PRODUCT MONOGRAPH

Pr **MOVISSE®**

Norethindrone Tablets, USP
0.35 mg

Oral Contraceptive

Mylan Pharmaceuticals ULC
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0.35 mg

PHARMACOLOGICAL CLASSIFICATION

Synthetic, steroidal oral contraceptive.

CLINICAL PHARMACOLOGY

The mechanism of contraception action of MOVISSE Tablets is multicausal, primarily at the local pelvic level and secondarily at the systemic level. The hormonal effect is mainly progestational.

Pelvic effects include changes in the cervical mucus and endometrium. Systemic effects involve mainly the inhibition of secretion of pituitary gonadotrophins which in turn prevents follicular maturation and ovulation.

Studies by Moghissi,[2,3,4] Beck,[5] Fortier and Lefebvre,[4,6] and others suggest the following priority of causes:

1. Inhibitory cervical mucus changes including increased viscosity and cell content, with inhibition of sperm transport or migration. Changes in cervical mucus reach their peak 3-4 hours after MOVISSE pill intake and the possibility of sperm penetration remains low for 16-19 hours.
2. Suppression of FSH levels and the LH surge.
3. Abnormal ovulation and deficient corpus luteum function. (Serum progesterone levels may be suppressed in the second half of the menstrual cycle when they are usually high, i.e. dysphasic.) Serum estrogens may be increased above normal early in the cycle.
4. Endometrial changes (progestational) unfavourable to implantation.

INDICATIONS AND CLINICAL USE

MOVISSE Tablets are indicated for conception control.

MOVISSE Tablets contain a low dosage of norethindrone without the addition of an estrogen agent. Progestin-only pills are often called "progestin-only pills" or the "mini-pill".

CONTRAINDICATIONS

Progestin-only pills should not be used by women who currently have the following conditions:

1. when pregnancy is suspected or diagnosed;
2. active liver disease or history of/or actual benign or malignant liver tumours;
3. known or suspected carcinoma of the breast;
4. undiagnosed abnormal vaginal bleeding;
5. hypersensitivity to any component of this product.

WARNINGS AND PRECAUTIONS

General

MOVISSE IS A PROGESTIN-ONLY PILL. THE COMBINED BIRTH CONTROL PILL (OR "THE PILL") CONTAINS BOTH AN ESTROGEN AND A PROGESTIN. THEREFORE, THIS PRODUCT MONOGRAPH DOES NOT DISCUSS THE SERIOUS HEALTH RISKS THAT HAVE BEEN ASSOCIATED WITH THE ESTROGEN COMPONENT OF COMBINED ORAL CONTRACEPTIVES.

When weighing the risk/benefit of oral contraceptive use, the physician should be familiar with the following conditions which may increase the risk of complications associated with oral contraceptive use:

- Current or past history of arterial/CV disease
- Benign or malignant liver tumor
- Acute or chronic hepatocellular disease with abnormal liver function
- Risk factors for arterial disease, e.g. smoking, hyperlipidemia, hypertension or obesity
- Migraine with focal aura
- Past ectopic pregnancy

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 counselled not to smoke.

Ectopic Pregnancy

The incidence of ectopic pregnancies for progestin-only oral contraceptive users is 5 per 1000 woman-years. Up to 10% of pregnancies reported in clinical studies of progestin-only only oral contraceptives users are extrauterine. Health providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain while on progestin-only oral contraceptives.

Delayed Follicular Atresia/Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally these enlarged follicles disappear spontaneously. Often they are asymptomatic; in some cases they are associated with mild abdominal pain. Rarely, they may twist or rupture, requiring surgical intervention.

Carcinoma of the Breast and Reproductive Organs

Some epidemiological studies of oral contraceptive users have reported an increased relative risk (RR=1.24) of developing breast cancer, particularly at a younger age and apparently related to duration of use. These studies have predominantly involved combined oral contraceptives and the hormonal contraceptives containing progesterone-only have not been widely used but there is data to determine that the use of POPs may also increase the risk.

A meta-analysis from 54 epidemiological studies reported that there is a small increase in the frequency of having breast cancer diagnosed in women who are currently using oral contraceptives (OCs) or had used them within the past 10 years compared to never-users. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Breast cancer is rare among women under 40 years of age whether or not they take OCs. While the background risk increases with age, the excess number of breast cancer diagnoses in current and recent progesterone-only pill (POP) users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in OC users, the biological effects of OCs or a combination of both.

The most important risk factor for breast cancer in POP users is the age women discontinue the POP; the older the age at stopping, the more breast cancers are diagnosed. Duration of use is less important and the excess risk gradually disappears during the course of the 10 years after stopping POP use.

The evidence suggests that compared with never-users, among 10,000 women who use POPs for up to five years but stop by age 20, there would be less than one extra case of breast cancer diagnosed up to 10 years afterwards. For those stopping by age 30 after 5 years use of the POP, there would be an estimated 2-3 extra cases (additional to the 44 cases of breast cancer per 10,000 women in this age group never exposed to oral contraceptives).For those stopping by age 40 after 5 years of use, there would be an estimated 10 extra cases diagnosed up to 10 years afterwards (additional to the 160 cases of breast cancer per 10, 000 never-exposed women in this age group).

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy.

Women receiving OCs should be instructed in self-examination of their breasts. They should notify their physicians whenever any masses are detected. A yearly clinical breast examination is also recommended.

It is important to inform patients that users of all contraceptive pills appear to have a small increase in the risk of being diagnosed with breast cancer, compared with non-users of oral contraceptives.

Women with breast cancer should not use oral contraceptives because the role of female hormones in breast cancer has not been fully determined.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of developing cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behaviour and other factors. There is insufficient data to determine whether the use of progestin-only pills increases the risk of developing cervical intraepithelial neoplasia.

Vaginal Bleeding

Irregular menstrual patterns are common among women using progestin-only oral contraceptives. If genital bleeding is suggestive of infection, malignancy or other abnormal conditions, such nonpharmacologic causes should be ruled out. If prolonged amenorrhea occurs, the possibility of pregnancy should be evaluated.

