PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]MINESTRIN® 1/20
(Norethindrone Acetate [NA] and Ethinyl Estradiol [EE] Tablets, USP)

1 mg NA and 20 mcg EE Tablets

Oral Contraceptive

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RECENT MAJOR LABEL CHANGES

CONTRAINDICATIONS (2)	12-2019
DRUG INTERACTIONS, Drug Interactions (9.2)	12-2019
WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic (7)	12-2019

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MINESTRIN® 1/20 is indicated for the control of conception.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

MINESTRIN® is contraindicated in 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 Dosage Forms, Strengths, Composition and Packaging.

MINESTRIN® 1/20 is contraindicated in patients with any of the following disorders:

- a history of or actual thrombophlebitis or thromboembolic disorders (such as deep vein thrombosis or pulmonary embolism);
- a history of or actual cerebrovascular disorders;
- a history of or actual myocardial infarction or coronary artery disease;
- valvular heart disease with complications;
- history of or actual prodromi of a thrombosis (e.g., transient ischaemic attack, angina pectoris);
- active liver disease, or history of or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia;
- undiagnosed abnormal vaginal bleeding;
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy;
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields;
- known or suspected pregnancy;
- current or history of migraine with focal aura;
- history of or actual pancreatitis if associated with severe hypertriglyceridaemia;
- presence of severe or multiple risk factor(s) for arterial or venous or thrombosis such as:
    - severe hypertension (persistent values of ≥160/100 mmHg)
    - uncontrolled hypertension
    - hereditary or acquired predisposition for venous or arterial thrombosis such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency,

hyperhomocysteinemia (e.g., due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
    - severe dyslipoproteinemia
    - over age 35 and smoke
    - diabetes mellitus with vascular involvement
    - major surgery associated with an increased risk of postoperative thromboembolism
    - prolonged immobilization
- Use with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir with or without dasabuvir (see WARNINGS AND PRECAUTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious cardiovascular events associated with the use of hormonal contraceptives. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, MINESTRIN® 1/20 should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

Patients should be counselled that birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV and AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

4 DOSAGE AND ADMINISTRATION

4.1 Recommended Dose and Dosage Adjustment

21-PILL PACK: One active tablet (white) is taken daily for three weeks, and then no tablets are taken for one week.

28-PILL PACK: One active tablet (white) is taken daily for three weeks, and then one inert tablet (lilac) is taken daily for one week.

For complete instructions, refer to Patient Medication Information section.

Safety and efficacy of MINESTRIN® 1/20 have been established in women of reproductive age and use of this product before menarche is not indicated. (See INDICATIONS).

4.2 Missed Dose

Please refer to Patient Medication Information section for details on missed dose.

5 OVERDOSAGE

In case of overdosage or accidental ingestion by children, the physician should observe the patient closely although no medication is required. Gastric lavage should be given if considered necessary.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

MINESTRIN® 1/20 is available in compact dispensers of 21 tablets (white) and 28 tablets (21 white tablets and 7 lilac inert tablets). Each white tablet contains 1 mg of norethindrone acetate and 20 mcg of ethinyl estradiol. Compact dispensers for MINESTRIN® 1/20 of 21 and 28 tablets are available in packages of 5.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	White Tablet 1 mg Norethindrone acetate 20 mcg Ethinyl estradiol	Acacia, Lactose monohydrate, Magnesium stearate, Modified corn starch, Sugar and Talc.
	Lilac Tablet (inert)	Acacia, FD Blue No. 1, FD&C Red No. 3, FD&C Red No. 40, Lactose monohydrate, Magnesium stearate, Modified corn starch, Sugar and Talc.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

Before MINESTRIN® 1/20 is 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 should be done 3 months after MINESTRIN® 1/20 is prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Workshop on screening for Cancer of the Cervix. For women who had 2 consecutive negative Pap smears, screening could be continued every 3 years up to the age of 69.

Discontinue medication at the earliest manifestation of:

A. **Thromboembolic and cardiovascular disorders,** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, proptosis and retinal thrombosis.
B. **Conditions which predispose to venous stasis and to vascular thrombosis** (eg, 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 Perioperative 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**

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

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

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

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

Carcinogenesis and Mutagenesis

Breast Cancer

Women who currently have or have had breast cancer should not use MINESTRIN® 1/20 because breast cancer is a hormonally-sensitive tumour (see **CONTRAINDICATIONS**).

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

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

Cervical Cancer
The most important risk factor for cervical cancer is persistent human papillomavirus infection. Some studies suggest that COC use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. For example, the results of one meta-analysis of 24 epidemiological studies indicated that among current users of oral contraceptives, the relative risk of invasive cervical cancer increased with increasing duration of use. The relative risk for 5 or more years' use versus never-use was 1.90 (95% confidence interval 1.69-2.13). The relative risk declined after use ceased and by 10 or more years was not significantly different from that in never-users. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

Hepatocellular Carcinoma
Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use (>8 years). However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small (<1 case/million users). A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs (See also Hepatic/Biliary/Pancreatic: *Hepatic nodules*).

Cardiovascular
Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive (OC) use in women who smoke.

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

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

Hypertension
COC use is contraindicated in women with uncontrolled hypertension (see **CONTRAINDICATIONS**

Patients with essential hypertension whose blood pressure is well controlled may be given MINESTRIN® 1/20, 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.

Driving and Operating Machinery
No studies on the effects of MINESTRIN® 1/20 on the ability to drive or use machines have been performed.

Endocrine and Metabolism
Diabetes
Current low-dose OCs 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 MINESTRIN® 1/20. 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 MINESTRIN® 1/20.

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

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

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

Genitourinary
Vaginal Bleeding
Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle when including all women and all cycles.

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

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

Venous Thromboembolism
The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts (following a 4-week or greater pill-free interval) the same or a different COC. Data from a large, prospective 3-armed

cohort study suggest that this increased risk is mainly present during the first 3 months. VTE is fatal in 1% to 2% of cases.

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

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

The risk of VTE with COCs has been shown to be related to the estrogen dose, as risk has decreased as doses have decreased from 100 µg to 50 µg to 30 µg. Whether doses as low as 10 µg are further protective is unknown. MINESTRIN® 1/20 provides a daily dose of ethinyl estradiol of 20 mcg for 21 of 28 days each cycle.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Arterial Thromboembolism
The risk for arterial thromboembolism (ATE) in users of oral contraceptives with <50 µg ethinyl estradiol ranges from about 1 to 3 cases per 10,000 woman-years. An ATE can include cerebrovascular accident, vascular occlusion, or myocardial infarction (MI). Arterial thromboembolic events may be fatal.

