PRESCRIBING INFORMATION

DEMULEN* 30

(Ethynodiol Diacetate plus Ethinyl Estradiol Tablets)

ORAL CONTRACEPTIVE

Pfizer Canada Inc
17,300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

Date of Preparation:
17 February 2014

Control No. 169881

* TM G.D. Searle & Co.
Pfizer Canada Inc, Licensee
© Pfizer Canada Inc 2014

PRESCRIBING INFORMATION

DEMULEN* 30

(Ethynodiol Diacetate plus Ethinyl Estradiol Tablets)

THERAPEUTIC CLASSIFICATION

Oral Contraceptive

ACTION

Estrogen-progestogen combinations act primarily through the mechanism of gonadotropin suppression due to the estrogenic and progestational activity of their components. Although the primary mechanism of action is inhibition of ovulation, alterations in the cervical mucus and the endometrium may also contribute to effectiveness.

INDICATIONS

DEMULEN 30
Prevention of Pregnancy.

CONTRAINDICATIONS

1. History of or actual thrombophlebitis or thromboembolic disorders.
2. History of or actual cerebrovascular disorders.
3. History of or actual myocardial infarction or coronary arterial disease.
4. Active liver disease or history of or actual benign or malignant liver tumours.
5. History of or known or suspected carcinoma of the breast.
6. History of or known or suspected estrogen-dependent neoplasia.
7. Undiagnosed abnormal vaginal bleeding.
8. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
9. When pregnancy is suspected or diagnosed.
10. Allergic reaction to ethynodiol diacetate, ethinyl estradiol or to any other ingredients in DEMULEN (see DOSAGE FORMS).
11. Hereditary or acquired thrombophilias
12. Severe dyslipoproteinemia
13. Heavy smoking (>15 cigarettes per day) and over age 35
14. Major surgery associated with an increased risk of postoperative thromboembolism
15. Prolonged immobilization
16. Disease of the heart valves with complication and irregular heart rhythm (thrombogenic valvulopathies and thrombogenic rhythm disorders)
17. Headache with focal neurological symptoms, such as aura
18. Diabetes with vascular involvement
19. Uncontrolled hypertension
20. Pancreatitis associated with severe hypertriglyceridemia (current or history)

WARNINGS

1. **Predisposing Factors for Coronary Artery Disease**

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

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

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

2. **Discontinue Medication at the Earliest Manifestation of the following:**

A. **Thromboembolic and Cardiovascular Disorders** such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

B. Conditions that Predispose to Venous Stasis and 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 **PRECAUTIONS**.

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.

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

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity, and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus[11], hemolytic uremic syndrome[12-14], chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis)[15], sickle cell disease[16], valvular heart disease and atrial fibrillation[17-18].

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria[19], systemic lupus erythematosus[20], hemolytic uremic syndrome[21], Sydenham's chorea[22-23] , herpes gestationis[24-25], and otosclerosis-related hearing loss[26].

The information contained in this section is principally from studies carried out in

women who used combination oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestogen administered orally remains to be determined.

PRECAUTIONS

1. **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 and a Papanicolaou smear should be taken if the patient has been sexually active.

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

2. **Pregnancy**

Fetal abnormalities have been reported to occur in the offspring of women who have taken estrogen-progestogen combinations in early pregnancy. Rule out pregnancy as soon as it is suspected.

3. **Breastfeeding**

In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. The long-term effects on the developing child are not known. However, cases of breast enlargement have been reported in breast-fed infants. The nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

4. **Hepatic Function**

Patients who have had jaundice including a history of cholestatic jaundice during pregnancy should be given oral contraceptives with great care and under close observation.

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

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic nodules have been reported to be associated with use of oral contraceptives, particularly in long-term users of oral contraceptives. These nodules include benign hepatic adenomas, focal nodular hyperplasia and other hepatic lesions. In addition, hepatocellular carcinoma has been reported. 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.