SEXUALLY TRANSMITTED INFECTIONS

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

Physical Examination and Follow-up

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

The first follow-up visit should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Workshop on Screening for Cancer of the Cervix. Their suggestion was that, for women who had two consecutive negative Pap smears, screening could be continued every three years up to the age of 69.

Hepatic Neoplasia

The incidence of both benign and malignant liver tumours (hepatic adenomas and hepatocellular carcinomas) is rare. Case-control studies have indicated that the risk of these tumours may increase in association with the use and duration of use of oral contraceptives. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. There is insufficient data to determine whether progestin-only pills increase the risk of developing hepatic neoplasia.

Migraine and Headache
The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

Carbohydrate and Lipid Metabolism
Some users may experience slight deterioration in glucose tolerance, with increases in plasma insulin, but women with diabetes mellitus who use progestin-only oral contraceptives do not generally experience changes in their insulin requirements. Nonetheless, prediabetic and diabetic women in particular should be carefully monitored while taking progestin-only pills.

Lipid metabolism is occasionally affected in that HDL, HDL_2, and apolipoprotein A-I and A-II may be decreased; hepatic lipase may be increased. There is usually no effect on total cholesterol, HDL_3, LDL, or VLDL.

Emotional Disorders
Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternative 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.

Special Populations

Pregnancy
MOVISSE ® is contraindicated during pregnancy. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the progestin contained in the oral contraceptive will damage the developing child.

Breast-feeding
In most women, progestin-only contraceptives, such as MOVISSE ®, do not affect the quantity and quality of breast milk or length of lactation. However, isolated post-marketing cases of decreased milk production have been reported. Studies with various orally administered progestin-only contraceptives have shown that small amounts of progestins pass into the breast milk of nursing mothers resulting in detectable steroid levels in infant plasma.

No adverse effects have been found on the health, growth or development of the infant.

Pediatrics (< 16 years of age):
Safety and efficacy of MOVISSE ® Tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics (> 65 years of age):
MOVISSE ® is not indicated for use in post-menopausal women.

Laboratory Tests

The following endocrine tests may be affected by progestin-only oral contraceptive use:

- Sex hormone-binding globulin (SHBG) concentrations may be decreased.
- Thyroxine concentrations may be decreased, due to a decrease in thyroid-binding globulin (TBG).

Results of laboratory tests should be interpreted in light of the fact that the patient is on oral contraceptives. LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made.

Tissue Specimens

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

Sexual Function/Reproduction

Return to Fertility

The limited available data indicate a rapid return of normal ovulation and no delay to fertility following discontinuation of progestin-only oral contraceptives.

Amenorrhea

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

DRUG INTERACTIONS

It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, including herbal preparations/remedies, before oral contraceptives are prescribed.

Some anti-epileptic drugs are known to induce or inhibit a number of hepatic enzymes in the cytochrome P450 system. See Table 1 for a list of drugs that may decrease the efficacy of MOVISSE.

Physicians are advised to consult the labelling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations and the possible need to adjust dosages.

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for other possible drug interactions with OCs which is adapted from Dickey RP, ed.: Managing Contraceptive Pill Patients, 5th edition, EMIS Inc. Medical Publishers 1987.

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

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	carbamazepine ethosuximide phenobarbital phenytoin primidone rufinamide	Induction of hepatic microsomal enzymes: Increased binding of progestin to SHBG.	Use higher dose OCs (50 mcg ethinyl estradiol), another drug or another method.
Antituberculosis	rifabutin rifampin	Increased metabolism of progestins.	Use another method.
Antifungals	griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
HIV Protease Inhibitors	nelfinavir ritonavir-boosted protease inhibitors darunavir (fos)amprenavir lopinavir	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	benzodiazepines barbiturates chloral hydrate glutethimide meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Other Drugs	bosentan	Induction of hepatic microsomal enzymes	Consider switching to a non-hormonal contraceptive method or adding a barrier method to oral contraceptive therapy.
	(fos)aprepitant	Induction of hepatic microsomal enzymes	Use another method

Significant changes (increase or decrease) in the plasma levels of norethindrone have been noted in some cases of co-administration of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors.

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.

ADVERSE REACTIONS

Adverse reactions reported with the use of progestin-only pills include:

- Menstrual irregularity is the most frequently reported side effect.
- Frequent and irregular bleeding is common, while long duration of bleeding episodes and amenorrhea are less likely.
- Headache, breast tenderness, nausea, and dizziness are increased among progestin-only oral contraceptive users in some studies.
- Androgenic side effects such as acne, hirsutism, and weight gain occur rarely.
- Decreased lactation has been reported very rarely.

Clinical Trial Adverse Drug Reactions

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

The safety of norethindrone tablets (0.35mg) was evaluated in 3099 subjects in two clinical trials. Of these, 2925 subjects participated in a clinical trial of norethindrone tablets (0.35mg) administered daily, and 174 subjects participated in a clinical trial of norethindrone tablets (0.35mg)/day administered on 21 days per cycle. Adverse drug reactions (ADRs) reported for ≥1% of norethindrone tablets (0.35mg)-treated subjects are shown in Table 2.

Table 2: Adverse Drug Reactions Reported by ≥1% of norethindrone tablets (0.35mg)-treated Subjects in Two Clinical Trials of norethindrone tablets (0.35mg)

System/Organ Class Adverse Reaction	**norethindrone tablets (0.35mg)** **%** **(N=3099)**
Nervous System Disorders	
Headache	5.6
Dizziness	1.8
Gastrointestinal Disorders	
Nausea	8.7
Vomiting	2.0
Reproductive System and Breast Disorders	
Metrorrhagia	34.3
Amenorrhea	5.4
Breast tenderness	1.3
General Disorders and Administration Site Conditions	
Fatigue	1.0
Investigations	
Weight increased	1.0

ADRs reported by <1% of norethindrone tablets (0.35mg) -treated subjects (N=3099) in the above clinical trials are shown in Table 3.