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (eg, due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant).

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

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

Hepatitis C
MINESTRIN® 1/20 must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see CONTRAINDICATIONS and DRUG INTERACTIONS). During clinical trials with ombitasvir, paritaprevir, ritonavir, with or without dasabuvir, ALT elevations 5 to >20 times the upper limit of normal (ULN) were significantly more frequent in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs. Physicians are advised to consult the labelling of concurrently-used HCV combination drug regimen ombitasvir, paritaprevir, ritonavir with or without dasabuvir to obtain further information about restarting MINESTRIN® 1/20.

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, which proves to cholestatic in type, the use of MINESTRIN® 1/20 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.

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

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

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

Monitoring and Laboratory Tests
Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (e.g., deep vein thrombosis, stroke, myocardial

infarction) at a young age. Breasts, liver, extremities and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

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

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 MINESTRIN® 1/20 and evaluation of the cause. Women with migraine headaches who take oral contraceptives may be at increased risk of stroke (see **CONTRAINDICATIONS**).

Ophthalmologic

Ocular Disease

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

Ocular Lesions

With use of COCs, there have been reports of retinal vascular thrombosis which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, MINESTRIN® 1/20 should be discontinued and the cause immediately evaluated.

Peri-Operative Considerations

There is an increased risk of thromboembolic complications in oral contraceptive users, after major surgery. If feasible, MINESTRIN® 1/20 should be discontinued and an alternative method substituted at least one month prior to MAJOR elective surgery. Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery.

Psychiatric

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

Renal

Fluid Retention

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

Sexual Health

Return to Fertility

After discontinuing MINESTRIN® 1/20 therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred, in order to date the pregnancy. An alternative contraceptive method should be used during this time.

Amenorrhea

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

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

Skin

Chloasma may occasionally occur with use of COCs, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs. Chloasma is often not fully reversible.

7.1 Special Populations

7.1.1 Pregnant Women

MINESTRIN® 1/20 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 breastfeeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low dose OCs are harmful to the nursing infant.

7.1.3 Pediatrics

Safety and efficacy of MINESTRIN® 1/20 have been established in women of reproductive age and use of this product before menarche is not indicated.

7.1.4 Geriatrics

MINESTRIN® 1/20 has not been studied in postmenopausal women and is not indicated in this population.

Non-Contraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.

2. Oral contraceptives reduce the likelihood of developing benign breast disease.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.
6. Other non-contraceptive benefits are outlined in the revised 1994 Report on Oral Contraceptives, Health Canada.

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:

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

The following 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: hemolytic uremic syndrome

Ear and labyrinth: auditory disturbances, otosclerosis-related hearing loss[a]

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

Gastrointestinal: abdominal pain, Crohn's disease[a], diarrhea, gastrointestinal symptoms (such as abdominal cramps and bloating), pancreatitis, ulcerative colitis[a]

General: edema

Hepatobiliary: cholestatic jaundice, gallstone formation[a], liver function disturbances[a]

Immune system: hypersensitivity

Infections and infestations: rhinitis, vaginal candidiasis, vaginitis,

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

Metabolism and nutrition: changes in appetite, hypertriglyceridemia (increased risk of pancreatitis when using COCs)[a], porphyria

Musculoskeletal and connective tissue: systemic lupus erythematosus[a]

Neoplasms benign, malignant and unspecified (incl cyst and polyps): increase in size of uterine leiomyomata

Nervous system: chorea, dizziness, headache, migraine, optic neuritis, Sydenham's chorea[a]

Psychiatric: changes in libido, mental depression, nervousness

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

Reproductive system and breast: amenorrhea during and after treatment, breakthrough bleeding, breast changes including tenderness, enlargement, and secretion, change in menstrual flow, dysmenorrhea, endocervical hyperplasias, possible diminution in lactation when given immediately post-partum, premenstrual-like syndrome, spotting, temporary infertility after discontinuance of treatment, vaginal discharge

Skin and subcutaneous tissue: chloasma or melasma which may persist, loss of scalp hair, hirsutism, erythema multiforme, erythema nodosum, hemorrhagic eruption, herpes gestationis[a], pruritis related to cholestasis[a], rash (allergic), urticaria

Vascular: hypertension[a], Raynaud's phenomenon

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

8.2 Clinical Trial Adverse Reactions

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

Adverse events reported in clinical trials of MINESTRIN® 1/20 at a frequency of ≥ 1% at cycles 1, 2, 3, 6, 9, 12, 18, 24, and Overall are shown in Table 1 below.

Table 1. Incidence of Adverse Reactions Reported at a Frequency of ≥ 1% of Patients with MINESTRIN® 1/20

Adverse Reactions	Incidence Rate (%)								
	1	2	3	6	9	12	18	24	Overall
Irregular Bleeding	44.99	36.10	31.97	26.53	22.69	23.41	20.36	25.40	27.45
Amenorrhea	0.00	5.66	5.33	6.21	4.70	6.52	6.10	6.14	5.75
Abdominal	7.31	5.19	5.19	3.64	2.99	3.56	2.91	1.06	3.68

Cramps/Pain									
Headache	6.56	3.75	3.55	3.52	2.69	0.94	2.18	2.65	3.11
Nausea	4.90	2.04	2.00	1.06	0.75	0.75	0.36	0.00	1.28
Backache	1.13	0.57	0.64	0.59	0.30	0.56	0.36	0.00	0.52
Dizziness	1.43	0.73	0.27	0.59	0.30	0.00	0.00	0.00	0.44

8.3 Less Common Clinical Trial Adverse Reactions

Adverse events reported in controlled clinical trials at a frequency of >0.2% to < 1% are shown in Table 2.

