
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Combination oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucoronidation. Decreased lamotrigine levels may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycaemic 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-dose 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.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.

Table 5: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Effect**	**Clinical comment**
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.
Hepatis C drug combinations	glecaprevir/ pibrentasvir and sofosbuvir/ velpatasvir/ voxilaprevir	Potential ALT elevations.	Avoid concomitant use.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.

Table 5: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Effect**	**Clinical comment**
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.

Several of the anti-HIV protease inhibitors have been studied with co-administration of combination oral contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestogen have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitor for further drug-drug interaction information.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 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.

9.7 Drug-Laboratory Test Interactions

Laboratory Tests

Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive.

The following laboratory tests are modified:

A. Liver Function Tests

Aspartate serum transaminase (AST) - variously reported elevations.

Alkaline phosphatase and gamma-glutamyl transferase (GGT) - slightly elevated.

B. Coagulation Tests

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

C. Thyroid Function Tests

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake.

D. Lipoproteins

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

E. Gonadotropins

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

F. Glucose tolerance

Oral glucose tolerance remained unchanged or was slightly decreased.

Tissue Specimens

Pathologists should be advised of hormonal contraceptive use when specimens from surgical procedures and/or Pap smears are submitted for examination.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and changes in the endometrium (which reduce the likelihood of implantation).

10.2 Pharmacodynamics

Norgestrel is a racemate containing equal parts of D- and L-enantiomers. The L-enantiomer has been tested in a broad range of biological assays and its inactivity has been confirmed. The D-enantiomer (named levonorgestrel) accounts for all the biological activity found in norgestrel, as levonorgestrel was twice as potent as the racemate in experiments in which norgestrel was effective.

10.3 Pharmacokinetics

Absorption: No specific investigation of the absolute bioavailability of Levonorgestrel and Ethinyl Estradiol Tablets in humans has been conducted. However, published literature

indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 43%.

The effect of food on the rate and extent of absorption of levonorgestrel and ethinyl estradiol following oral administration of Levonorgestrel and Ethinyl Estradiol Tablets has not been evaluated.

The mean plasma pharmacokinetic parameters of Levonorgestrel and Ethinyl Estradiol Tablets following a single dose of two tablets in normal healthy women under fasting conditions are reported in Table 6.

Table 6: Summary of Mean ± SD Pharmacokinetic Parameters Following a Single Dose Administration of Levonorgestrel and Ethinyl Estradiol Tablets in Healthy Female Subjects Under Fasting Conditions

Analyte	C_{max} (mean ± SD)	$t_{½}$ (mean ± SD)	AUC_{0-4} (mean ± SD)	T_{max}
Levonorgestrel	5.6 ± 1.5 ng/mL	29.8 ± 8.3 hours	60.8 ± 25.6 ng*hr/mL	1.4 ±0.3 hrs
Ethinyl Estradiol	145 ± 45 pg/mL	15.4 ± 3.2 hours	1307 ± 361 pg*hr/mL	1.6 ±0.5 hrs

Distribution: The apparent volume of distribution of levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5-99% protein-bound, principally to the sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Ethinyl estradiol is about 95-97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of combination levonorgestrel and ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than when predicted based on single-dose kinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol and a possible reduction in hepatic metabolic capacity.

Metabolism: Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Levonorgestrel and its Phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl

estradiol by hepatic CYP3A4. Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation. Hydroxylation at the 4-, 6- and 16-positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Elimination: About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Levonorgestrel and Ethinyl Estradiol Tablets was found to be about 30 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyl estradiol after a single dose of Levonorgestrel and Ethinyl Estradiol Tablets was found to be about 15 hours.

Special Populations and Conditions

Pediatrics: The safety and efficacy of Levonorgestrel and Ethinyl Estradiol Tablets has not been established in women under the age of 18 years.

Use of Indayo before menarche is not indicated.

Geriatrics: Indayo is not indicated for use in post-menopausal women.

Genetic Polymorphism: No data are available.

Ethnic Origin: No formal studies on the effect of race on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol Tablets have been conducted.

Hepatic Insufficiency: No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol Tablets. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency: No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Levonorgestrel and Ethinyl Estradiol Tablets.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 to 30 °C).
Keep out of reach and sight of children and pets.