Table 3: Adverse Drug Reactions Reported by <1% of norethindrone tablets (0.35mg)-treated Subjects in Two Clinical Trials of norethindrone tablets (0.35mg)

System/Organ Class Adverse Reaction
Psychiatric Disorders
Depression
Nervousness
Gastrointestinal Disorders
Gastrointestinal Disorder
Skin and Subcutaneous Tissue Disorders
Acne
Hirsutism
Musculoskeletal and Connective Tissue Disorders
Pain in extremity
Reproductive System and Breast Disorders
Genital discharge
General Disorders and Administration Site Conditions
Edema

Post-Market Adverse Drug Reactions

Adverse drug reactions first identified during post-marketing experience with norethindrone tablets (0.35mg) are included in Table 4.

Table 4: Adverse Drug Reactions Identified During Post-Marketing Experience with norethindrone tablets (0.35mg) from Spontaneous Reporting

Immune System Disorders
Anaphylactic/Anaphylactoid reaction, Hypersensitivity
Gastrointestinal Disorders
Abdominal pain
Hepatobiliary Disorders
Hepatitis, Jaundice cholestatic
Skin and Subcutaneous Tissue Disorders
Alopecia, Rash, Rash pruritic
Pregnancy, Puerperium and Perinatal Conditions
Ectopic pregnancy
Reproductive System and Breast Disorders
Breast pain, Menstruation delayed, Menstruation irregular, Ovarian cyst, Suppressed lactation, Vaginal hemorrhage, Menorrhagia, Withdrawal bleed when product is stopped

TREATMENT OF OVERDOSE OR ACCIDENTAL INGESTION

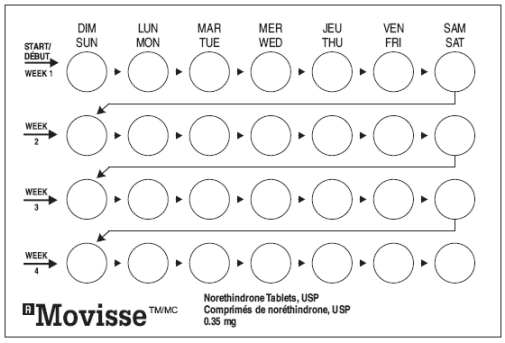
In case of overdose or accidental ingestion by children, the physician should observe the patient closely although generally no treatment is required.. There have been no reports of serious ill effects from overdosage. Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in females. There are no antidotes and treatment should be symptomatic.

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

DOSAGE AND ADMINISTRATION

MOVISSE® 28-Tablet Regimen:
The dosage of MOVISSE tablets is one tablet daily without interruption for 28 days.

28-Day Regimen Package



Starting Progestin-Only Pills

1. For the initial cycle of therapy, patients should start treatment from day 1† up to and including day 5 of their menstrual period. Then they should continue taking one tablet every day until their package is empty. Without missing a day, they should start taking MOVISSE from a new package.

† If the first progestin-only pill is taken on another day, it is recommended that an additional method of birth control (such as latex or polyurethane condoms and spermicidal foam or gel) be used every time the patient has sex during the next 48 hours.

2. If the patient has had a miscarriage or an abortion, she can start progestin-only pills the next day.

3. Patients should take one pill at the same time every day for 28 days. After finishing a pack, they should begin a new pack the next day, NOT MISSING ANY DAYS ON THE PILLS. Their period should occur during the last seven days of using the pill pack. MOVISSE tablets are taken every day, even when patients are having some menstrual bleeding.

Breast-feeding

1. For women who are fully breast-feeding (not giving their babies any food or formula), they may start taking MOVISSE tablets 6 weeks after delivery.
2. For women who are partially breast-feeding (giving their babies some food or formula), they should start taking MOVISSE tablets 3 weeks after delivery.

Switching Pills

1. To switch from 21-Day combined oral contraceptive pills to progestin-only pills, patients should start taking their first MOVISSE tablet (progestin-only pill) the day after they finish the last **active** combined pill.

   To switch from a 28-Day combined oral contraceptive regimen, patients should not take any of the 7 **inactive** pills from the combined pill pack.

   Many women have irregular periods after switching to progestin-only pills, but this is normal and to be expected.

2. For women who switch from progestin-only pills to combined pills, the first **active** combined pill is taken on the first day of their period, even if their progestin-only pill pack is not finished.

3. If the patient is breast-feeding, she can switch to another method of birth control at any time, except she should not switch to the combined pills until she has stopped breast-feeding or at least until 6 months after delivery.

Administration

It is recommended that MOVISSE tablets be taken at the same time every day until the pack is empty. Progestin-only pills must be taken at the same time every day since their action is time dependent.

When the pack is finished after 28 days, the next pack is started ON THE NEXT DAY. Women are not to wait any days between packs.

Vomiting and/or diarrhea may reduce absorption of oral contraceptives resulting in decreased serum concentrations and therefore may reduce contraceptive efficacy. Physicians should advise patients of the need for a backup contraceptive method in the case of such gastrointestinal symptoms.

For women who take other drugs or herbal products concurrently, the pill may not work as well. See the Drug Interactions section, for a list of drugs that may decrease the effectiveness of MOVISSE or increase breakthrough bleeding. They should be advised to use a backup method, until they can check for possible drug interactions with their doctor or clinic.

Missed Dose

If a patient is more than 3 hours late taking her progestin-only pill, she should take the missed pill as soon as she remembers then go back to taking progestin-only pills at her regular time.

Inform patients to use a backup method, every time they have sex, for 48 hours after missing a pill.