Table 2. Incidence of Adverse Reactions Reported at a Frequency of > 0.2% to < 1% of Patients with MINESTRIN® 1/20

Adverse Reactions	**Incidence Rate (%)**								
	1	***2***	***3***	***6***	***9***	***12***	***18***	***24***	***Overall***
Vaginal Discharge	0.75	0.98	0.64	0.82	0.30	0.94	0.00	1.06	0.62
Breast Soreness	0.68	0.57	0.64	0.23	0.60	0.56	0.00	1.06	0.43
Itching	0.45	0.33	0.55	0.59	0.60	0.37	0.00	1.06	0.42
Nervousness	0.90	0.49	0.18	0.35	0.30	0.00	0.00	0.53	0.38
Monilia Vaginitis	0.30	0.33	0.46	0.47	0.45	0.19	0.00	0.00	0.36
Fatigue	0.98	0.65	0.27	0.35	0.30	0.37	0.00	0.00	0.35
Leg Pain/Ache	0.38	0.65	0.46	0.35	0.45	0.19	0.00	0.00	0.25
Bloating	0.15	0.16	0.18	0.12	0.00	0.19	0.00	0.53	0.21

8.4 Post-Market Adverse Reactions

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
- Hypertension
- Benign hepatic tumors

- Gallbladder disease

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 less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Dysmenorrhea
- Amenorrhea during and after treatment
- Temporary infertility after discontinuation of treatment
- Edema
- Chloasma or melasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Endocervical hyperplasia
- Possible diminution in lactation when given immediately post-partum
- Cholestatic jaundice
- Migraine
- Increase in size of uterine leiomyomata
- Rash (allergic)
- Mental depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Premenstrual-like syndrome
- Intolerance to contact lenses
- Change in corneal curvature (steepening)
- Cataracts
- Optic neuritis
- Retinal thrombosis
- Changes in libido
- Chorea
- Changes in appetite
- Cystitis-like syndrome
- Rhinitis
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis

- Porphyria
- Impaired renal function
- Raynaud's phenomenon
- Auditory disturbances
- Hemolytic uremic syndrome
- Pancreatitis

9 DRUG INTERACTIONS

9.1 Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent. 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.

Refer to the revised 1994 Report on Oral Contraceptives, Health Canada, for possible drug interactions with OCs.

9.2 Drug-Drug Interactions

Table 3.
Drugs which may decrease the efficacy of oral contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry	For short course, use additional method or use another drug. For long course, use another method.
	Rifabutin Rifampin	Increased metabolism of progestins. 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.	
Anticonvulsants	Carbamazepine Ethosuximide	Induction of hepatic microsomal enzymes.	Use higher dose oral contraceptives (50 µg

Class of Compound	Drug	Proposed Mechanism	Suggested Management
	Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	ethinyl estradiol), another drug or another method.
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.
HCV Protease Inhibitors	Telaprevir	Uncertain, but may be due to an effect on GI transporters, leading to a decrease in the AUC of ethinyl estradiol.	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir. Additional methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir.
HIV Protease Inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Sedatives and Hypnotics	Barbiturates Benzodiazepines 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.
Other Drugs	Antihistamines Analgesics Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	
	Bosentan	Induction of hepatic microsomal enzymes.	Consider switching to a non-hormonal contraceptive method or

Class of Compound	Drug	Proposed Mechanism	Suggested Management
			adding a barrier method to oral contraceptive therapy

Table 4.
Modification of other drug action by oral contraceptives

Class of Compound	Drug	Modification of other drug action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another method
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another method. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-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.

Class of Compound	Drug	Modification of other drug action	Suggested Management
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.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other 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.

Class of Compound	Drug	Modification of other drug action	Suggested Management
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, 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 (eg, ritonavir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin and the potential to affect hepatic metabolism 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 inhibitors for further drug-drug interaction information.

Effects of Combined Oral Contraceptives on Other Drugs
COCs containing ethinyl estradiol such as MINESTRIN®1/20 may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Contraindicated co-administration
Ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (direct-acting antiviral medicinal products) have been shown to be associated with increases in ALT levels 5 to >20 times the upper limit of normal in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

9.3 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.

9.4 Drug-Laboratory Test Interactions

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

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

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

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

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

Glucose Tolerance
Oral glucose tolerance remained unchanged or was slightly decreased.

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

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MINESTRIN® 1/20 achieves its contraceptive effect primarily by inhibition of ovulation through gonadotropin suppression.

It is well established that oral contraceptives containing estrogen and progestogen affect hypothalamic, pituitary and ovarian functions. They may alter many other physiological systems. Although the exact mechanisms of action are incompletely understood, there is universal agreement that the inhibition of the “ovulatory peak” of luteinizing hormone (LH) is a constant and contributing factor. Oral contraceptives may exert their contraceptive action in at least 4 ways.

1. Alteration of the physical and chemical properties of the cervical mucus, thereby inhibiting sperm penetration.

2. Endometrial changes hindering implantation.

3. Inhibition of ovulation.

4. Subtle changes in the hypothalamic-pituitary-ovarian axis with possible altered corpus luteum function. The steroid profiles quite often indicate either an absence of or an insufficient luteal activity, or a significant and gradual decrease in several of the indices of luteal function.

Probably none of these factors alone accounts for the high degree of anti-fertility effect of any oral contraceptive. They may all play a part in the production of effective contraception.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C-25°C).

12 SPECIAL HANDLING INSTRUCTIONS

Keep out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

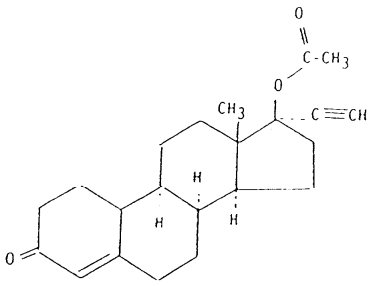
Drug Substance

Proper name: **Norethindrone Acetate**

Chemical name: 17-alpha-ethinyl-19-nortestosterone acetate ester

Molecular formula and molecular mass: $C_{22}H_{28}O_3$ and 340.07

Structural formula:



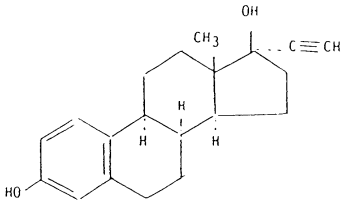
Physicochemical properties: A white solid with a melting point of 157° to 163°C, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water.

Proper name: **Ethinyl Estradiol**

Chemical name: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-

Molecular formula and molecular mass: $C_{20}H_{24}O_2$ and 296.41

Structural formula:



Physicochemical properties: A fine white, odourless crystalline powder, insoluble in water but soluble in vegetable oils and organic solvents.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Summary of Drug Experience for MINESTRIN® 1/20, 28-Day Regimen

Total Subjects Enrolled in Study	1431
Total Subjects Still Active	0
Total Study Days of Experience	430618
Total Cycles of Experience	15899
Number of Pregnancies	
Treatment Failure	4
Subject Failure	6
Pregnancies Per 100 Woman Years (Pearl Index)	
Therapeutic Effectiveness	0.30
Subject Failure	0.45
Use Effectiveness	0.75

Menstrual Cycle

Information on the incidence of spotting and bleeding is presented in Table 3.