12 SPECIAL HANDLING INSTRUCTIONS

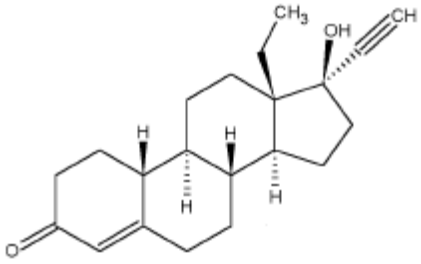
Not applicable

PART II: SCIENTIFIC INFORMATION

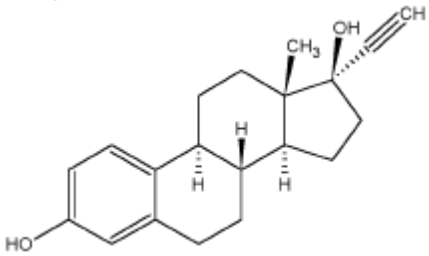
13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Levonorgestrel Ethinyl Estradiol
Chemical name:	Levonorgestrel: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one Ethinyl Estradiol: 17α-Ethynyl-1,3,5(10)-estratriene-3,17-β-diol
Molecular formula and molecular mass:	Levonorgestrel: $C_{21}H_{28}O_2$, 312.45 Ethinyl Estradiol: $C_{20}H_{24}O_2$, 296.40
Structural formula:	Levonorgestrel:



Ethinyl Estradiol:



Physicochemical properties:

Solubility:

Levonorgestrel:	Practically insoluble in water and n-hexane, slightly soluble in acetone and ethanol, sparingly soluble in dichloromethane and soluble in chloroform.
Ethinyl Estradiol:	Freely soluble in ether, ethanol, acetone, dioxane, soluble in alkali hydroxide solutions, sparingly soluble in chloroform and practically insoluble in water.

Melting Point:

Levonorgestrel:	Between 232° C and 239°C (range should not exceed 4°C)
Ethinyl Estradiol:	Ethinylestradiol is found to exist in an anhydrated form and a hemihydrate. The anhydrated form melts between 180°C and

185°C (according to USP: 180°C to 186°C). The hemihydrate melts between 145°C and 152°C. (In the USP monograph the melting range 142 to 146 °C is assigned to a second polymorphic form, which corresponds to the melting range of the hemihydrate).

Biological Properties:

Levonorgestrel: This is a synthetic progestogen in the (-)-isomer of norgestrel. It is the biologically active form of the racemic norgestrel.

Ethinyl Estradiol: This is a synthetic estrogen.

14 CLINICAL TRIALS

General Information

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

14.1 Clinical Trials by Indication

Prevention of pregnancy

Table 7 - Summary of patient demographics for clinical trials in the prevention of pregnancy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
SEA-301	A Phase III, Parallel, Randomized, Multicenter, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Levonorgestrel and Ethinyl Estradiol Tablets Extended Oral Contraceptive Therapy - 84-Day Active Cycle	Levonorgestrel and Ethinyl Estradiol Tablets: levonorgestrel (150 µg); ethinyl estradiol (30 µg), oral Control*: levonorgestrel (150 µg); ethinyl estradiol (30 µg), oral Duration: One year (4 x 91-day cycles)	Levonorgestrel and Ethinyl Estradiol Tablets: 456 Control*: 226	Levonorgestrel and Ethinyl Estradiol Tablets: 27.8 (18-40) Control*: 27.83 (19-40)	Female (100%)

*Control: a conventional monthly oral contraceptive containing similar strength synthetic estrogens and progestins

In a one year (4 x 91-day cycles) multicenter open-label clinical trial, 456 women 18 to 40 years of age, were studied to assess the safety and efficacy of Levonorgestrel and Ethinyl Estradiol Tablets. The racial demographic of all enrolled women was: Caucasian (76.97%), African-American (10.96%), Hispanic (7.02%), Asian (2.19%), and Other (2.85%). The weight range for these women treated was 84 to 304 lb (BMI: 14.47 to 45.29), with a mean weight of 156.39 lb (BMI: 26.16). Among the women in the trial, 18.86% were current smokers; 63.16% were continuous users of oral contraceptives, 28.95% were prior users of oral contraceptives, and 7.68% were fresh starts.