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

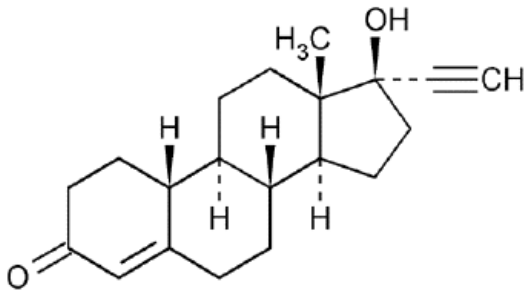
Counselling Issues

The following points should be discussed with prospective users before prescribing progestin-only oral contraceptives:

- the necessity of taking pills at the same time every day, including throughout all bleeding episodes;
- the need to use a backup method such as condoms and spermicides for the next 48 hours whenever a progestin-only oral contraceptive is taken 3 or more hours late;
- the potential side effects of progestin-only oral contraceptives, particularly menstrual irregularities;
- the need to inform the clinician of prolonged episodes of bleeding, amenorrhea or severe abdominal pain;
- the importance of using an effective barrier method in addition to progestin-only oral contraceptives if a woman is at risk of contracting or transmitting STIs/HIV.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE
Common Name: Norethindrone
Chemical Name: 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one
Structural Formula:



Molecular Wt: 298.42
Molecular Formula: $C_{20}H_{26}O_2$

DESCRIPTION
Norethindrone is a white to practically white powder with a melting range of 202°C - 208°C. It is practically insoluble in water, soluble in chloroform, dioxin and in methylene chloride, sparingly soluble in acetone, ethanol anhydrous, ethanol (95%) and in tetrahydrofuran, slightly soluble in ether.

COMPOSITION
Each MOVISSE Tablet (green, unscored, debossed with **406** on one side and plain on the other side) contains 0.350 mg norethindrone. Each tablet also contains inert ingredients, namely, corn starch, D&C Yellow # 10, ethyl cellulose, FD&C Blue # 1, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyvinyl pyrrolidone, sodium starch glycolate and talc.

STORAGE RECOMMENDATIONS
Store between 15 °C - 30 °C. Leave contents in protective packaging until time of use.

AVAILABILITY OF DOSAGE FORMS

MOVISSE® Tablets are available in a 28-Day Regimen Package that contains:

- 28 GREEN tablets each containing 0.35 mg norethindrone

ANIMAL PHARMACOLOGY

Bio-assay of norethindrone using the Clauberg method indicated an oral potency approximately 5 times that of ethisterone and at least 20 times that of progesterone.[8] However, by the McGinty test, norethindrone produces no progestational effect, nor does it maintain pregnancy in the oophorectomized rabbit.[9]

Subcutaneously, norethindrone produces an estrogenic effect on the female rat reproductive tract which is less than 1% that of estrone. Oral administration increased the estrogenic potency with the same assays by 10-25 times. [9] Conversely, the estrogen-blocking activity of norethindrone as measured using the rat uterine weight and vaginal cornification tests is 30-40 times that of progesterone.[10]

Norethindrone was subjected to androgenic assays involving increase in weight of the seminal vesicles and ventral prostates of castrated rats. No significant effect on either organ could be detected after 12 mg had been given in divided doses over a period of 14 days.[11]

CLINICAL PHARMACOLOGY

Following the oral administration of 10-20 mg of norethindrone daily, the human endometrium exhibits marked progestational changes.[12,13] In this respect, norethindrone 1 mg in combination with 50 mcg of mestranol given daily will maintain cervical mucus in a state compatible with that consistently found in the luteal phase of the menstrual cycle.[14,15] This latter reaction may be due to the antiestrogenic activity of norethindrone. Norethindrone has an inhibiting effect on the endometrium and this was utilized to devise an assay of antiestrogen activity.[16] This endometrial inhibition is intensified with increasing dose levels of the drug in a range of 0.05 - 1.0 mg/day.

Although the concept of endometrial inhibition is valuable as an antiestrogenic assay, it must be considered also in its role as an indicator of antigonadotrophic activity. Evidence of the ovulation suppression capacity of norethindrone was obtained using doses of 10 mg, 2.5 mg, and 0.5 mg daily. The presence or absence of ovulation was inferred from the amount of pregnanediol excreted in the urine of the treated patients. Table 5 illustrates the incidence of ovulatory cycles.

Table 5: The Effect of Norethindrone on Ovulation (20-day Cyclic Administration) as Determined by Urinary Pregnanediol

Dose mg/day	Number of Treated Cycles	Number of Ovulations
10.0	45	2
2.5	7	1
0.5	52	5

Further support for the ovulatory inhibiting effect of norethindrone has been obtained from direct visualization of the ovary at laparotomy. Five women who had ovulatory pregnanediol values in the immediate pretreatment cycle were given 2 mg daily of norethindrone continuously for up to 3 months before elective surgery. In all five cases, there was no evidence of matured follicles or corpora lutea.

Inferences concerning the androgenicity of norethindrone in oral contraceptives and the significance of these findings have been questioned by several authors since the concept of "masculinization" of the female fetus was based on pregnant women being treated with doses up to 200 mg/day for periods as long as 34 weeks.[18-37]

The subject has been well documented in the medical literature as demonstrated by the following:[38]

"The possibility of masculinization of the fetus and an increase in fetal abnormalities if oral contraceptives were taken after conception had occurred was early recognized as a hypothetical hazard. This was based partly on the androgenicity of the 19-nor steroids in laboratory animals and partly on reports of several such cases when pregnant women had taken large doses of progestogens therapeutically in the first 13 weeks of pregnancy.

"Despite fairly frequent reports of women who have continued to take oral contraceptives after conception has occurred without realizing they were pregnant, there have been no recorded cases of masculinization of the fetus and no increase in fetal abnormalities resulting from the medication.

"This is presumed to be because the dose of progestogens in oral contraceptive products is so much lower than the amount required to produce these effects."

The masculinization of the fetus has not been reported with the use of MOVISSE Tablets.

Post-therapy Fertility Studies

In the small number of follow-up patients available for study, there have been no problems demonstrated in patients who wish to conceive. Of the patients that were known to conceive, 91% (39/43) conceived in less than 3 months, and an additional 9% (4/43) conceived in less than 12 months.

TOXICOLOGY

Subacute and chronic toxicity studies have been performed with norethindrone. The lifetime toxicity study in dogs has been completed. The lifetime toxicity study in monkeys is complete.