5. **Hypertension**

Patients with essential hypertension whose blood pressure is well-controlled may be given oral contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

6. **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.

7. **Diabetes**

Current low dose OCs exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

8. **Ocular Disease**

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

9. **Breasts**

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 eight years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

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

10. **Vaginal Bleeding**

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

11. **Fibroids**

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation of the use of OCs.

12. **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 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.

13. **Metabolic and Endocrine Diseases**

In metabolic or endocrine diseases and when metabolism of calcium and phosphorus is abnormal, careful clinical evaluation should precede medication and a regular follow-up is recommended.

14. **Connective Tissue Disease**

The use of oral contraceptives in some women has been associated with positive lupus erythematous cell tests and with clinical lupus erythematous. In some instances exacerbation of rheumatoid arthritis and synovitis have been observed.

15. **Laboratory Tests**

Results of laboratory tests should be interpreted in the light of the fact that the patient is on OCs. The laboratory tests listed below are modified.

A. **Liver function tests**

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

B. **Coagulation tests**

Minimal elevation of test values reported for such parameters as Factors VII, VIII, IX and X. Increased platelet aggregation, decreased antithrombin III.

C. **Thyroid function tests**

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

D. **Lipoproteins**

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

E. **Gonadotropins**

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

16. **Tissue Specimens**

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

17. **Return to Fertility**

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

18. **Amenorrhea**

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

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

19. **Thromboembolic Complications - Post-surgery**

There is an increased risk of post-surgery thromboembolic complications in oral contraceptive users, after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery.

Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery.

20. **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.

During concomitant use of DEMULEN and substances that may lead to decreased ethinyl estradiol serum concentrations, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of DEMULEN. In the case of prolonged use of such substances COCs should not be considered the primary contraceptive.

Refer to the revised 1994 Report on Oral Contraceptives, Health Canada, for possible drug interactions with OCs (see Appendix A).

In addition, the following drugs may also interact with DEMULEN: ritonavir, indinavir, St John's wort, fluranizine, topiramate, lamotrigine, rifabutin, fluconazole, atorvastatin, dexamethasone, and modafinil.

21. **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.

22. **Immune: Angioedema**

COC may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

23. **Vaginal Bleeding**

Breakthrough bleeding/spotting may occur in women taking COCs, especially during the first three months of use. The type and dose of progestin may be important. If this bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions. If pathology has been excluded, continued use of the COC or a change to another formulation may solve the problem.

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

EFFECTS ON MENSES

- increased menstrual cycle regularity
- decreased menstrual blood loss
- decreased incidence of iron deficiency anemia secondary to reduced menstrual blood loss
- decreased incidence of dysmenorrhea

EFFECTS RELATED TO OVULATION INHIBITION

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancy

EFFECTS ON OTHER ORGANS OF THE REPRODUCTIVE TRACT

- decreased incidence of acute salpingitis
- decreased incidence of endometrial cancer (50 per cent)
- decreased incidence of ovarian cancer (40 per cent)

- potential beneficial effects on endometriosis
- improvement of acne vulgaris, hirsutism, and other androgen-mediated disorders.

EFFECTS ON BREASTS

- decreased incidence of benign breast disease (fibroadenomas and fibrocystic breast disease)
- decreased incidence of breast biopsies

The non-contraceptive benefits of oral contraceptives should be considered in addition to the efficacy of these preparations when counselling patients regarding contraceptive method selection.

Oral contraceptives **do not protect** against sexually transmitted diseases including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **in combination with** oral contraceptives.