The demographics of women receiving Nordette (N=226) were similar to those receiving Levonorgestrel and Ethinyl Estradiol Tablets.

14.2 Study Results

In a 1-year controlled clinical trial, 4 pregnancies occurred in women 18-35 years of age during 809 completed 91-day cycles of Levonorgestrel and Ethinyl Estradiol Tablets during which no

backup contraception was utilized. This represents an overall use-efficacy Pregnancy rate of 1.98 per 100 women-years of use.

14.3 Comparative Bioavailability Studies

A two-way blinded, single-dose, randomized, two-period, two-treatment, crossover, fasting comparative bioavailability study of INDAYO (0.15 mg Levonorgestrel and 0.03 mg Ethinyl estradiol) tablets (Senador Laboratories Private Limited) versus Seasonale® (0.15 mg Levonorgestrel and 0.03 mg Ethinyl estradiol) Tablets (Duramed Pharmaceuticals Inc.) was conducted in 27 healthy, adult female volunteers.

Comparative bioavailability data from the subjects that were included in the statistical analysis (N = 26 for levonorgestrel and N = 27 for ethinyl estradiol) are presented in the following table:

Levonorgestrel (2 x 0.15 mg/0.03 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72h} (ng*hr/mL)	77.96 89.10 (50.60)	78.59 88.34 (48.55)	99	94 - 105
AUC_I (ng*hr/mL)	103.26 119.1 (51.73)	103.84 117.6 (50.07)	99	94 - 105
C_{max} (ng/mL)	5.79 6.24 (36.27)	6.74 7.26 (38.44)	86	81 - 92
$T_{½}$[3] (h)	38.68 (30.16)	38.58 (27.88)		
T_{max}[3] (h)	2.18 (28.16)	1.47 (30.90)		

[1] INDAYO® (Levonorgestrel and Ethinyl Estradiol) Tablets, 0.15 mg/0.03 mg, (Senador Laboratories Private Limited)

[2] Seasonale® (Levonorgestrel and Ethinyl Estradiol) Tablets, 0.15 mg/0.03 mg (Duramed Pharmaceuticals Inc., Canada)

[3] Expressed as the arithmetic mean (CV%) only

Ethinyl Estradiol (2 x 0.15 mg/0.03 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[1]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg*hr/mL)	1722 1827 (31.46)	1755 1857 (31.17)	98	94 - 102
AUC_I (pg*hr/mL)	1865 1970 (30.07)	1898 2000 (29.90)	98	95 - 102
C_{max} (pg/mL)	150.1 156.6 (27.31)	167.2 175.9 (30.92)	90	86 - 94
$T_{½}$[3] (h)	15.55 (17.04)	15.49 (19.42)		
T_{max}[3] (h)	1.87 (30.20)	1.79 (21.15)		

[1] INDAYO® (Levonorgestrel and Ethinyl Estradiol) Tablets, 0.15 mg/0.03 mg (Senador Laboratories Private Limited)
[2] Seasonale® (Levonorgestrel and Ethinyl Estradiol) Tablets, 0.15 mg/0.03 mg (Duramed Pharmaceuticals Inc., Canada)
[3] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

Not applicable.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Levonorgestrel and ethinyl estradiol have been extensively studied and are well-characterized pharmaceuticals. These approved pharmaceuticals in combination are both safe and effective when indicated for the prevention of pregnancy.

Carcinogenicity:

The association of mammary tumours in beagle dogs and steroid contraceptive use has been extensively reported in the published literature. Much of the published literature looked at the suitability of the beagle dog as a test model to assess the tumourigenic potential of certain progestogens in inducing mammary tumours and comparing it to the human model. Early toxicology studies in beagle dogs showed the overall incidence of mammary tumours were more common and frequent by a factor of three to four than in women. However, the beagle dog differs significantly from other animal species and humans mainly due to its differences in reproductive physiology and endocrinology. The beagle dog species are more susceptible to

show mammary tumours as they have a fairly high natural incidence of mammary cancer. Some of the published literature has reported that many of the more potent progestogens have been shown to induce mammary tumours compared to the less potent progestational compounds. Evidence has shown that long-term administration of norgestrel has less progestational activity and incidence of mammary tumours over more potent progestogens.

