

# **PRODUCT MONOGRAPH**

**PrMINESTRIN® 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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## PrMinestrin® 1/20

(Norethindrone Acetate [NA] and Ethinyl Estradiol [EE] Tablets, USP)

### PART I: HEALTH PROFESSIONAL INFORMATION

#### INDICATIONS AND CLINICAL USE

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

#### 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.

#### CONTRAINDICATIONS

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

- History of/or actual thrombophlebitis or thromboembolic disorders
- History of/or actual cerebrovascular disorders
- History of/or actual myocardial infarction or coronary arterial disease
- Active liver disease or history of/or actual benign or malignant liver tumors
- Known or suspected carcinoma of the breast
- 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
- When pregnancy is suspected or diagnosed

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

**Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive users over 35 years of age. Women should be counseled not to smoke.**

**Oral contraceptives DO NOT PROTECT against sexually transmitted diseases (STDs) including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms IN COMBINATION WITH oral contraceptives.**

### 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.

### 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 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.

## **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.

### **Discontinue medication at the earliest manifestations of the following:**

- A. Thromboembolic and cardiovascular disorders, such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
- B. Conditions which predispose to venous stasis and to vascular thrombosis, e.g., immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **Peri-Operative Considerations**.
- C. Visual defects, partial or complete.
- D. Papilledema or ophthalmic vascular lesions.
- E. Severe headache of unknown etiology or worsening of pre-existing migraine headache.

## **Hypertension**

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.

## **Endocrine and Metabolism**

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.

## **Genitourinary**

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

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

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

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

## **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.

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

Patients, who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given MINESTRIN 1/20 with great care and under close observation.

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

If a patient develops jaundice, which proves to be 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.

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.

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.

## **Neurologic**

The onset or exacerbation of migraine or the development of headache of a new pattern, which is recurrent, persistent or severe, requires discontinuation of MINESTRIN 1/20 and evaluation of the cause.

## **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, 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.

## **Sexual Function/Reproduction**

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.

## **Special Populations**

### **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.

## **Nursing Women:**

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.

## **Monitoring and Laboratory Tests**

Results of laboratory tests should be interpreted in the light that the patient is on OCs. The following laboratory tests are modified:

- **Liver Function Tests:** Aspartate serum transaminase (AST) – variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) – slightly elevated.
- **Coagulation Tests:** Minimal elevation of test values reported for such parameters as Factors VII, VIII, IX, and X.
- **Thyroid Function Tests:** Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T<sub>3</sub> resin uptake.
- **Lipoproteins:** Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.
- **Gonadotropins:** LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of MINESTRIN 1/20 before measurements are made.

Pathologists should be advised of MINESTRIN 1/20 therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

## **ADVERSE REACTIONS**

Adverse events reported in clinical trials of MINESTRIN 1/20 at a frequency of  $\geq 1\%$  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  $\geq 1\%$  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 Cramps/Pain	7.31	5.19	5.19	3.64	2.99	3.56	2.91	1.06	3.68
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

### **Less Common Clinical Trial Adverse Drug 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

### **Post-Market Adverse Drug 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

## **DRUG INTERACTIONS**

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.

## **DOSAGE AND ADMINISTRATION**

**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 **Part III: Consumer Information** (under Usual Dose).

## **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 suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTIONS AND CLINICAL PHARMACOLOGY**

### **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.

### **DOSAGE FORMS, 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.

## PART II: SCIENTIFIC INFORMATION

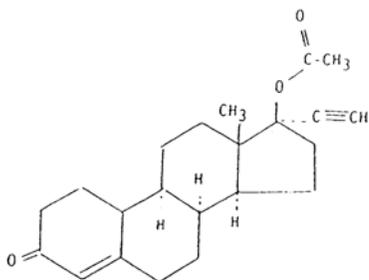
### PHARMACEUTICAL INFORMATION

#### Drug Substance

##### **Proper name: Norethindrone Acetate**

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

Molecular Formula and Molecular Weight:  $C_{22}H_{28}O_3$  and 340.07

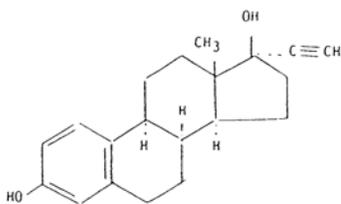


Physicochemical properties: A white solid with a melting point of 157° to 163°C, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water.