ADVERSE REACTIONS

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

- Thrombophlebitis
- Pulmonary embolism
- Mesenteric thrombosis
- Neuro-ocular lesions, (e.g., retinal thrombosis)
- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension
- Benign hepatic tumours
- 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 percent or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.
- Other adverse reactions:

Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Dysmenorrhea
Amenorrhea during and after treatment
Infertility after discontinuance of treatment
Edema
Chloasma or melasma which may persist
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)

Endocervical hyperplasias

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

Arterial thromboembolism

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Numerous cases of the ingestion, by children, of estrogen progestogen combinations have been reported. Although mild nausea may occur, there appears to be no other reaction. Treatment should be limited to a laxative such as citrate of magnesia with the aim of removing unabsorbed material as rapidly as possible.

DOSAGE

A. 21-DAY PACK:

With this type of birth control pill, the patient is 21 days on pills with seven days off pills. The patient must not be off the pills for more than seven days in a row.

1. **The first day of the patient's menstrual period (bleeding) is day 1 of a cycle.** The doctor may advise the patient to start taking the pills on Day 1, on Day 5, or on the first Sunday after a period begins. If a period starts on Sunday, the patient starts that same day.

2. The pack must be labelled correctly before starting. The pack is pre-printed with a Sunday starting day. If the patient is starting on a day other than a Sunday, she should use the Flexi-start™ sticker labels provided. The patient peels off the label with the chosen starting day and applies it over the pre-printed days on top of the card.

3. The patient takes one pill at approximately the same time every day for 21 days; **then she takes no pills for seven days.** She starts a new pack on the eighth day. She will probably have a period during the seven days off the pill.

(This bleeding may be lighter and shorter than a usual period.)

B. 28-DAY PACK:

With this type of birth control pill, the patient takes 21 pills which contain hormones and seven pills which contain no hormones.

1. **The first day of the patient's menstrual period (bleeding) is day 1 of a cycle.** The doctor may advise the patient to start taking the pills on Day 1, on Day 5, or on the first Sunday after a period begins. If a period starts on Sunday, the patient starts that same day.

2. The pack must be labelled correctly before starting. The pack is pre-printed with a Sunday starting day. If the patient is starting on a day other than a Sunday, she should use the Flexi-start™ sticker labels provided. The patient peels off the label with the chosen starting day and applies it over the pre-printed days on top of the card.

3. The patient takes one pill at approximately the same time every day for 28 days. She begins a new pack the next day, **not missing any days on the pills.** The patient's period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

1. **The patient takes a pill at approximately the same time every day until the pack is empty.**

   - The patient should try to associate taking the pill with some regular activity like eating a meal or going to bed.

   - The patient must not skip pills even if she has bleeding between monthly periods or feels sick to her stomach (nausea).

   - The patient must not skip pills even if she does not have sex very often.

2. **When a pack is finished:**

   - **21 Pills:**

     The patient must wait seven days to start the next pack. A period will begin during that week.

   - 28 Pills:

     The patient starts the next pack **on the next day**. She takes one pill every day. She does not wait any days between packs.

DOSAGE FORMS

DEMULEN* 30

Each white circular, biconvex, film-coated, tablet, 6.0 mm in diameter, impressed “SEARLE 930" on one side contains ethynodiol diacetate 2 mg and ethinyl estradiol 0.03 mg (30 μg). Inert orange-coloured tablets are impressed “SEARLE” on one side, “P” on the other.

Non-medicinal ingredients include: Active tablets: corn starch, ethylcellulose, hydroxypropylcellulose, lactose, magnesium stearate, povidone, sodium acid phosphate, sodium phosphate dibasic anhydrous, titanium dioxide. Placebo tablets: FD & C Yellow No. 6 Lake, lactose, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

Available in 21 day dispensers, each containing 21 active tablets.

Also available in 28 day dispensers (21 active and 7 inert tablets).

Appendix A

1994 Report on Oral Contraceptives, Health Canada

ORAL CONTRACEPTIVES (OCs) AND DRUG INTERACTIONS

Since the introduction of oral contraceptives more than 30 years ago, there have been many reports of drug interactions with these agents. Some are well documented and of clinical significance but others are less so and are of questionable or unknown clinical relevance. There are two major types of interactions between OCs and concomitant drugs. First, the efficacy of OCs may be altered usually decreased by interacting agents. Second, OCs may alter the efficacy, or alter the adverse effects, of other drugs.