Steroid-related canine mammary tumours were unlikely to be indicative of a potential hazard to women.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrSEASONALE® levonorgestrel and ethinyl estradiol tablets, 0.15 mg and 0.03 mg, submission control 279010, Product Monograph, Teva Canada Limited. (FEB 14, 2024)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrINDAYO®

Levonorgestrel and Ethinyl Estradiol Tablets, USP

Read this carefully before you start taking **Indayo** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Indayo**.

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 particularly in women over 35 years of age. The risk also increases with the number of cigarettes smoked. For this reason, women who smoke and are over 35 years of age should not use Indayo.

Birth control pills DO NOT PROTECT against Sexually Transmitted Infections (STIs), including HIV/AIDS.

For protection against STIs, it is advisable to use latex or polyurethane condoms AND take your birth control pills.

Indayo provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of hormonal exposure per year). This higher exposure may increase the risk of developing blood clots.

What is Indayo used for?

Indayo is used for the prevention of pregnancy in women (18 years of age and older). Indayo should be used in women who have had their first menstrual period (menarche).

How does Indayo work?

Indayo is a birth control pill. It is considered to be a combination oral contraceptive. This is because it contains two female sex hormones, levonorgestrel and ethinyl estradiol. It has been shown to be effective in preventing pregnancy when taken as prescribed by your healthcare professional.

Combination hormonal contraceptives like Indayo work in two ways:

1. To stop the monthly release of an egg by the ovaries.
2. To 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 if Indayo is not used correctly.

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

There are differences in these pregnancy rates. This is because not all people use birth control as carefully or as regularly as they should. This does not apply to subdermal implants or IUDs since these are implanted under the skin or in the uterus. If you are careful and use your birth control regularly, pregnancy rates should be lower. Some types of birth control will require more effort than taking a single pill every day.

What are the ingredients in Indayo?

Medicinal ingredients: Levonorgestrel and ethinyl estradiol

Each pink active tablet contains the following inactive ingredients: lactose monohydrate, D&C Red No. 27, FD&C Blue No. 2, FD&C Yellow No. 5, magnesium stearate, polacrilin potassium and red iron oxide.

Each white inert tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate and polacrilin potassium.

Indayo comes in the following dosage forms:

Pink tablets containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol.

White tablets containing no medicinal ingredients.

Do not use Indayo if:

- you have or have a history of blood clots in the legs or somewhere else in your body
- you have or have a history of a stroke, heart attack, or coronary artery disease (including angina pectoris), or a condition that may be a first sign of a stroke (such as a ministroke or small reversible stroke)
- you have a disease of the heart valves with complications
- you have the following risk factors for blood clots:
  - severe high blood pressure
  - diabetes with complications
  - known abnormalities of the blood clotting system such as:
    - Factor V Leiden mutation
    - activated protein C (APC) resistance
    - antithrombin-III-deficiency
    - protein C deficiency
    - protein S deficiency
    - hyperhomocysteinaemia
    - prothrombin mutation G20210A
    - antiphospholipid-antibodies
  - very high blood cholesterol or triglyceride levels
  - you have or will have a major surgery (including to the legs, pelvis or nervous system)
  - you cannot stand or move for long periods of time, including prolonged bed rest
  - smoke heavily (more than 15 cigarettes per day) and are over age 35
- you have or have a history of migraine headaches with focal aura (flashes or light, blind spots and other vision changes)
- you have liver disease
- you have or have had liver tumours (cancerous or non-cancerous)
- you have or have had jaundice. This is where the skin or whites of the eyes turn yellow. This may have been related to other medicines you were taking or may have happened during pregnancy.
- you have or think you have cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- you have unusual vaginal bleeding without a known reason
- you have loss of vision due to blood vessel disease of the eye
- you are pregnant or think you might be pregnant

- you have or have a history of pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- you are allergic to ethinyl estradiol, levonorgestrel or to any of the non-medicinal ingredients in Indayo (see **What are the ingredients in Indayo?**)
- you are using antiviral medications to treat Hepatitis C Virus (HCV) which contain the combination of glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Indayo. Talk about any health conditions or problems you may have, including if you:

- smoke
- have a history of breast disease (such as breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol
- have or have a family history of diabetes
- have or have a history of heart, liver or kidney problems
- have a history of seizures/epilepsy
- have a history of depression
- have cholestasis. This is a condition where bile flow from the liver is decreased.
- wear contact lenses
- have uterine fibroids (benign tumours of the uterus)
- are breast feeding
- have systemic lupus erythematosus. This is a disease of the immune system that affects the joints, skin, kidneys, blood cells, brain, heart and lungs.
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have hemolytic uremic syndrome. This is when there is an abnormal breakdown of blood cells, which clog the kidneys.
- have sickle cell disease. This is a disease that affects haemoglobin, a molecule in red blood cells that delivers oxygen throughout the body.
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- have been told that you have a condition called hereditary or acquired angioedema or if you have had episodes of swelling in body parts such as hands, feet, face or airway passages.
- have a history of a skin condition called chloasma (hyperpigmentation)
- are overweight
- have a family history of blood clot disorders, heart attacks or strokes

Other warnings you should know about:

<u>Blood Clot in Legs, Lungs, Heart, Eyes or Brain</u>

Women who use birth control that contains hormones are more likely to develop blood clots. Blood clots are the most common serious side effects of birth control pills. The risk for clots is highest during the first year a woman uses a hormonal birth control. The risk is also high if a

woman restarts the same or new hormonal birth control. Clots can occur in many areas of the body and can lead to blindness or impaired vision as well as damage to or loss of a limb and death.

While you are taking Indayo, if you have any of the below symptoms, talk to your healthcare professional right away. These are signs of blood clots:

- sharp pain in your chest
- coughing up blood
- sudden shortness of breath
- crushing chest pain or chest heaviness
- irregular heartbeat
- sudden severe or worsening headache
- feeling full
- vomiting
- dizziness, trouble walking
- fainting, seizures
- anxiety, confusion
- changes in vision
- changes in speech
- pain and / or swelling in your calf
- weakness or numbness in your face, arm or leg
- sudden pain, swelling and slight blue or red discoloration of an arm or leg
- discomfort radiating to your back, jaw, throat or stomach

Blood clots can develop whether or not you are using hormones for birth control. They can also happen if you are pregnant. The risk is higher in users of combined hormonal contraceptives (CHCs), including Indayo than in nonusers, but it is not as high as the risk during pregnancy. You should talk to your healthcare professional about the available options.

Cancer

Using birth control pills may increase the risk of certain cancers including cancer of the breast, cervix and liver.

Breast cancer: The risk of breast cancer in women increases as you get older. It also increases if there is family history of breast cancer, meaning if your mother or sister have or had breast cancer. Other factors that increase your risk for breast cancer are being obese, never having children, or having your first full-term pregnancy at a late age.

If you have breast cancer now, or had it in the past, do not use birth control pills. The hormones in these pills can affect some cancers.

Some women who use birth control pills may have a higher risk of developing breast cancer before menopause. These women may have used birth control pills for a long time (more than eight years), or may have started using birth control pills at an early age.

In a few women, using of birth control pills can speed up the growth of a breast cancer that has not yet been found. Finding breast cancer early can reduce the effect of the cancer on a woman's life expectancy. The risks for breast cancer related to using birth control pills seem to be small. You should, however, have a healthcare professional check your breasts at least once per year.

While you are taking Indayo, check your breasts often. See your healthcare professional if you notice any changes, such as:

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

Cervical cancer: Human Papilloma Virus (HPV) is an important risk factor for cervical cancer. However, it is possible that women who use birth control pills may have a higher chance of getting cervical cancer.

Liver cancer: Liver cancer (hepatocellular carcinoma) and liver tumors may be linked to oral birth control pills. The risk for liver cancer increases the longer these pills are used. However, liver tumors are extremely rare. If you feel severe abdominal pain or find a lump in your abdomen, talk to your healthcare professional right away. Do not use Indayo if you have a history of liver tumors (cancerous or noncancerous).

Gallbladder disease

The risk for gallbladder disease that needs surgery is higher in women using birth control pills. The risk is highest in the first year of use and increases the longer these pills are used.

Pregnancy, Breastfeeding, Miscarriage and Abortions

Use in pregnancy: Birth control pills should not be taken by pregnant women. Stop taking Indayo if you get pregnant. You should talk to your healthcare professional about risks to your unborn child from any medication taken during pregnancy.