Table 3. Percentage of Total Incidence

Effect	Cycle 1	Cycle 2	Cycle 3	Cycle 6	Cycle 12	Cycle 24	Overall
Intermenstrual							
Spotting	26.3	17.5	14.7	11.4	10.1	6.9	11.4
Light	19.3	16.5	14.6	12.8	12.7	14.8	13.1
Moderate	13.5	11.3	9.7	9.3	9.0	6.9	8.9
Heavy	5.0	3.0	2.7	2.7	2.6	1.6	2.3

Irregular Bleeding	44.9	36.1	31.9	26.5	23.4	25.4	27.4
Amenorrhea	0	5.6	5.3	6.2	6.5	6.1	5.7

Weight Changes

Information on weight changes is presented in Table 4.

Table 4. Summary of Weight Gain or Loss

Last Weight Data Available During	Decrease	No Change	Increase	Median Weight Change (lbs.)
	No. of Subjects (%)	No. of Subjects (%)	No. of Subjects (%)	
Cycle Interval 1-3	385 (35.84)	252 (23.46)	437 (40.68)	0.00
Cycle Interval 4-6	337 (40.31)	88 (10.52)	411 (49.16)	0.00
Cycle Interval 7-12	311 (42.60)	41 (5.61)	378 (51.78)	1.27
Last Cycle	177 (39.86)	31 (6.98)	236 (53.15)	1.60
Total	**1210 (39.23)**	**412 (13.35)**	**1462 (47.40)**	**1.10**

Approximately 47% of subjects gained weight, 39% lost weight and in 13% there was no weight change. The overall median weight change was 1.1 pounds.

Patient Drop Out

The largest number of patient drop out was 419 subjects or 29.2% due to loss of contact; 344 or 24.0% dropped because of adverse reactions. Irregular bleeding and amenorrhea headed the list of adverse reaction reasons for dropping from the study. Continuing in numerical sequence, 88 or 6.1% moved from the area of study, 60 or 4.1% dropped for personal reasons, 55 or 3.8% dropped to become pregnant, 55 or 3.7% changed method of contraception, 40 or 2.7% dropped for medical reasons, 22 or 1.5% dropped giving no reason and 3 subjects or 0.2% were pregnant before starting the study.

Cytology

Initial Papanicolaou smears were taken for almost all the subjects enrolled. Patients were selected at random to have updated Pap smears throughout the study. A total of 3075 Pap

smears were done during 57 cycles of observations. Over 97% of the Pap smears were classified within the normal range. There were 19 Grade III smears, 2 Grade IV, and 1 Grade V smears. Four reports were not specified. Overall, there were only three subjects who had a confirmed diagnosis of carcinoma-in-situe.

15 NON-CLINICAL TOXICOLOGY

Detailed Pharmacology

Both norethindrone (NET) and ethinyl estradiol (EE) have been subject to extensive biological examination over the past two decades. Norethindrone, using the Clauberg assay with rabbits, has been variously estimated to possess an oral progestational activity at least 10 times that of injected progesterone. Only slight estrogenic activity along with some androgenic activity (9% that of methyl testosterone) has been evident. Ethinyl estradiol has been demonstrated to be slightly more active than 17ß-estradiol using the vaginal cornification test in rats.

Norethindrone/ethinyl estradiol, in the ratio of 1.0/0.035, fed to female rats for 22 days at a daily dose of 0.15 mg/kg was effective in reducing the littering activity during a period of 15 days cohabitation with fertile males. Subsequent to the dosing period, these females regained their fertility.

Estrogenic, progestational and antigonadotropic characteristics are revealed for the endocrine profile of this combination. In female rats, a uterotropic effect is clearly demonstrated for a range of 0.1-0.4 mcg, total oral dose. In rabbits a McPhail index of 2.6 is recorded at a total oral dose of 0.8 mg of this progestogen/estrogen combination. At a total dose of 450 mcg (based on EE content) compensatory ovarian hypertrophy is completely inhibited in hemicastrate female rats.

Toxicity Studies of Norethindrone Acetate in Animals

The LD_{50} value of norethindrone acetate on intraperitoneal administration to rats was greater than 1000 mg per kg body weight. The drug produced no toxic effects or abnormalities when administered orally to dogs in a single 30 mg dose.

Administration of norethindrone acetate by the drug-diet method in rats over a period of 41 weeks produced depression in food intake and weight gain comparable to that following the use of norethindrone. Animals received average daily doses of 6, 14, and 27 mg per kg body weight.

Hematocrit, hemoglobin and leukocyte counts were not noticeably affected. Cholesterol values were low in all drug-fed animals, but all other microchemical determinations (minerals, transaminase, proteins, bilirubin, glucose and urea nitrogen) revealed normal values. Histologic examination of tissues showed functional depression of testes and seminal vesicles and atrophy of pituitary and adrenal glands at the two higher dosage levels. Liver cell atrophy and several deviations of a minor nature were also noted. Results indicated that the acetate is as well tolerated as norethindrone in continuous long-term use.

Long-Term Use of Norethindrone in Monkeys

Long-term oral administration of norethindrone to female rhesus monkeys produced only temporary changes in ovarian function. Six monkeys were treated for two years and 12 monkeys for one year at a dosage of 2.5 mg daily for 21 days of each cycle. This is comparable to a dosage of 25 mg daily for eight-and four-year periods in humans.

Extensive studies were conducted on the blood, bone marrow, and on the various other tissues and organs, particularly the ovaries. The only noteworthy differences between control and treated animals were found in the genital organs and the pituitary. The treated monkeys could

not be differentiated from control on the basis of general health, alertness, and behaviour. Bleeding usually started on the third or fourth day after discontinuation of drug administration each month, lasted three or four days, and was never heavy.

Ovaries from animals treated for one or two years were small, whitish with only small follicles visible, and no sign of recent rupture or of corpora lutea. Germinal epithelium was intact, and the layer of primordial ovocytes and young follicles appeared normal. Inside this cortical layer were small and medium-sized vesicular follicles and many corpora atretica, remnants of old follicles. Follicles had developed normally until the vesicular stage and then degenerated before attaining their full preovulatory growth. Ovocytes appeared normal in all stages of development until the last pre-ovulatory step when maturation was inhibited.