The potential for drug interactions with OCs seems more likely today, and the occurrence perhaps more frequent, due to the expanding use of low-dose estrogen OCs. Confounding factors make the actual incidence and therapeutic significance of these interactions difficult to determine. It is well accepted that approximately one per cent of women will experience contraceptive failure while taking OCs. Failure may occur because of improper use of the OC, (i.e. not taking OCs at the same time each day, missing pills, etc.) The efficacy of OCs also may be diminished in women with certain diseases (e.g. persistent diarrhea). Contraceptive failure also could be due to concomitant drug therapy. Most of the information concerning drug interactions with OCs comes from case reports and data reported retrospectively.
Clinical trials have not been done because of the large numbers of patients that would need to be recruited and the ethical considerations of conducting such trials. Therefore, clinicians must rely on the information available and interpret it carefully.

Several mechanisms are thought to be responsible for altering the efficacy of OCs:

- interference with absorption of the OCs from the GI tract;
- increased levels of plasma sex hormone binding globulin (SHBG) leading to decreased levels of active steroid;
- competition between the OCs and interacting drug for the same metabolizing enzyme;

- microsomal enzyme induction (or inhibition) in the liver, which may increase or decrease the metabolism of the OC; and
- interference with the enterohepatic recirculation of steroid metabolites.

Unexpected spotting or breakthrough bleeding may suggest reduced contraceptive efficacy. If the efficacy of the OC is reduced sufficiently, pregnancy may result.

The proposed mechanisms of known and suspected drug interactions that have been reported with OCs are reviewed in Tables 2 and 3 at the end of this section. Table 2 lists those drugs that interfere with the efficacy of OCs. Most anticonvulsant agents, including phenobarbital, phenytoin, primidone, carbamazepine and ethosuximide, have been implicated in contraceptive failure with OCs.
These agents induce hepatic microsomal enzymes responsible for the metabolism of OCs, leading to increased metabolism and lower effective levels of steroids. It also has been reported that an increase in SHBG leads to lower free progesterone levels. As these anticonvulsants are often prescribed to women of childbearing age, it is generally recommended that an alternative method of contraception be used. Some experts suggest using an OC with 50 µg or more of ethinyl estradiol. The benefits of this approach must be weighed against the increased risk of adverse effects such as thromboembolic disorders. No reports of an interaction between valproic acid and OCs could be found.

Anti-infective agents also have been implicated in the failure of OCs. Rifampin was the first drug reported to interfere with OCs. Like the anticonvulsants, rifampin is a hepatic microsomal enzyme inducer, and can effectively reduce steriod levels. Griseofulvin, an antifungal agent, may also interact with OCs in a similar way. Women receiving OCs and rifampin or griseofulvin should be counselled about the possible interaction and be advised about alternative methods of birth control.

Perhaps more controversial is the proposed interaction between OCs and broad-spectrum antibiotics. This interaction may be mediated through some of the mechanisms mentioned above. Some anti-infectives may cause hepatic microsomal enzyme induction (as seen with

rifampin and griseofulvin). Adverse effects of antibiotics, such as diarrhea, may speed transit time through the gastrointestinal tract and decrease absorption of the OC. In addition, antibiotics may alter gut bacterial flora.
It is known that approxiamtely 60 per cent of ethinyl estradiol is metabolized on its first pass through the liver, and the conjugates are excreted in the bile. Bacteria in the gut hydrolyse the conjugates back to active ethinyl estradiol, which is then reabsorbed. Antibiotic-induced alterations in gut bacteria could reduce this enteroheptic recirculation of ethinyl estradiol.