Use after pregnancy, miscarriage or an abortion: You will be at an increased risk for blood clots. Your healthcare professional will tell you when to start using Indayo after childbirth, miscarriage or an abortion.

Pregnancy after stopping Indayo: You will have a menstrual period when you stop using Indayo. Wait until after your next period before getting pregnant. This will help to better date the pregnancy. Talk to your healthcare professional about other forms of birth control you can use during this time.

Breast-feeding: If you are breast-feeding, talk to your healthcare professional before starting the birth control pill. Other types of birth control, instead of a birth control pill, are recommended until your baby has stopped breast-feeding. The hormones in the pill may lower the amount and quality of your breast milk. This may not happen, however, if you wait until after breast-feeding is established.

Skin conditions

Chloasma may develop while you are using Indayo. This appears as yellowish-brown patches on the skin, particularly of the face. It is more likely to happen if you have previously had chloasma gravidarum. This is when these patches appear on the skin of the face during pregnancy. This is commonly known as "the mask of pregnancy". If you have or had chloasma, avoid too much exposure to the sun while using Indayo.

Surgery

Tell your healthcare professional if you are scheduled for major surgery. You may need to stop using Indayo four weeks before surgery. You may need to wait a time period after surgery or bed rest before restarting Indayo. Talk to your healthcare professional about other forms of birth control you can use during this time.

Vaginal bleeding

You should expect to have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Indayo treatment you may have 20 or more days of unplanned bleeding or spotting (bleeding when you are taking the pink pills). This bleeding or spotting tends to decrease during late cycles. Do not stop taking Indayo because of the bleeding. If the spotting continues for more than a few days or if the bleeding is heavy, talk to your healthcare professional.

While you are taking Indayo, you should have your period when you are taking the white pills. If you were not taking Indayo as directed by your healthcare professional or miss your period, you should have a pregnancy test. This will rule out if the missed period is because you are pregnant.

Check-Ups and Tests

Before starting Indayo, you will need to have examinations and tests. Your healthcare professional will conduct a physical exam. They will examine your breasts, liver, arms and legs. They will conduct a pelvic exam which includes a PAP smear. Your healthcare professional will also ask you some questions about your personal health history and that of your close relatives. They will also measure your blood pressure and do blood tests.

While you are taking Indayo, you will need regular check-ups with your healthcare professional to identify side effects associated with its use. Your first check-up should be about three months after starting Indayo. Afterward, you will see your healthcare professional at least once a year.

If you are scheduled for any laboratory tests, be sure to tell your healthcare professional that you are taking Indayo. This is because birth control pills can affect some blood tests.

If you see a different healthcare professional be sure to tell them that you are taking Indayo.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Certain drugs may interact with birth control pills (including Indayo) and prevent them from working properly. This can make them less effective in preventing pregnancy or cause unexpected bleeding (spotting or breakthrough bleeding). Birth control pills may also interfere with how other drugs work. If you are taking medicines or herbal products that might make Indayo less effective, a barrier method of birth control should also be used.

The following may interact with Indayo:

- drugs used for the treatment of epilepsy including primidone, phenytoin, barbiturates, carbamazepine, lamotrigine, ethosuximide and phenobarbital
- drugs used for the treatment of HIV infections or AIDS
- drugs used for the treatment of tuberculosis including rifampin
- drugs used to treat bacterial infections including penicillins, tetracyclines, troleandomycin, cotrimoxazole, ampicillin, chloramphenicol, metronidazole, neomycin, nitrofurantoin and sulfonamides
- drugs used to prevent organ rejection including cyclosporine
- drugs used to treat fungal infection including griseofulvin
- St. John's Wort, an herbal product used to treat depression and other conditions
- drugs used to lower cholesterol including clofibrate
- drugs used to treat high blood pressure including guanethidine, methyldopa, reserpine and beta blockers
- antidiabetic drugs and insulin (for diabetes)
- drugs used to help you relax or sleep including benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate, chlordiazepoxide, lorazepam, oxazepam, and diazepam
- drugs used to treat fever, pain or inflammation including meperidine, prednisone, phenylbutazone, acetaminophen, antipyrine and ASA
- drugs used to treat depression including clomipramine
- some nutritional supplements including Vitamin E, Vitamin B12, and folic acid
- antacids
- hepatitis C drug combinations containing, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir.
- drugs used to treat lung problems including theophylline
- drugs used to treat allergies including antihistamines
- drugs used to treat migraine headaches
- aminocaproic acid, used to help treat bleeding
- alpha-II adrenoreceptor agents including clonidine
- drugs used to prevent blood clots
- drugs used to treat mental health problems including phenothiazines

This is not a complete list of possible drug interactions with Indayo. Talk to your healthcare professional for more information about drug interactions.