Uteri of treated monkeys had proliferative endometria with no decidual changes in the stroma. The vaginal tracts exhibited moderate to considerable epithelial cornification. Mammary glands were in the resting stage. Pituitaries of treated monkeys showed a decrease of basophilic cells.

Normal ovulatory cycles resumed shortly after medication was stopped. The sexual skin increased in redness, the vaginal epithelium became highly carnified during ovulation, and corpora lutea developed in the ovaries. The number and appearance of ova were normal, as was the rate of atresia. Endometria were proliferative or secretory.

The ability to conceive also returned. The conception rate in the treated group compared favourably with that in the control group. Babies of treated animals were all normal at birth, and the females developed normally.

In summary, it was concluded from these studies that continuous administration of norethindrone for periods of one and two years suppressed ovulation without permanent effects on ovarian function and fertility of monkeys.

Chronic Oral Toxicities in Monkeys

Chronic oral toxicity studies were conducted in 8 immature rhesus monkeys – 4 males and 4 females. Norethindrone was administered in the amount of 2.5 mg per kg daily, five days a week for 183 days. No gross or microscopic signs of drug toxicity were found from blood studies, biopsies or at autopsy. As might be anticipated, testicular atrophy occurred in the males. There was also evidence of hormonal stimulation of the sexual skin and mammary glands of both sexes and of the uterine mucosa in females.

Long-Term Oral Studies of the Combination

Dogs

A combination of 50 parts norethindrone acetate to one part ethinyl estradiol was administered orally for 7 years at dosage levels of 0.051, 0.51, and 1.275 mg/kg/day (equivalent to 1, 10 and 25 times the human dose) in 28-day cycles (21 days of drug administration followed by 7 days of drug withdrawal). Sixteen dogs were initiated as controls and at each dosage level.

All dogs were observed daily. Body weights were recorded weekly. Mammary examinations were conducted once each month. Ophthalmoscopic examinations (indirect technique) were done every six months. Clotting studies were conducted for all dogs twice during the control period, six times during the first year, and semiannually thereafter. Urinary steroid outputs were done once during the control period and annually thereafter.

One control dog and 9 treated dogs died or were sacrificed in extremis during the study. At the end of 7 years of study, the number of dogs surviving in each group was 15, 15, 14 and 10 at the control, 0.051, 0.51, and 1.275 mg/kg/day dosage levels, respectively.

One dog at the 0.051 and 0.51 mg/kg/day dosage levels, and 2 dogs at the 1.275 mg/kg/day dose levels were hysterectomized during the study.

At the end of 7 years of study, nodules were palpated in the mammary tissue of 5 control dogs, 5 dogs at the 0.051 mg/kg/day dosage level, 6 dogs at the 0.51 mg/kg/day level and 6 dogs at the 1.275 mg/kg/day level. Frequently, nodules disappeared after variable periods of time. Only rarely did nodules reach or exceed 10 mm in diameter, and commonly the behaviour of these indicated that they were cystic in nature.

Alopecia was seen more frequently for treated dogs than for control dogs. Red or brown vaginal discharge was seen most frequently for control dogs and dogs at the 0.051 mg/kg/day dosage level. It was rarely noted for dogs at the 0.51 and 1.275 mg/kg/day dosage levels following 18 months of study.

Treated dogs showed greater body weight gains than control dogs.

No changes considered to be related to treatment were seen in the mammary development, behaviour or in urinary steroid output.

Fibrinogen concentrations were somewhat greater for treated dogs than for control dogs during the 6^{th} and 7^{th} years of study. No other unusual changes were noted in clotting studies.

Ophthalmologic examinations revealed eye changes for several dogs in each group. No drug relationship was noted with respect to the occurrence of these changes.

Drug related gross lesions consisting of alopecia and enlarged and/or cystic uteri were observed in a number of dogs at terminal sacrifice. Organ weight effects were limited to increase in uterine weights of individuals in most experimental groups.

Microscopically, drug related changes included absence of ovulation in all dogs in the high-dose group and most dogs in the mid-dose group, and increased incidence and severity of cystic endometrial hyperplasia and uterine adenomyosis in dogs in the high dose group.

The occurrence of benign tumors in vaginas and uteri of several dogs in the high dose group was considered drug related.

Hyperplastic nodules and benign tumors occurred in mammary glands of dogs both in control and treated groups, but the incidence at the high-dose level was somewhat greater. No malignant mammary neoplasm occurred in any of the dogs in this study.

Monkeys

A combination of 50 parts of norethindrone acetate to one part ethinyl estradiol was administered orally to mature female rhesus monkeys in a long-term study for a period of 10 years at dosage levels of 0.051, 0.51, and 2.55 mg/kg/day (1, 10, and 50 times the human dose). The dosing regimen consisted of consecutive cycles of 21 days of drug administration followed by 7 days of drug withdrawal. Sixteen monkeys were assigned to each treatment group; while an additional 16 animals received the food vehicle only.

Daily observations of general health revealed no evidence of overt effects of drug treatment or significant changes in behaviour. The percent body weight gain of surviving animals was comparable, although the body weights of the treated groups were less than controls at some intervals.

Red vaginal discharge occurred with greater frequency in control and low-dose groups and was usually observed in the withdrawal phase of the mid-and high-dose groups, reflecting the pharmacologic action of the drug combination. No drug related alterations were noted in vaginal cytology or mammary development.

A retinal macular granularity, with and without foci of altered reflectivity, was noted in both control and treated animals beginning at 6 years. Although the incidence and severity of these alterations appeared to be greater in treated animals, no definite relationship to drug administration was considered to have been established.

Reduced total platelet count and increased fibrinogen concentrations were noted more frequently for treated monkeys during the initial 90 months and 48 months of study, respectively. An occasional animal showed an elevated postprandial glucose concentration, but no treatment or dosage relationship was apparent. No drug related alteration in urinary steroid output was observed.

Small nodules were palpable in or near the mammary tissue of five, four, three, and two monkeys in the control, 0.051, 0.51, and 2.55 mg/kg/day dosage groups, respectively, at least at one examination. Detailed physical examinations also revealed an abdominal mass in 2 control monkeys, slight curvature of the spine in 2 low-dose animals, and a pulsating saphenous vein in a high-dose animal.