There have been several well-documented case reports of pregnancy occurring while women, correctly using OCs, were taking antibiotics, especially ampicillin and tetracycline. Contraceptive failures have also been reported with chloramphenicol, isoniazid, neomycin, nitrofurantoin, penicillin V, sulfonamides, erythromycin and cotrimoxazole. The number of case reports is small compared to the number of women receiving OCs. However, that fact does not diminish the clinical implications of the interaction, even if it occurs only in a few women. As many women on OCs are likely to be prescribed antibiotics sometime, the controversy expands to how to counsel these patients. Some experts believe that an alternative form of birth control should not be recommended during a short course of antibiotic therapy. Others believe that because of the potential risk of interaction, and the inability to predict those who are likely to experience interaction, all women should be advised of the risk, and additional methods of contraception should be recommended. Women to be placed on long-term antibiotic therapy, such as tetracycline for acne, should also be advised of the interaction.

There are a few drugs and classes of drugs in Table 2 for which the evidence of reduced OC efficacy is questionable.

The most recent evidence concerning the interaction between OCs and clofibrate indicates that OCs probably have more of an effect on reducing the efficacy of clofibrate than the opposite, (see Table 3 under Cholesterol Lowering Agents). The same is probably true for analgesics in that OCs actually reduce the efficacy of ASA and acetaminophen (see Table 3 under Antipyretics). It has been reported that long-term use of OCs and phenylbutazone may result in an increased incidence of breakthrough bleeding. Although it has been reported that

antihistamines may reduce OC efficacy, this was not supported by the results of a pharmacokinetic study with OCs, doxylamine and diphenhydramine. The antimigraine preparations in Table 3 refer primarily to ergotamine preparations that also contain barbiturates. As mentioned previously with the anticonvulsants, barbiturates can increase the metabolism of OCs, leading to reduced efficacy.

It should be mentioned that there are a few drugs that may actually increase the action and/or plasma concentration of OCs. There is little information in the literature on these types of interactions, possibly because the interaction is likely to increase the efficacy of the OC. However, there is also the possibility of increased risk of toxicity with the OCs. There are two potential interactions worth noting. When vitamin C and OCs are given concurrently, there is an increase in plasma ethinyl estradiol levels. This should not be of concern unless a person stops intake of regular vitamin C which may cause a drop in steroid plasma levels. Acetaminophen can also increase ethinyl estradiol levels by decreasing its metabolism during absorption. Again, this should not be clinically significant unless a person stops taking regular high doses of acetaminophen abruptly. If patients are on OCs and either vitamin C or acetaminophen, it is recommended that they be slowly tapered off these agents if they are to be stopped.
As shown in Table 3, OCs can interfere with the efficacy of other drugs. OCs may increase the levels of some clotting factors and reduce antithrombin III levels, diminishing the effect of anticoagulants. Paradoxically, OCs also may enhance the effects of anticoagulants. It is probably best to avoid concomitant use of these drugs. OCs also can affect the blood levels of theophylline. When these drugs are used together, the clearance of theophylline is decreased by up to 30 to 40 per cent, due to decreased oxidation via cytochrome P-450 and P-448 systems. This effect is greater in smokers because of the induction of theophylline metabolism. Smoking itself can lead to an increased risk of cardiovascular effects due to OCs. Alcohol too, is affected by OC use. Ethanol is eliminated at a slower rate in OC users because up to 25 per cent of ethanol undergoes metabolism via hepatic microsomal enzymes. It is recommended that women using OCs should not increase their consumption of alcohol.

In conclusion, OCs are among the most commonly used drugs in the world, with approximately 60 to 70 million women using them. Although they are extremely safe

compounds, OCs have potential interactions with many drugs, which could possibly lead to contraceptive failure. When one considers the possibility of multiple drug regimens, the perplexing pharmacologic nature of OCs and their failure rate of about 1 per cent, the situation only becomes more complex.

Physicians and pharmacists clearly have a role to play in providing accurate information to the patient,discussing the potential ramifications with her and listening to her concerns.