Antacids may affect how Indayo is absorbed in your body. If you need to use antacids, like TUMS, take them 2 hours before or 2 hours after taking Indayo.

The effects of caffeine and alcohol may be increased. This is because birth control pills affect how these are metabolized.

Do not use Indayo if you have Hepatitis C and are being treated with glecaprevir / pibrentasvir or sofosbuvir / velpatasvir / voxilaprevir. Using these drugs at the same time as Indayo can cause problems with your liver, such as an increase in the ALT liver enzyme. You can usually start Indayo about 2 weeks after finishing treatment with these combination drugs used for Hepatitis C, but talk to your healthcare professional before taking Indayo.

How to take Indayo:

1. BE SURE TO READ THESE DIRECTIONS:
   - Before you start taking your pills.
   - Anytime you are not sure what to do.
2. Decide with your healthcare professional what time of day is best for you to start taking your first pill. It is important that you take the pill at about the same time each day. Pick a time of day that will be easy to remember.
3. Look at your Extended-Cycle Tablet Dispenser. The Indayo Extended-Cycle Tablet Dispenser has 3 trays with cards that hold 91 individual sealed pills. The 91 pills consist of 84 pink pills that contain hormones and 7 white pills that contain no hormones. Tray 1 and Tray 2 each contain 28 pink pills. Tray 3 contains 28 pink pills and 7 white pills (35 pills in total). Check the pill pack for:
   - where to start taking pills
   - in what order to take the pills
4. Your healthcare professional will tell you to start taking the pills on the first Sunday after your period begins. If your period starts on Sunday, start the same day.
5. Take 1 pill at approximately the same time every day for 91 days. Begin a new Extended-Cycle Tablet Dispenser the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last seven days of using that pill pack, while you are taking the white pills. You should expect to have 4 menstrual periods per year.
6. Taking Indayo:
   - Take Indayo exactly as directed by your healthcare professional.
   - Take your pill at approximately the same time every day. Try to associate taking your pill with a regular activity like eating a meal or going to bed. This will help you remember to take it.
   - Start taking Indayo the first Sunday after your period starts. If your period starts on Sunday, start that same day.
   - Take Indayo according to this schedule:
     - Take 1 pink pill each day for 84 days in a row. You should always begin a pack by starting with the pink colored pills. You should always take the pink colored pills first.
     - Then, take 1 white pill for 7 days in a row.
     - Start the next pack on the day after your last white pill. Do not wait any days between packs.

- Be sure to take all the pills in each pack.
- Do not skip any of the pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach.
- Do not skip pills even if you do not have sex very often.
- Use another barrier method of birth control (such as a condom) for the first 7 days of your first cycle of Indayo.

Indayo may not work as well as it should to prevent pregnancy if you:

- miss pills
- don't take your pills as directed by your healthcare professional
- have gastrointestinal problems such as vomiting or diarrhea
- are taking certain medicines

If this happens, you should use another method of birth control, like condoms (barrier method). Do this while taking Indayo and until you start a new pack of Indayo. Talk to your healthcare professional if you are not sure.

You might notice bleeding or spotting during the first few months of taking Indayo. Do not stop taking your pills even if you have irregular bleeding. If the bleeding lasts for more than a few days, talk to your healthcare professional.

If you do not get your period when you are taking the white pills, talk to your healthcare professional. You might be pregnant.

Usual dose:

Take 1 pink pill a day. When all 84 pink pills are done, take 1 white pill a day for 7 days.

Overdose:

Symptoms of overdose may include:

- nausea
- vomiting
- breast tenderness
- dizziness
- abdominal pain
- drowsiness, fatigue
- vaginal bleeding.

If you think you, or a person you are caring for, have taken too much Indayo, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss pink coloured pills, you could get pregnant. The more pink pills you miss, the more likely you are to get pregnant. If you miss one or more pink coloured pills and do not have a period that month, you may be pregnant. If this happens, talk to your healthcare professional.