##### **Proper name: Ethinyl Estradiol**

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

Molecular Formula and Molecular Weight:  $C_{20}H_{24}O_2$  and 296.41



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

## CLINICAL TRIALS

### 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
<u>Number of Pregnancies</u>	
Treatment Failure	4
Subject Failure	6
<u>Pregnancies Per 100 Woman Years (Pearl Index)</u>	
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**

<b>Last Weight Data Available During</b>	<b>Decrease</b>	<b>No Change</b>	<b>Increase</b>	<b>Median Weight Change (lbs.)</b>
	<b>No. of Subjects (%)</b>	<b>No. of Subjects (%)</b>	<b>No. of Subjects (%)</b>	
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
<b>Total</b>	<b>1210 (39.23)</b>	<b>412 (13.35)</b>	<b>1462 (47.40)</b>	<b>1.10</b>

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.

**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 17β-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 uterotrophic 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.

## **TOXICOLOGY**

### **Toxicity Studies of Norethindrone Acetate in Animals**

The LD<sub>50</sub> 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 cornified 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**

#### **A. 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<sup>th</sup> and 7<sup>th</sup> 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.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

Pr **MINESTRIN® 1/20**  
**Norethindrone Acetate and Ethinyl Estradiol**

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 with age and with the number of cigarettes smoked. It becomes important in women older than 35 years of age, who use hormonal birth control. For this reason, combination birth control pills, including **MINESTRIN 1/20**, should not be used by women who are over 35 years of age and smoke.

**Sexually Transmitted Infections**

Combination birth control pills, including **MINESTRIN 1/20**, **DO NOT PROTECT** against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, you must use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

**What is MINESTRIN 1/20 used for?**

**MINESTRIN 1/20** is used to prevent pregnancy.

**MINESTRIN 1/20** is a tablet, therefore it is known as a birth control pill or oral contraceptive. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your healthcare professional. Pregnancy is always more risky than taking birth control pills, except in smokers over 35.

**How does MINESTRIN 1/20 work?**

**MINESTRIN 1/20** is a combination birth control pill. It contains two female sex hormones norethindrone acetate and ethinyl estradiol. Combination birth control pills work in two 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).

**Other ways to prevent pregnancy**

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly, however, other methods of birth control are effective enough for many women. The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported pregnancies per 100 women per year

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

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

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort than many couples undertake successfully.

#### **Non-Contraceptive Benefits of Combination Birth Controls Pills**

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

- Reduction in the incidence of cancer of the uterus and ovaries.
- Reduction in the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and premenstrual syndrome (PMS).
- Acne, excessive hair growth and male hormone-related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

#### **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 have had:**

- allergy (hypersensitivity) to norethindrone acetate, ethinyl estradiol or any of the other ingredients in MINESTRIN 1/20 (see **What are the ingredients in MINESTRIN 1/20?**)
- unusual vaginal bleeding that has not yet been diagnosed
- blood clots in the legs, lungs, eyes or elsewhere, or inflammation of the veins (thrombophlebitis)
- a stroke, heart attack or heart disease (e.g. angina or chest pain) or a condition that may be the

first sign of a stroke (such as transient ischemic attack or small reversible stroke)

- loss of vision due to blood vessel disease of the eye
- problems with blood clotting that increases your risk for developing blood clots
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependant cancer
- liver tumor(s)
- jaundice (yellowing of the eyes or skin) or liver disease
- migraine headaches
- scheduled for major surgery
- prolonged bed rest
- you are pregnant or think you might be pregnant

**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:**

- smoke
- have a history of breast disease (e.g. breast lumps) or a family history of breast cancer
- have high blood pressure
- have high blood fat levels (triglycerides or cholesterol)
- have diabetes
- have heart or kidney problems
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver problems or jaundice
- have problems with your gallbladder or pancreas
- wear contact lenses
- have uterine fibroids (benign tumours of the uterus)
- are breastfeeding
- are unable to digest lactose or milk products, are on a lactose-free diet
- have a family history of blood clots, heart attacks or strokes

**Other warnings you should know about:**

If you see a different healthcare professional, inform him or her that you are using MINESTRIN 1/20.