Short-term Rat Study

Seminal vesicles of immature male rats receiving 1 mg norethindrone daily by the oral route for 41 days weighed approximately 1/10 those of the control group. Weights of central prostate, testes and levator ani muscles also were lower in the treated group as compared with

controls. In adult intact male rats, oral doses as high as 8 mg/kg daily of norethindrone administered for 14 days produced considerable inhibition in the growth of these organs; however, testes, seminal vesicles and prostates appeared to be histologically mature.

Long-term Monkey Studies

Long-term oral administration of norethindrone to female Rhesus monkeys produced only temporary changes in ovarian functions.

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. Observations made in this study may not necessarily be comparable with the effects of a continuous daily administration of norethindrone.

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 the controls 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 there was 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 pre-ovulatory 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 conceptual 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 cyclic 21-day administration of norethindrone for periods of one and two years suppressed ovulation without permanent effects on ovarian function and fertility of monkeys.

An additional study in 8 immature Rhesus monkeys, 4 males and 4 females was conducted where norethindrone was administered in the amount of 2.5 mg/kg daily, 5 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.

Lifetime Studies in Dogs and Monkeys

Lifetime studies of norethindrone alone administered orally to Beagle dogs (seven-year) and Rhesus monkeys (ten-year) have been completed.[41]

Dogs:

Norethindrone was administered orally for a period of 84 months (seven years) to mature female Beagle dogs daily at dosage levels of 0.007, 0.07 and 0.175 mg per kg per day (1, 10 and 25 times the human dosage). An additional group of dogs was administered 0.25% agar and served as a control group. Each group was assigned 16 test animals.

There were no remarkable changes in general behaviour, body weight, ophthalmologic or hematologic parameters.

Clinicopathologic changes which were considered to be drug-related were increased fibrinogen, serum glutamic pyruvic transaminase and blood glucose.

The histopathologic changes which represented the exaggerated pharmacologic effects of the drugs were cystic changes in the uterus and gallbladder and inhibition of ovulation. The presence of endometrial-like glands in the lamina propria of the vagina was of uncertain etiology.

This seven-year drug-safety study revealed no significant adverse changes attributable to long-term use of this compound.

Monkeys:

Seventy-two young mature female Rhesus monkeys were assigned to four groups of 16 monkeys each. The monkeys received oral doses of norethindrone daily for 10 years at dosage levels of 0.007, 0.07, and 0.35 mg/kg/day. An additional group of monkeys received vehicle only and served as a control group.

During the course of the ten-year study, fifteen monkeys died or were sacrificed in extremis (3, 4, 3 and 5 monkeys of the control, low, intermediate and high dosage groups,

respectively). The deaths occurred during the first 75 months of the study and none were considered to be drug-related.

Body weight gains of the treated groups generally paralleled those of the controls and comparable clinical signs were observed in the treated and control groups throughout the study.

An abdominal mass first reported at 36 months was noted in a low dosage monkey. It was subsequently diagnosed as localized amyloid deposition in the liver.

Red vaginal discharge was noted more frequently and for a longer period in the control and low-dosage groups than in the intermediate- and high-dosage groups.

No drug-related mammary gland masses or secretory activity occurred in this study. One intermediate dosage monkey had a nodule in the mammary gland which was palpable since 106 months on study. There was an increase in ductal epithelial hyperplasia affecting one or both mammary glands (1, 1, 1 and 3 monkeys of the control, low, intermediate and high dosage groups, respectively).

Vaginal cytology indicated that increased numbers of immature (basal/parabasal cells mostly) and often cervical cells were present in the smears of most of the high and intermediate dosage animals. Mature cells dominated in the smears of low dosage and control animals. Atypical cells were noted in the smears of four monkeys, one from the high dose and three from the control group. These atypical cells were noted in the same high dose monkey at two different time points, once during study month 36 and again during study month 51. In the control group animals, three different monkeys were observed with atypical cells, one monkey during study month 51, another monkey during study month 68 and a third monkey during study month 90.

Salient clinicopathologic findings for the entire ten-year study which are considered to be drug-related are as follows: a dose-related increase in fibrinogen; increased serum glutamic pyruvic transaminase values later in the study in one or more dosage groups as compared to the control; a dose-related decrease in T_3 Uptake; dose-related increases in T_4 as Thyroxine and T_3 (RIA) – the CF T_4 Index was marginally increased at the high and intermediate doses; and, frequently higher triglyceride values in the higher dosage groups. Histopathologic examination of the liver and thyroid gland revealed no morphologic changes which could account for these changes. Changes in fibrinogen, T_3 Uptake, T_4 as Thyroxine, and T_3 (RIA) were found to be statistically significant at varying interims. Differences among treated groups in SGPT, CF T_4 Index, and triglycerides were statistically significant at infrequent intervals, but are nevertheless considered to be drug-related. All of these changes have been reported with oral contraceptive administration in women.

Organ weight changes were considered significant if both absolute and relative organ weights had the same type of change. The mean weights of the left adrenal and right ovaries were less in the high dosage than in the control and (for ovary) the low dosage groups. The counterpart organ in each case tended to be smaller in the high dosage group, but failed to achieve

significance in both absolute and relative weights. The mean weight of the uteri of both high and intermediate dosage groups were lower than the control and low dose groups. Other organs had no meaningful changes.

Histopathologic evaluation showed changes in the reproductive organs only at the high and intermediate dosage levels. These changes were characterized as lack of recent corpora lutea, mucosal atrophy of the uteri and vaginas, atrophy of the myometrium, and increased mucus secretion of the cervix. All of these changes were related to the pharmacological action of the drug. Amyloidosis of the pancreatic islets and occasionally the myometrium was seen with low frequency in various drug treatment groups.

The oral administration of norethindrone for 10 years to monkeys at doses ranging from 0.007 to 0.35 mg/kg/day, equivalent to one to 50 times the clinical dose, resulted in expected clinical signs and clinical pathologic and morphologic pathologic changes. These changes are attributed to the pharmacologic influence of steroids upon the genital organs and liver biochemical parameters. In general, these changes were dose-related where the low dosage group was comparable to the control group.