Missing pills can cause spotting or light bleeding, even when you make up these missed pills.

If you forget more than one pill two months in a row, talk to your healthcare professional about ways to make pill-taking easier or about using another method of birth control.

Always be sure to have on hand a back-up method of birth control. These are types that do not include hormones, like latex or polyurethane condoms and spermicidal foam or gel. You will need back-up birth control if you miss pills and in some other situations. Always talk to your healthcare professional if you are not sure whether you need to use back-up birth control.

If you **MISS 1** pink pill:

1. Take the missed pill as soon as possible and take the next pill at the usual time. This means you take 2 pills in 1 day. On the days you take 2 pills to make up for the missed pill, you could feel a little sick to your stomach.
2. Keep taking 1 pill a day until the pack is finished.

If you **MISS 2** pink pills in a row:

1. Take 2 pills on 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 barrier method of birth control (such as condoms or spermicide) if you have sex in the 7 days after you miss the pills.

If you **MISS 3 OR MORE** pink pills in a row:

1. Do not remove the missed pills from the pack as they will not be taken. Keep taking 1 pill every day as indicated on the pack until you have completed all of the pills in the pack. For example: if you resume taking the pill on Thursday, take the pill under “Thursday” and do not take the previous missed pills. You may experience bleeding during the week following the missed pills.
2. Use a back-up barrier method of birth control (such as condoms or spermicide) if you have sex in the 7 days after you miss the pills. **If you miss your period when you are taking the white pills, you might be pregnant. Talk to your healthcare professional right away.**

If you **MISS ANY** of the 7 white pills:

1. Safely dispose of the pills you missed.
2. Keep taking 1 pill each day until the pack is empty.
3. You do not need to use a back-up barrier method of birth control.

If you are not sure about the number or the colour of pills missed:

Talk to your healthcare professional right away.

What are possible side effects from using Indayo?

These are not all the possible side effects you may have when taking Indayo. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects may occur:

- bleeding or spotting between periods
- nausea, vomiting, feeling sick to the stomach
- abdominal cramps, bloating
- changes in weight, changes in appetite
- breast tenderness
- difficulty wearing contact lenses
- darkening of the skin (particularly on the face)
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc.)
- flu-like symptoms (fever, cough, sore throat, runny nose, feeling tired)
- urinary tract infection or inflammation
- vaginal infection
- diarrhea
- changes in libido
- abdominal cramps
- bloating
- constipation
- muscle cramps, muscle spasms
- neck pain, joint pain, back pain
- acne, aggravated acne
- fluid retention
- headache
- nervousness
- dizziness
- insomnia
- loss of scalp hair

Some of these side effects, especially bleeding or spotting, nausea, vomiting, and feeling sick to the stomach may subside within the first 3 months of use. If the problem doesn't go away, talk to your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Blood clot in the eye: sudden partial or complete loss of vision			**X**
Breast changes (breast lumps/breast cancer): pain and tenderness, lumps, nipple discharge		**X**	
Deep vein thrombosis (blood clot in the leg): swelling of one leg or one foot, pain or tenderness in the leg, difficulty standing or walking, feeling of warmth in the leg, red or discoloured skin on the leg, sudden pain, swelling and slight blue discolouration of an extremity			**X**
Depression (sad mood that won't go away)**:** difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse.			**X**
Edema: unusual swelling of extremities		**X**	
Gallbladder disease: nausea, vomiting, pain on the upper right side of the abdomen,		**X**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
especially after meals, loss of appetite, fever			
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations			**X**
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, itching all over your body			**X**
Liver tumor: abdominal pain, nausea or vomiting or lump in the abdomen		**X**	
Myocardial infarction (heart attack): pressure or squeezing pain in the chest, jaw, left arm, between the shoulder blades or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			**X**
Pulmonary embolism (blood clot in the lung): sharp chest pain, coughing of blood, sudden shortness of breath			**X**
Stroke: sudden, severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness or numbness in an arm or leg			**X**

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Unexpected vaginal bleeding		**X**	
UNKNOWN FREQUENCY			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			**X**

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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.

Storage:

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children and pets.

If you want more information about Indayo:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the importer / distributor's website www.sandoz.ca, or by calling 1-800-361-3062.

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