No drug related gross lesions were seen in animals that died, were sacrificed in extremis during the study or were terminally sacrificed. A frequent cause of death in this study, which is a common occurrence in non-human primates, was acute gastric dilatation. The lesions observed at necropsy appeared spontaneous and unrelated to drug administration.

A statistically significant decrease ($p<0.05$) in the mean absolute uterine weight at the high-dose level was drug related.

Microscopically, drug related lesions included uterine atrophy, slightly increased incidence of occurrence of mucus and inflammatory cells in the cervical canal, and dilatation of acini and ducts in mammary glands of monkeys from the high-dose group, were considered to be related to the pharmacologic effect of the test combination.

No drug related neoplasms were observed in the study. A low overall incidence of neoplasms was seen in all organs and tissues examined. A total of 6 neoplastic microscopic lesions were noted during this entire study; an adenoma (pancreatic duct origin) in a low-dose animal; a granulosa cell carcinoma (ovary) in a control animal with metastasis to liver, lymph node, and lung; and a leiomyoma (uterus) and 2 papillomas (skin) in high-dose animals. With the exception of the granulosa cell carcinoma, no malignant neoplasms were identified.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrMINESTRIN® 1/20
Norethindrone Acetate [NA] and Ethinyl Estradiol [EE] Tablets, USP

Read this carefully before you start taking **MINESTRIN® 1/20** 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 **MINESTRIN® 1/20**

Serious Warnings and Precautions

Smoking

Cigarette smoking increases the risk of serious heart and blood vessel problems. This risk increases as you get older, particularly once you are 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 MINESTRIN® 1/20.

Sexually Transmitted Infections

Birth control pills, including MINESTRIN® 1/20, do not protect against sexually transmitted infections (STIs), including HIV and AIDS. To protect yourself against STIs, use latex or polyurethane condoms when you have sex and take your birth control pills.

What is MINESTRIN® 1/20 used for?

MINESTRIN® 1/20 is used to prevent pregnancy.

MINESTRIN® 1/20 is a birth control pill. It is considered to be a combination oral contraceptive. This is because it contains two female sex hormones: norethindrone acetate and ethinyl estradiol. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your healthcare professional.

How does MINESTRIN® 1/20 work?

Combination birth control pills work in a few ways:

1. They stop the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).
3. Uterine changes that prevent pregnancy
4. Changes in the function of the corpus luteum (a hormone-producing structure in the ovaries)

Other ways to prevent pregnancy

There are other methods of birth control are available. They are usually less effective than birth control pills. If used properly, the other methods of birth control are effective enough for many women.

The following table lists pregnancy rates for different types of birth control. A pregnancy rate is 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	I 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 IUDs since they are implanted 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 MINESTRIN® 1/20?

Medicinal ingredients: norethindrone acetate and ethinyl estradiol
Non-medicinal ingredients: acacia, lactose monohydrate, magnesium stearate, modified corn starch, sugar and talc. In addition, for lilac tablets: FD Blue No. 1, FD&C Red No. 3, & FD&C Red No. 40

MINESTRIN® 1/20 comes in the following dosage forms:
MINESTRIN® 1/20 is available in compact dispensers of 21 tablets (white) and 28 tablets (21 white tablets and 7 lilac “reminder” tablets). Each white tablet contains 1 mg of norethindrone acetate and 20 mcg of ethinyl estradiol.

Do not use MINESTRIN® 1/20 if:

- you have or had a blood clot in the legs (deep vein thrombosis), lung (pulmonary embolism), eyes or somewhere else in your body;
- you have or had inflammation of a vein. This is called thrombophlebitis;
- you had a stroke or heart attack;
- you have coronary artery disease (including angina) or a condition that may be a first sign of stroke (such as ministroke or small reversible stroke);

- you have or had a disease of the heart valves with complications;
- you have liver disease (including hepatitis C) or have a history of liver tumours (cancerous or non-cancerous);
- you have or had jaundice. This is when 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 you think you have breast cancer, cancer of the endometrium (lining of the uterus) or a cancer that is sensitive to hormones;
- you have unusual vaginal bleeding without a known reason
- you have blood vessel disease of the eye that has caused loss of vision;
- you are pregnant or think you may be pregnant;
- you have or had migraine headaches;
- you have or had inflammation of the pancreas (pancreatitis) and high levels of fat in your blood (triglycerides);
- you have severe high blood pressure or high blood pressure that is not under control;
- you have a blood clotting disorder such as:
    - Factor V Leiden mutation,
    - Activated protein C (APC) resistance,
    - Protein C deficiency,
    - Protein S deficiency
    - Hyperhomocysteinemia
    - Prothrombin mutation G20210A
    - Antiphospholipid-antibodies
- you have diabetes with complications
- you have an unusual amount of lipoproteins in your blood;
- you are over age 35 and you smoke;
- you are scheduled for major surgery;
- you have or will have long periods where you are not mobile including prolonged bed rest;
- you are taking medicines to treat Hepatitis C called ombitasvir, paritaprevir, ritonavir, with or without dasabuvir. Using these drugs at the same time as MINESTRIN® 1/20 can cause problems with your liver, such as an increase in the ALT liver enzyme. You must finish your hepatitis C treatment first before starting MINESTRIN® 1/20. Your healthcare professional will tell you when to start, stop or restart MINESTRIN® 1/20 if you need to take these hepatitis C drugs.
- you are allergic to ethinyl estradiol, norethindrone acetate or to any of the other ingredients in MINESTRIN® 1/20.

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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MINESTRIN® 1/20 Talk about any health conditions or problems you may have, including if you:

- have a history of breast disease (such as breast lumps) or family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes

- have heart or kidney disease
- have a history of seizures or have epilepsy
- have a history of depression
- have cholestasis. This is a condition where the bile flow from the liver is decreased.
- wear contact lenses
- have uterine fibroids. These are benign tumours of the uterus;
- are under 18 years of age
- are in menopause
- have porphyria. This is a disease of blood pigment that is passed down in families (inherited)
- have systemic lupus erythematosus. This is a disease of the immune system that affects many organs of the body.
- have inflammatory bowel disease including Crohn's disease or ulcerative colitis
- have haemolytic uremic syndrome. This is when there is an abnormal breakdown of blood cells, which clogs the kidney.
- have sickle cell disease. This is a disease that affects hemoglobin, a molecule in red blood cells that delivers oxygen throughout the body.
- have problems with the valves in your heart and/or have an irregular heart beat
- have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, eyes or airway passages.