Teratology

A study was done to determine the teratogenetic effect of norethindrone on the embryo and developing fetus of the hooded female rat (Long-Evans derived). The potential of the drug to produce fetal resorption and fetal malformation was specifically investigated. At a dose level of 0.7 mg/kg (which is approximately 100 x the human dose), no significant effect on the fetus was seen.

A similar study was conducted on New Zealand white rabbits. As with the rat study no significant effect on the fetus was observed at a dose level of 0.7 mg/kg.

A perinatal and postnatal study was conducted on Long-Evans derived hooded rats to determine the effects on late fetal development, maternal labour, delivery and lactation and the growth and reproductive performance of the offspring. At the high-dose level, (0.35 mg/kg), there was a growth retardation in the F1 generation. At the lower-dose level, (0.07 mg/kg), there was retardation in skeletal development in those stillborn fetuses that were cleared and stained. No other significant effects attributed to the compound were observed.

CLINICAL STUDIES

Norethindrone has been available by prescription since 1957 as a progestational agent, and has been used extensively in the treatment of amenorrhea, menstrual irregularity, functional uterine bleeding, infertility, habitual and threatened abortion, premenstrual tension, and dysmenorrhea.

More recently, it has been utilized as the progestational component of several oral contraceptives, in combination with ethinyl estradiol or its 3-methyl ether. A new concept of contraception has evolved from the investigations of the progestational components, namely,

the use of continuous low-level doses in amounts which produce contraception and, at the same time, permit menstrual bleeding.[42-54]

An evaluation of norethindrone was undertaken using daily doses as low as 0.05 mg. The contraceptive results are summarized in Table 6.

Table 6: Pregnancy Rates by Doses of Norethindrone

Dose	Patients	Pregnancies	Overall Pregnancy
0.05 mg	110	13	40.0
0.1 mg	146	11	32.8
0.2 mg	297	16	13.6
0.5 mg	66	0	0
1.0 mg	21	0	0

It is readily apparent from the above table that norethindrone in doses lower than 0.35 mg resulted in an unacceptable incidence of pregnancy. Experience indicated that higher doses than 0.35 mg resulted in a greater variation in the duration of interbleeding intervals.

Clinical Evaluation of norethindrone tablets (0.35 mg)
Volume
Clinical studies to date with norethindrone tablets (0.35 mg) involved 2,963 patients who completed a total of 26,713 months of use.

Effectiveness
In this group, 55 pregnancies occurred. Twenty-seven resulted from failure of the method, resulting in a corrected pregnancy rate of 1.2. Twenty-eight were attributed to failure of the patients to take the tablets correctly, resulting in a patient failure pregnancy rate of 1.3. The overall pregnancy rate was therefore 2.5.

Menstrual Pattern
Length of Inter-Bleeding Intervals: 76% of inter-bleeding intervals fell between 19 and 60 days.

Duration of Flow: 75% of observations fell between 4 and 6 days. Duration of flow was greater than 9 days in 4.5% of total observations.

Amount of Flow: In 78.7% of observations the amount of flow was recorded as moderate.

Spotting: Occurred to some degree in 29.5% of subjects. The highest rate of spotting (12.4%) occurred in the first month of therapy, reduced to 6.9% in the sixth month and 2.6% in the 18th month.

Table 7: A comparison of Dysmenorrhea and Premenstrual Tension

	Dysmenorrhea	Premenstrual Tension
Decrease	40.1%	37.1 %
No Change	46.8 %	52.8 %
Increase	6.3 %	3.0 %
Not Comparable	6.8 %	7.1%

Other Side Effects:

Gastrointestinal Disturbances - Occurred in 10.9% of patients and 2.3% of inter-bleeding intervals in this study. Nausea occurred in 8.9% of patients, vomiting in 2%. Other unspecified gastrointestinal symptoms occurred in 0.8% of patients.

Weight Changes - An increase occurred in 44.5% of patients, a decrease in 36% of patients and no change in 19.5% of patients, compared to the last pre-therapy recorded weight.

The majority of those who gained weight, 553 out of 906 (55%) gained less than 5 lbs.

The majority of those who lost weight, 511 out of 820 (62%) lost less than 5 lbs.

Thrombophlebitis - 69 subjects had reported a history of phlebitis prior to therapy, but none of these subjects developed phlebitis or pulmonary embolism during therapy.

Other complaints reported are considered to be mainly of mild degree, low incidence or unrelated to therapy.

COMPARATIVE BIOAVAILABILITY STUDY

A double blind, randomized, single-dose, two-treatment, two-period, crossover bioequivalence study of MOVISSE (norethindrone) 0.35 mg tablets (Mylan Pharmaceuticals ULC) and MICRONOR® (norethindrone) 0.35 mg tablets (Jannsen-Ortho Inc.) was performed in healthy, adult, female volunteers (n=32) under fasting conditions.

The results of the bioequivalence study are tabulated below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Norethindrone (2 x 0.35 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng*hr/mL)	48.97 53.14 (41.34)	50.97 55.05 (39.80)	96.07 %	90.52 % – 101.97 %
AUC_I (ng*hr/mL)	52.48 56.88 (41.14)	54.45 58.60 (38.81)	96.39 %	90.83 % – 102.28 %
C_{max} (ng/mL)	7.58 8.085 (37.25)	8.23 8.640 (32.85)	92.10 %	83.56 % – 101.52 %

$T_{½}^{€}$ (h)	9.748 (23.36)	9.780 (23.84)		
$T_{max}^{§}$ (h)	1.972 (33.07)	2.031 (19.46)		

* MOVISSE, 0.35 mg (norethindrone) Mylan Pharmaceuticals ULC.

† MICRONOR, 0.35 mg (Jannsen-Ortho Inc.) was purchased in Canada.

§ Expressed as the median (range) only.

€ Expressed as the arithmetic mean (CV%) only.

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CONSUMER INFORMATION
PrMOVISSE®

Norethindrone tablets, USP
0.35 mg

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MOVISSE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- prevention of pregnancy

What it does:

MOVISSE Tablets are progestin-only pills (POP) which contain a low dosage of norethindrone without the addition of an estrogen agent. It has been shown to be effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

Progestin-only birth control pills work in different ways including:

1. They prevent ovulation (release of the egg from the ovary) in about half of the cycles.
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. They also affect other hormones, the fallopian tubes and the lining of the uterus.