Drug and disease histories of the patient should be gathered and blood levels of the interacting drugs may have to be monitored. With the uncertainly of many of these drug interactions, individualized patient therapy is very important.

Table 2*
Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carpamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 ug ethinyl estradiol), another drug, or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolic of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	Pheylbutazone** Antihistamines ** Analgesics ** Antimigraine** Preparations** Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

* Adapted from Dickey R.P., (ed): *Managing Contraceptive Pill Patients*. 5th edition. Creative Informatics Inc.,Durant,OK,1987
**Refer to previous text on page 3.

Table 3*

Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

Table 3 (concluded)
Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake; or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine, and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake; or supplement.

*Adapted from Dickey R.P., (ed): *Managing Contraceptive Pill Patients*, 5th edition, Creative Informatics Inc., Durant, OK, 1987

g:\corpaffr\monograf\DEMjun98.pi

References:

1. Back, D.J. and M.L.E. Orme. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinetics*, 1990, 18: 472-484.

2. Dickey, R.P. Managing Contraceptive Pill Patients, 7th edition. Edited by A.A. Yuzpe. Essential Medical Information Systems (EMS) Canada, 1993.

3. Fazio, A. Oral Contraceptive drug interactions: important considerations. South Med J, 1991, 84: 997-1002.

4 Hansten, P.D. and J. R. Horn. Drug Interactions and Updates. Applied Therapeutics Inc., Vancouver, Washington, U.S., 1990.

5. Hatcher, R. A., F. Stewart, J. Trussell et al. Contraceptive Technology, 15th edition. Irvington Publishers Inc., New York, 1990.

6. Tatro, D.S. Drug Interaction Facts: Facts and Comparisons. Wolters Klumer Co., St. Louis, MO, 1992.

7. Zuccero, F. J. and M. J. Hogan. Evaluations of Drug Interactions. PDS Publishing Company, St. Louis, MO, 1992.

8. Stockely, I.H. ed. Drug Interactions. Blackwell Scientific Publications, London, 1991.

9. Halperin, J.A., exec. dir. USP DI, Drug Information for the Health Care Professional. The United States Pharmacopeial Convention Inc., Rockville, Maryland, 1993.

10. Shenfield, G.M. Oral contraceptives: Are drug interactions of clinical significance? Drug Saf, 1993, 9: 21-37.

11. Asherson RA, Cervera R, Font J. Multiorgan thrombotic disorders in systemic lupus erythematosus: a common link? Lupus. 1992 1:199-203.

12. Kwaan HC, Ganguly P. Introduction: thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome Semin Hematol. 1997;34(2):81-9.

13. Sibai BM, Kustermann L, Velasco J. Current understanding of severe preeclampsia, pregnancy-associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and post partum acute renal failure: different clinical syndromes or just different names? Curr Opin Nephrol Hypertension. 1994;3:436-45.

14. Stewart CL, Tina LU. Hemolytic uremic syndrome. Pediatr Rev. 1993 Jun;14(6):218-24.

15. Koenigs KP, McPhedran P, Spiro HM. Thrombosis in inflammatory bowel disease. J Clin Gastroenterol. 1987 Dec;9(6):627-31.

16. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sickle cell disease. Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 243-6.

17. Adams HP, Biller J. Ischemic cerebrovascular disease. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, editors. Neurology in clinical practice. Boston: Butterworth-Heinemann; 1996. p. 1014-9.

18. Carlone JP, Keen PD. Oral contraceptive use in women with chronic medical conditions. Nurse Pract. 1989 Sep;14(9):9-10, 2-3, 6.

19. Gross U, Honcamp M, Daume E, Frank M, Dusterberg B, Doss MO. Hormonal oral contraceptives, urinary porphyrin excretion and porphyrias. Horm Metab Res. 1995 Aug;27(8):379-83.