Other warnings you should know about:

If you and your healthcare professional decide that, for you the benefits of MINESTRIN® 1/20 outweigh the risks, you should be aware of the following:

<u>The Risks of Using Combination Birth Control Pills</u>

Blood clot in legs, lungs, heart, eyes or brain
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. 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 MINESTRIN® 1/20, if you have any of the below symptoms, contact your healthcare professional right away. These are signs of blood clots.

- sharp pain in your chest
- coughing up blood
- sudden shortness of breath
- pain and / or swelling in your calf
- crushing chest pain or chest heaviness
- sudden severe or worsening headache
- vomiting
- dizziness
- fainting
- changes in vision,
- changes in speech
- weakness or numbness in an arm or leg

- sudden pain, swelling and slight blue discoloration of an arm or leg

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 MINESTRIN® 1/20, 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, or
- Any lumps you can see or feel.

Cervical cancer
Women who use birth control pills may have a higher chance of getting cervical cancer. However, this may be due to other reasons including infection with the Human Papilloma Virus (HPV). HPV is an important risk factor for cervical cancer. However, it is possible that oral birth control pills may also cause such cancers.

Liver cancer
Liver cancer (hepatocellular carcinoma) and liver tumours may be linked to oral birth control pills. The risk for liver cancer increases the longer these pills are used. However liver tumours are extremely rare. If you feel severe abdominal pain or find a lump in your abdomen, contact your healthcare professional right away.

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.

Use after pregnancy, miscarriage or an abortion
You will be at increased risk for blood clots. Your healthcare professional will advise you of the appropriate time to start the use of MINESTRIN® 1/20 after childbirth, miscarriage or therapeutic abortion.

Pregnancy after stopping MINESTRIN® 1/20
You will have a menstrual period when you stop using MINESTRIN® 1/20. Wait until after your next period before getting pregnant. This will help to better date the pregnancy. Speak to your healthcare professional about other forms of birth control you can use during this time.

Use while breastfeeding
If you are breastfeeding, talk to your healthcare professional before starting MINESTRIN® 1/20.

Other types of birth control, instead of a birth control pill, are recommended until your baby has stopped breastfeeding. 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 nursing is established.

Skin conditions
Chloasma may develop while you are using MINESTRIN® 1/20. 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 MINESTRIN® 1/20. Sunlight contains invisible rays (ultraviolet light) that can burn the skin.

Surgery or medical treatment
Be sure to tell your healthcare professional if you are scheduled for surgery or other medical treatment. You may need to stop using MINESTRIN® 1/20 four weeks before surgery. You may need to wait until after your first period following surgery before restarting MINESTRIN® 1/20.

Check-ups and tests
Before starting MINESTRIN® 1/20, you will need to have examinations and tests. Your healthcare professional will conduct a physical exam. He or she will examine your breasts, liver, arms and legs and will conduct a pelvic exam. Your healthcare professional will also ask you some questions about your personal health history and that of your close relatives. He or she will also measure your blood pressure and do blood tests.

While you are taking MINESTRIN® 1/20, you will need to have regular check-ups with your healthcare professional. Your first check up should be about three months after starting MINESTRIN® 1/20.

Afterward, you will see your healthcare professional about once per year. At these visits, your healthcare professional will conduct physical and internal exams. He or she will also measure your blood pressure and do blood tests.

If you are scheduled for any laboratory tests, be sure to tell your healthcare professional that you are taking MINESTRIN® 1/20. This is because birth control pills can affect some blood tests.

Certain medicines may interact with combination birth control pills and prevent them from working properly. This makes them less effective in preventing pregnancy or causing unexpected bleeding (spotting or breakthrough bleeding).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Also tell any doctor or dentist (or the dispensing pharmacist) who prescribes another medicine that you use MINESTRIN® 1/20. They can tell you if you need to use a back-up method of birth control and if so, for how long.

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

The following may interact with MINESTRIN® 1/20:

- medicines to treat epilepsy (including primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate)
- medicines to treat tuberculosis (including rifampicin, rifabutin)
- medicines used to treat HIV infections (including ritonavir)
- medicines for Hepatitis C virus (HCV) (including ombitasvir, paritaprevir/ritonavir, with or without dasabuvir, telaprevir)
- medicines to treat bacterial infections (including penicillins, tetracyclines, metronidazole)
- medicines to treat fungal infections (including griseofulvin)
- medicines to lower cholesterol (including clofibrate)
- medicines to prevent blood clots
- St. John's wort, an herbal product used to treat depression and other conditions
- medicines to treat high blood pressure including guanethidine, methyldopa, beta blockers, reserpine;
- medicines to treat diabetes including insulin and oral drugs that lower blood sugar;
- medicines to lower the immune system including prednisone and cyclosporine
- medicines to help you relax or sleep including benzodiazepines, chlordiazepoxide, lorazepam, oxazepam, diazepam, phenothiazines, reserpine, barbiturates, chloral hydrate, glutethimide, meprobamate
- medicines to help with pain medication (including meperidine)
- medicines to treat depression (including clomipramine)
- other medicines such as phenylbutazone, antihistamines and medicines used to treat migraines
- some nutritional supplements (including Vitamin E and Vitamin B12)
- antacids (use 2 hours before or after taking MINESTRIN® 1/20)
- a medicine to help treat bleeding called aminocaproic acid;
- medicines to treat lung diseases such as asthma and COPD (bronchitis, emphysema) including theophylline;
- medicines to slow the heart rate including isoproterenol;
- medicine to treat high blood pressure in the blood vessels between the heart and the lungs (pulmonary hypertension) including bosentan;

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

This is not a complete list of possible drug interactions with MINESTRIN® 1/20. Talk to your healthcare professional for more information about interactions with other medicines.

How to take MINESTRIN® 1/20:

1. **Read these Instructions:**

   - Before you start taking your pills, and
   - Any time you are not sure what to do

2. **Look at your pill pack to see if it has 21 or 28 pills:**

   - 21-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then no pills for one week.

     or

   - 28-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

3. You can use a second method of birth control (e.g., latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will help as a back up in case you forgot to take your pills.

4. When you get any medical treatment, tell your healthcare professional that you are using birth control pills.

5. **Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months taking birth control pills**. If you do feel sick, do not stop taking MINESTRIN® 1/20. The problem will usually go away. If it does not go away, check with your healthcare professional or clinic.