Effectiveness of Birth Control Pills:

The progestin-only pill is slightly less effective than combination birth control pills. The typical failure rate is estimated to be closer to 5 percent, due to late or missed pills.

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

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

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

The chance of becoming pregnant increases with incorrect use.

Other ways to prevent pregnancy:

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

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

Reported pregnancies per 100 women per year:

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Progestin-only pill†	1 to 5
Condom with spermicidal foam or gel	1 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

†About 1 in 200 progestin-only pill users will get pregnant in the first year if they all take progestin-only pills perfectly (that is, on time, every day). About 1 in 20 "typical" progestin-only pill users (including women who are late taking pills or miss pills) gets pregnant in the first year of use.

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

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

When it should not be used:

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

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

- unusual vaginal bleeding that has not yet been diagnosed;
- smoker and over age 35;
- known or suspected cancer of the breast;
- liver tumours either benign or cancerous;
- acute liver disease;
- if you are taking certain drugs for epilepsy (seizures) or for tuberculosis (see **INTERACTIONS WITH THIS MEDICATION**);
- you are pregnant or if pregnancy is suspected; and/or
- allergic reaction to norethindrone or to any of the other ingredients in MOVISSE (see **What the nonmedicinal ingredients are**).

What the medicinal ingredients are:
Norethindrone

What the nonmedicinal ingredients are:
corn starch, D&C Yellow # 10, ethyl cellulose, FD&C Blue # 1, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyvinyl pyrrolidone, sodium starch glycolate and talc.

What dosage forms it comes in:

MOVISSE® (norethindrone) Tablets are available in a 28-day regimen.

28-day Regimen Package contains: 28 GREEN tablets each containing 0.35 mg norethindrone.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age. Women should not smoke.

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

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

There are also conditions that your doctor will want to watch closely or that might cause your doctor to recommend a method of contraception other than birth control pills.

BEFORE you use MOVISSE, talk to your doctor or pharmacist if the following apply to you:

- breast disease (e.g., breast lumps) or a family history of breast cancer
- diabetes
- cigarette smoking
- migraine headaches
- depression
- fibroid tumours of the uterus
- pregnant or breast-feeding
- plans for forthcoming surgery.

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

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

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

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

MOVISSE should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

If you don't have your period for 6 months or more after stopping MOVISSE, contact your doctor.

Use MOVISSE only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant. If you and your doctor decide that, for you, the benefits of MOVISSE outweigh the risks, you should be aware of the following risks:

THE RISKS OF USING MOVISSE

1. Ectopic Pregnancy
An ectopic pregnancy is a pregnancy outside the womb. Because progestin-only pills protect against pregnancy, the chance of having a pregnancy outside the womb is very low. If you do get pregnant while taking progestin-only pills, you have a slightly higher chance that the pregnancy will be ectopic than do users of some other birth control methods.

2. Ovarian Cysts
These cysts are small sacs of fluid in the ovary. They are more common among progestin-only pill users than among users of most other birth control methods. They usually disappear without treatment and rarely cause problems.

WARNING: If you have sudden or severe pain in your lower abdomen or stomach area, you may have an ectopic pregnancy or an ovarian cyst. If this happens, you should contact your doctor or clinic immediately.

3. Breast Cancer
Some studies in women who use combined oral contraceptives that contain both estrogen and progestin have reported an increase in the risk of developing breast cancer, particularly at a younger age and apparently related to duration of use. There is data to determine that the use of progestin-only pills may also increase this risk.

In progestin-only pill (POP) users, the older the age at stopping, the more breast cancers are diagnosed.
The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

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

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

4. Cervical Cancer
Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives and there is insufficient data to determine whether the use of progestin-only pills increases the risk of developing cancer of the cervix.

5. Liver Tumours
In rare cases, combined oral contraceptives can cause benign liver tumours. These benign liver tumours can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with combined oral contraceptives and liver cancers in studies in which a few women who developed these very rare cancers were found to have used combined oral contraceptives for long periods of time. There is insufficient data to determine whether progestin-only pills increase the risk of liver tumours.

6. Diabetic Women
Diabetic women taking progestin-only pills generally require changes in the amount of insulin they are taking. However, your physician may monitor you more closely under these conditions.

7. Use During Pregnancy
Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing. There is no evidence, however, that the progestin-only pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

8. Use After Pregnancy, Miscarriage or An Abortion
Your doctor will advise you of the appropriate time to start the use of MOVISSE after childbirth, miscarriage, or therapeutic abortion.

9. Pregnancy After Stopping MOVISSE
You will have a menstrual period when you stop taking MOVISSE. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternative methods of contraception during this time.

10. Use While Breast-Feeding
In most women, progestin-only contraceptives, such as MOVISSE, do not affect the quantity and quality

of breast milk or length of lactation. However, isolated post-marketing cases of decreased milk production have been reported. Studies with various orally administered progestin-only contraceptives have shown that small amounts of progestins pass into the breast milk of nursing mothers resulting in detectable steroid levels in infant plasma.

No adverse effects have been found on the health, growth or development of the infant.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

Drugs that may interact with MOVISSE include:

- drugs used for the treatment of epilepsy (e.g., primidone, phenytoin, carbamazepine, rufinamide)
- drugs used for the treatment of tuberculosis (e.g. rifampin, rifabutin)
- drugs used for HIV/AIDS (e.g., nelfinavir, ritonavir-boosted protease inhibitors, darunavir, (fos)amprenavir, lopinavir, nevirapine);
- (fos)aprepitant (drug used for nausea);
- bosentan (drug used for pulmonary hypertension);
- antifungals (griseofulvin);
- the herbal remedy St. John's wort (primarily used for the treatment of depressive moods); and
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)

The pill may also interfere with the working of other drugs.

Please inform your doctor and pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use MOVISSE. They can tell you if you need to use an additional method of contraception and if so, for how long.