Tell your healthcare professional if you are scheduled for any laboratory tests since certain blood tests may be affected by birth control pills, including MINESTRIN 1/20.

Tell your healthcare professional if you are scheduled for MAJOR surgery or if your ability to move around will be limited for a long period of time. In these cases, you should talk to your healthcare professional about stopping the use of MINESTRIN 1/20 four weeks before surgery and not using MINESTRIN 1/20 for a period of time after surgery or during bed rest.

MINESTRIN 1/20 should be used only under the supervision of a healthcare professional, with regular follow-up to check for side effects associated with its use. Your visits may include a blood pressure check, a breast exam and a pelvic exam, including a Pap smear. Visit your healthcare professional three months or sooner after the initial examination. Afterward, visit your healthcare professional at least once a year. You must use MINESTRIN 1/20 exactly as prescribed. Otherwise, you may become pregnant.

**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:**

### **The Risks of Using Combination Birth Control Pills**

#### **1. Circulatory problems (including blood clots in the legs, lungs, heart, eyes, or brain)**

Blood clots are the most common serious side effects of birth control pills. The risk of developing clots is high during the first year a woman uses a hormonal form of birth control. The risk is also higher if you restart a hormonal birth control (the same product or a different product) after a break of 4 weeks or more. Clots can occur in many areas of the body.

Seek immediate medical help if any of the following symptoms occur:

- Sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- Pain and/or swelling, redness, skin feeling “warm to the touch” in the calf. These symptoms could indicate a possible blood clot in the leg.
- Crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- Sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye.

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

Women who use hormonal birth control have a higher risk of developing blood clots. The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

#### **2. Breast cancer**

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

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

**Ask your healthcare professional for advice and instructions on how to perform regular breast self exams.**

#### **3. Cervical cancer**

Some studies have found an increase in cancer of the cervix in women who use hormonal birth control pills however; there is not enough evidence to say for sure that hormonal birth control does not cause these cancers.

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor

for cervical cancer. In women who use combination birth control pills for a long time the chance of getting cervical cancer may be slightly higher. This may not be caused by the birth control pill itself but may be related to sexual behavior and other factors.

#### **4. Liver tumors**

The short and long-term use of birth control pills has been linked with the growth of liver tumors or liver injury (hepatitis and problems with how the liver works). Such tumors are **EXTREMELY** rare.

Contact your healthcare professional immediately if you experience yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or a lump in the abdomen.

#### **5. Gallbladder disease**

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

#### **6. Use in pregnancy**

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

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

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

#### **8. Pregnancy after stopping MINESTRIN 1/20**

You will have a menstrual period when you stop using MINESTRIN 1/20. You should not get pregnant until another menstrual period occurs within four to six weeks. In this way, the pregnancy can be more accurately dated. Contact your healthcare professional for recommendations on alternate methods of birth control during this time.

#### **9. Use while breastfeeding**

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

Combination birth control pills can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established. Small amounts of oral contraceptive are present in breast milk.

**Certain medicines may interact with combination birth control pills and prevent them from working properly making 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.

The following may interact with MINESTRIN 1/20:

- medicines used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate)
- medicines used for the treatment of tuberculosis (e.g., rifampicin, rifabutin)
- medicines used for treatment of HIV infections (e.g., ritonavir)
- medicines used for Hepatitis C virus (HCV) (e.g., boceprevir, telaprevir)
- antibiotics used to treat bacterial infections (e.g., penicillins, tetracyclines, metronidazole)
- antifungals used to treat fungal infections (e.g. griseofulvin)
- medicines used to lower cholesterol (e.g. clofibrate)
- blood thinners used to prevent blood clots
- the herbal remedy St. John's wort used to treat depression
- medicines used to lower high blood pressure
- insulin and other medicines used to treat diabetes
- prednisone and cyclosporine used to suppress the immune system
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (e.g. clomipramine)
- other medicines such as phenylbutazone, antihistamines and medicines used to treat migraines
- some nutritional supplements (e.g. Vitamin E and Vitamin B12)
- antacids (use 2 hours before or after taking MINESTRIN 1/20)
- bosentan used to treat high blood pressure in the lungs

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 MINESTRIN 1/20, 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 may wish to use a second method of birth control (e.g., latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back up in case pills are forgotten while you are getting used to taking them.