20. Petri M, Robinson C. Oral contraceptives and systemic lupus erythematosus. Arthritis Rheum. 1997 May;40(5):797-803.

21. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Hemolytic uremic syndrome. Summary of contraindications to oral contraceptives New York: Parthenon Publishing Group; 2000. p. 211-8.

22. Galimberti D. Chorea induced by the use of oral contraceptives. Report of a case and review of the literature. Ital J Neurol Sci. 1987 Aug;8(4):383-6.

23. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sydenham's chorea. Summary of contraindications to oral contraceptives New York: Parthenon Publishing Group; 2000. p. 415-9.

24. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Herpes gestationis. Summary of contraindications to oral contraceptives New York: Parthenon Publishing Group; 2000. p. 367-70.

25. Morgan JK. Herpes gestationis influenced by an oral contraceptive. Br J Dermatol. 1968 Jul;80(7):456-8.

26. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Otosclerosis. Summary of contraindications to oral contraceptives New York: Parthenon Publishing Group; 2000. p. 387-91.

PART III: CONSUMER INFORMATION

PrDEMULEN* 30
(Ethynodiol Diacetate plus Ethinyl Estradiol tablets)

This leaflet is part III of a three-part "Product Monograph" published when DEMULEN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DEMULEN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DEMULEN 30 is used for the prevention of pregnancy.

What it does:
DEMULEN is a birth control pill (oral contraceptive) that contains two female sex hormones (ethinyl estradiol and ethynodiol diacetate). DEMULEN has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers over 35. The chance of becoming pregnant increases with incorrect use.

Birth control pills work in two ways:
1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix (opening of the uterus). This slows the movement of the sperm through the mucus and through the uterus (womb).

Effectiveness of Birth Control Pills
Combination birth control pills (like DEMULEN) 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.

Other Ways to Prevent Pregnancy
Other methods of birth control are available to you. They are usually less effective than birth control pills. However, when used properly, they 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 system (IUS)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill (progesterone-only 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 IUSs 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 IUSs 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 birth control 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 always should be supervised by your doctor.

Do not use DEMULEN if you have any of the following:
- History of or actual thrombophlebitis

(inflammation of the veins) or thromboembolic disorders-, such as-blood clots in the legs, lungs, eyes, or elsewhere.
- History of or actual cerebrovascular disorders, such as a stroke.
- History of or actual myocardial infarction or coronary arterial disease, heart attack or chest pain.
- Jaundice or active liver disease, or history of or actual benign or malignant liver tumours.
- History of or known or suspected carcinoma of the breast or sex organs.
- History of or known or suspected tumours associated with estrogen containing products.
- Undiagnosed abnormal vaginal bleeding.
- Loss of vision due to blood vessel disease of the eye.
- When pregnancy is suspected or diagnosed.
- Disease of the heart valves with complications
- Irregular heart rythm
- Migraines with visual and/or sensory disturbances
- Diabetes affecting you circulation
- Severe high blood pressure
- History of or actual pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood.
- Allergic reaction to ethynodiol diacetate, ethinyl estradiol or to any other ingredients in DEMULEN (see What the important nonmedicinal ingredients are)
- Known abnormalities of the blood clotting system that increases your risk for developing blood clots
- Very high blood cholesterol or triglyceride levels
- Heavy smoking (>15 cigarettes per day) and over age 35
- You are scheduled for major surgery
- Prolonged bed rest

What the medicinal ingredient is:
The medicinal ingredients are: ethynodiol diacetate and ethinyl estradiol.

What the important nonmedicinal ingredients are:
DEMULEN 30: corn starch, ethylcellulose, hydroxypropylcellulose, lactose, magnesium stearate, povidone, sodium acid phosphate, sodium phosphate dibasic anhydrous, titanium dioxide.

Placebo tablets: FD & C Yellow No. 6 Lake, lactose, lactose monohydrate, magnesium stearate, microcrystalline cellulose.