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

PROPER USE OF THIS MEDICATION

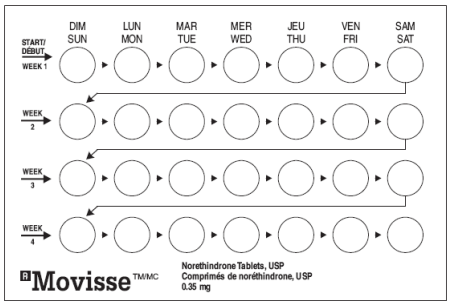
HOW TO TAKE MOVISSE (PROGESTIN-ONLY PILLS):

1. **READ THESE DIRECTIONS**
   - before you start taking your pills, and
   - any time you are not sure what to do.

2. **LOOK AT YOUR PILL PACK**
   28-PILL PACK: 28 active pills (with a hormone) taken daily for 28 days.

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

28-Day Regimen Package



3. You may wish to use a second method of birth control (e.g. latex or polyurethane condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a backup in case pills are forgotten while you are getting used to taking them.

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic. The most common side effect of progestin-only pills is a change in menstrual bleeding. Your period may be either late or early and you may have some spotting.
6. **MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could

feel a little sick to your stomach on the days you take two pills to make up for missed pills.

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
   - when you start a pack late, or
   - if you are more than 3 hours late or you miss one or more progestin-only pills.

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

9. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES,** your pills may not work as well. Use a backup method, such as latex or polyurethane condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

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

11. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**

12. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:
- before you start taking your pills, and
- any time you are not sure what to do.

YOUR MOVISSE TABLETS ARE IN A 28-DAY PILL PACKAGE. With this type of birth control pill, you take 28 pills which contain only one hormone, a progestin.

STARTING PROGESTIN-ONLY PILLS

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** With MOVISSE Tablets, it is best to start your first package of progestin-only pills on the first day of your menstrual period (Day 1)†. Then you simply continue taking one tablet every single day until your package is empty. Without missing a day, start taking MOVISSE Tablets from your new package.

† If you decide to take your first progestin-only pill on another day, use an additional method of birth control (such as latex or polyurethane condoms and spermicidal foam or gel) every time you have sex during the next 48 hours.

2. If you have had a miscarriage or an abortion, you can start progestin-only pills the next day.

3. Take one pill at the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS ON THE PILLS**. Your period should occur during the last seven days of using that pill pack. MOVISSE Tablets are taken every day, even when you are having some menstrual bleeding.

INSTRUCTIONS FOR USING YOUR PACKAGE. FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the Package by selecting the day label that starts with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, attach the day label that begins with **TUE** in the space provided.

   OR

   For Sunday start: No day label is required. The Package is printed for a Sunday start. (The first Sunday **after** your period begins, or, if your period starts on Sunday, start that **same day**.)

2. Place the day label on the dispenser over the printed days of the week. Having the Package labelled with the days of the week will help remind you to take your pill every day.

3. To begin taking your pills, start with the pill next to the word **START**. This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the Package.

4. On the following day, take the next pill in the same row, always proceeding from left to right

(→). Each row will always begin on the same day of the week.

IF YOU ARE BREAST-FEEDING

1. If you are fully breast-feeding (not giving your baby any food or formula), you may start taking your pills 6 weeks after delivery.

2. If you are partially breast-feeding (giving your baby some food or formula), you should start taking your pills 3 weeks after delivery.

IF YOU ARE SWITCHING PILLS

1. If you are switching from the combined pills to progestin-only pills, and you were on a 21-Day regimen, take the first progestin-only pill the day after you finish the last active combined pill. If you have been on a 28-Day regimen, do not take any of the 7 inactive pills from the combined pill pack. You should know that many women have irregular periods after switching to progestin-only pills, but this is normal and to be expected.

2. If you are switching from progestin-only pills to the combined pills, take the first active combined pill on the first day of your period, even if your progestin-only pill pack is not finished.

3. If you are breast-feeding, you can switch to another method of birth control at any time, except do not switch to the combined pills until you stop breast-feeding or at least until 6 months after delivery.

WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.** Progestin-only pills must be taken at the same time every day since its action is time dependent. Every time you take a pill late, and especially if you miss a pill, you are more likely to get pregnant.
   - Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
   - Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
   - Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK OF 28 PILLS**
   - Start the next pack ON THE NEXT DAY. Take one pill every day. Do not wait any days between packs.

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

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

WHAT TO DO IF YOU MISS PILLS

IF YOU ARE MORE THAN 3 HOURS LATE OR MISS TAKING YOUR PROGESTIN-ONLY PILLS

1. Take a missed pill as soon as you remember you missed it.
2. Then go back to taking progestin-only pills at your regular time.
3. But be sure to use a backup method (such as a condom and/or a spermicide) every time you have sex for the next 48 hours.

If you are not sure what to do about the pills you have missed, keep taking progestin-only pills and use a backup method until you can talk to your doctor or clinic.

Always be sure you have on hand:

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some users of birth control pills have side effects. The most common side effect of progestin-only pills is a change in menstrual bleeding. Your periods may be either early or late. You may have some spotting between periods or you may not have a period.

Taking pills late or missing pills can result in some spotting or bleeding.
Less common side effects of progestin-only pills include headaches, tender breasts, nausea, vomiting, tiredness, weight gain, dizziness, acne, extra hair on your face or body, loss of hair, rash, abdominal pain, yellowing of the skin or eyes (jaundice), and tubal pregnancy.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom/effect		Talk with your doctor or pharmacist	Stop taking drug and talk with your doctor or pharmacist
Common	Abnormal Vaginal bleeding	√	
Uncommon	Sudden or severe pain in lower abdomen	√	
	Allergic reaction		√

HOW TO STORE IT

Store in original packaging, between 15°C - 30°C.
Leave contents in protective packaging until time of use. Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at MedEffect®
  (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at www.mylan.ca

The full Product Monograph, prepared for health professionals can be obtained by contacting Mylan Pharmaceuticals ULC at: 1-844-596-9526

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