4. When receiving any medical treatment, be sure to tell your 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 sex very often.**
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 Adult 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 appropriate 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”. Having the compact dispenser labeled 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 correspond to 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 proceeding from left to right. Each new row will always begin on the same day of the week.
2. Take one pill at approximately the same time every day for 21 days. Try to associate 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 correspond to 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 proceeding from left to right. Each new row will always begin on the same day of the week.
2. Take one pill at approximately the same time every day for 28 days. Try to associate 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.

<b>Day 1 Start</b>
<p><b>Miss 1 Pill</b> 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.</p>
<p><b>Miss 2 Pills in a Row</b></p> <p><b>First 2 Weeks:</b></p> <ol style="list-style-type: none"><li>1. Take 2 pills the day you remember and 2 pills the next day.</li><li>2. Then take 1 pill a day until you finish the pack.</li><li>3. Use a non-hormonal backup method of birth control if you have sex in the 7 days after you miss the pills.</li></ol> <p><b>Third Week:</b></p> <ol style="list-style-type: none"><li>1. Safely dispose of the rest of the pill pack and start a new pack that same day.</li><li>2. Use a non-hormonal backup method of birth control if you have sex in the 7 days after you miss the pills.</li><li>3. You may not have a period this month.</li></ol> <p><b>If you miss 2 periods in a row, call your healthcare professional.</b></p>
<p><b>Miss 3 or More Pills in a Row</b></p> <p><b>Anytime in the cycle:</b></p> <ol style="list-style-type: none"><li>1. Safely dispose of the rest of the pill pack and start a new pack that same day.</li><li>2. Use a non-hormonal backup method of birth control if you have sex in the 7 days after you miss the pills.</li><li>3. You may not have a period this month.</li></ol> <p><b>If you miss 2 periods in a row, call your healthcare professional.</b></p>

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

- irregular bleeding
- lack of a period or breakthrough bleeding, bleeding between periods
- painful menstrual cramps
- headache, severe headache, migraine
- dizziness
- nausea
- vomiting
- weight gain
- change in appetite
- difficulty wearing contact lenses
- breast tenderness
- vaginal irritation or infections
- urinary tract (bladder) infections or inflammation
- back pain
- nervousness
- skin pigmentation changes
- acne
- increase or decrease in hair growth
- changes in sex drive (libido)

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNCOMMON</b> <b>Blood clot in the lung:</b> sharp pain in the chest, coughing blood, sudden shortness of breath			√
<b>Blood clot in the leg:</b> pain in the calf, swelling, redness, skin feeling “warm to the touch”			√
<b>Heart attack:</b> crushing chest pain or heaviness, heartburn, shortness of breath, nausea, cold sweat, dizziness			√
<b>Stroke:</b> sudden severe or worsening headache, vomiting, dizziness, fainting, vision or speech problems, weakness or numbness in the arm or leg			√
<b>Blood clot on the eye:</b> sudden partial or complete loss of vision or double vision			√

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>Liver problems including liver tumour:</b> abnormal liver test, yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or lump in the abdomen, loss of appetite			√
<b>Depression:</b> persistent sad mood			√
<b>Edema:</b> swelling of the arms or legs		√	
<b>Breast changes (breast lumps/breast cancer):</b> pain and tenderness, lumps, nipple discharge		√	
Unexpected (abnormal) vaginal bleeding		√	
<b>Allergic reaction:</b> 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.

<p><b>Reporting Side Effects</b></p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> <li>• Visiting the Web page on Adverse Reaction Reporting (<a href="https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html">https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html</a>) for information on how to report online, by mail or by fax; or</li> <li>• Calling toll-free at 1-866-234-2345.</li> </ul> <p><i>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.</i></p>
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**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 (<https://www.canada.ca/en/health-canada.html>); the manufacturer's website [www.allergan.ca](http://www.allergan.ca), or by calling 1-800-668-6424.

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