6. **Missing pills can also cause some spotting or light bleeding**, even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

7. **Do not stop taking MINESTRIN® 1/20 or skip any pills even if you are sick to your stomach, have bleeding between your periods or do not have a lot of sex.**

8. **If you miss pills at any time, you could get pregnant. The greatest risks for pregnancy are**:

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

9. **Always be sure you have ready**:

   - **Another kind of birth control** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
   - **An extra full pack of pills.**

10. **If you have vomiting or diarrhea, or if you take certain medicines**, such as antibiotics, MINESTRIN® 1/20 may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your healthcare professional or clinic.

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

12. **If your questions are not answered here, call your healthcare professional or clinic**.

Usual dose:

Decide with your healthcare professional or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-Day or a 28-Day type.

Label the pill pack by selecting the correct day label strip: **Day 1** or **Sunday** start (see below for explanation). Place the day label strip in the space where you see the words "Place Day Label Here". Labelling the dispenser with the days of the week will help remind you to take your pill every day.

A. MINESTRIN® 1/20 21-Day Pill Pack

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

1. **The first day of your menstrual period (bleeding) is Day 1 of your cycle**. Your healthcare professional may tell you to start taking MINESTRIN® 1/20 on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. MINESTRIN® 1/20 is recommended for a Day 1 start.

    - On the day you have been told to start taking MINESTRIN® 1/20, take the first pill in the top row (where you see the word "start"). The day on the day label on top of the first pill should match the day of the week you are starting on. To remove the pill, push it through the back of the compact dispenser.

    - On the following day, take the next pill in the row, always from left to right. Each new row will always begin on the same day of the week.

2. Take one pill at around the same time every day for 21 days. Try to link taking MINESTRIN® 1/20 with a regular activity such as eating a meal or going to bed.

3. **Then, do not take any pills for seven days**. You will probably have a period during the seven days you do not take MINESTRIN® 1/20. This bleeding may be lighter and shorter than your usual period.

4. Start a new pack on the eighth day.

B. MINESTRIN® 1/20 28-Day Pill Pack

With this type of birth control pill, you take 21 pills, which contain hormones, and seven "reminder" pills, which contain no hormones.

1. **The first day of your menstrual bleeding (period) is Day 1 of your cycle.**

   Your healthcare professional may advise you to start taking MINESTRIN® 1/20 on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. MINESTRIN® 1/20 is recommended for a Day 1 start.

   - On the day you have been told to start taking MINESTRIN® 1/20, take the first pill in the top row (where you see the word "start"). The day on the day label on top of the first pill should match the day of the week you are starting on. To remove the pill, push it through the back of the compact dispenser.

   - On the following day, take the next pill in the row, always from left to right. Each new row will always begin on the same day of the week.

2. Take one pill at around the same time every day for 28 days. Try to link taking MINESTRIN® 1/20 with a regular activity such as eating a meal or going to bed. Your period should occur during the last seven days of using that pill pack (i.e. while you are taking the lilac "reminder" pills).

3. Begin a new pack the next day. **Do not miss any days.**

Overdose:

If you think you have taken too much MINESTRIN® 1/20, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

The following chart explains what you should do if you miss one or more of your birth control pills on a Day 1 start. If you are not using a Day 1 start, check with your healthcare professional or clinic.

Day 1 Start
Miss 1 Pill Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.
Miss 2 Pills in a Row **First 2 Weeks:** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a backup (barrier) method of birth control if you have sex in the 7 days after you miss the pills. **Third Week:** 1. Throw away the pills you missed and start a new pack that same day. 2. Use a backup method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss 2 periods in a row, call your healthcare professional.**
Miss 3 or More Pills in a Row **Anytime in the cycle:** 1. Throw away the pills you missed and start a new pack that same day. 2. Use a backup method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss 2 periods in a row, call your healthcare professional.**

28-Day Pill Pack: If you forget any of the seven lilac “reminder” pills (without hormones) in Week 4, just throw away the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a backup method.

What are possible side effects from using MINESTRIN® 1/20?

These are not all the possible side effects you may feel when taking MINESTRIN® 1/20 If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- breast tenderness
- change in appetite
- changes in sex drive (libido)
- difficulty wearing contact lenses
- dizziness
- headache, severe headache, migraine
- problems with hearing
- cold fingers or toes (also known as Raynaud's disease)
- runny or stuffy nose
- increase or decrease in hair growth
- irregular bleeding
- lack of a period or breakthrough bleeding, bleeding between periods, spotting
- nausea
- nervousness
- uncontrolled movement of the arms or legs (also called chorea)
- painful menstrual cramps
- change in menstrual flow
- skin pigmentation changes
- stomach cramps/pain
- urinary tract (bladder) infections or inflammation
- vaginal irritation or infections
- vaginal pain or discharge
- temporary change in the ability to get pregnant after stopping the pills
- changes in the size of benign tumours (also called fibroids) on the uterus
- vomiting
- bloating
- not able to have as much carbohydrates
- weight gain

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 **Pulmonary embolism** (Blood clot in the lung): sharp pain in the chest, coughing blood, sudden shortness of breath			√
Deep vein thrombosis (Blood clot in the leg): pain in the calf, swelling, redness, skin feeling “warm to the touch”			√

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	
Myocardial Infarction (Heart attack): crushing chest pain or heaviness, heartburn, shortness of breath, nausea, cold sweat, dizziness			√
Stroke: sudden severe or worsening headache, vomiting, dizziness, fainting, vision or speech problems, weakness or numbness in the arm or leg			√
Blood clot on the eye: sudden partial or complete loss of vision or double vision			√
Liver problems including liver tumour: abnormal liver test, yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or lump in the abdomen, loss of appetite			√
Depression: persistent sad mood accompanied by difficulty in sleeping, weakness, lack of energy, fatigue			√
Edema: swelling of the arms or legs		√	
Breast changes (breast lumps/breast cancer): pain and tenderness, lumps, nipple discharge		√	
Jaundice: Yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine, or light-coloured bowel movements		√	
Unexpected (abnormal) vaginal bleeding		√	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad

enough to interfere with your daily activities, talk to 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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Store at room temperature (15°C-25°C).

Keep out of reach and sight of children.

If you want more information about MINESTRIN® 1/20:

- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.allergan.ca, or by calling 1-800-668-6424

This leaflet was prepared by Allergan Inc.

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