What dosage forms it comes in:
DEMULEN 30: Each white circular, biconvex, film-coated, tablet, 6.0 mm in diameter, impressed "SEARLE 930" on one side contains ethynodiol diacetate 2 mg and ethinyl estradiol 0.03 mg. Inert orange-coloured tablets are impressed "SEARLE" on one side, "P" on the other.

Available in 21 day dispensers, each containing 21 active tablets.
Also available in 28 day dispensers (21 active and 7 inert tablets).

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 OC- users over 35 years of age. You should not use birth control pills while smoking.

Oral contraceptives **do not protect** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex condoms **in combination with** oral contraceptives.

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.

If you see a different doctor, inform him or her that you are taking DEMULEN 30.

BEFORE you use DEMULEN talk to your doctor or pharmacist if:
- Pregnant or breastfeeding
- History of jaundice or other liver disease
- High blood pressure
- Migraines and headaches
- Diabetes or family history of diabetes
- Wear contact lenses
- Family history of breast disease (e.g. breast lumps) or a family history of breast cancer
- Fibroid tumours on the uterus
- History of emotional disorders, especially

depression
- Metabolic or endocrine diseases and abnormal metabolism of calcium and phosphorus
- Rheumatoid arthritis or synovitis
- Hereditary or history of angioedema (episodes of swelling in body parts such as hands, feet, face, or airway passage)
- Abnormal level of fat in the blood stream (high cholesterol or triglycerides)
- Smoke cigarettes
- Heart or kidney disease
- Epilepsy
- Gallbladder or pancreatic disease
- Family history of blood clots, heart attacks or strokes.
- Persistent irregular vaginal bleeding
- Overweight
- Systemic lupus erythematosus
- Inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- Hemolytic uremic syndrome
- Sickle cell disease
- Problems with the valves in your heart and/or have an irregular heart rhythm

If you detect any new masses on your breasts while taking DEMULEN you should advise your doctor.

If you have to undergo a **major** elective surgery, you should advise your surgeon that you are taking DEMULEN. You should consult your doctor about stopping the use of DEMULEN four weeks before surgery and not use DEMULEN for a time period after surgery or during bed rest.

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

DEMULEN 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. Use DEMULEN 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.

Breakthrough bleeding/spotting may occur while you are taking an oral contraceptive, especially during the first three months of use. If this bleeding persists or recurs, you should advise your doctor. Women with history of amenorrhea (absence of menstrual periods) or oligomenorrhea (irregular or infrequent menstrual periods) may remain anovulatory or become amenorrheic following discontinuation of oral contraceptives.

The Risks of Using Birth Control Pills

1. **Circulatory disorders (including blood clots in legs, lungs, heart, eyes or brain)**
   Blood clots are the most common serious side effect of birth control pills. Clots can occur in many areas of the body.

   - In the brain, a clot can result in a stroke.
   - In a blood vessel of the heart, a clot can result in a heart attack.
   - In the legs and pelvis, a clot can break off and travel to the lung resulting in a pulmonary embolus.
   - In a blood vessel leading to an arm or leg, a clot can result in damage to or loss of a limb.

   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.

   Women who use birth control pills have a higher incidence of blood clots. While the risk of blood clots increases with age in both pill users and non users, the increased risk from the pill appears to be present at all ages. 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 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.

Women with the following conditions should be examined yearly by their doctors no matter what method of contraception they use:

- a history of breast cancer in the family
- breast nodules or thickenings
- discharge from the nipple

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

3. Cervical cancer

Some studies have found an increase of cancer of the cervix in women who use hormonal contraceptives, although this finding may be related to factors other than the use of oral contraceptives. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

4. Dangers to developing child if birth control pills are used during pregnancy

Oral contraceptives should not be taken by pregnant women because they may damage the developing child. An increased risk of heart and limb and other defects has been associated with the use of sex hormones, including oral contraceptives, during pregnancy. In addition, the developing female child whose mother has received DES (diethylstilbestrol), an estrogen, during pregnancy has a risk of developing cancer of the vagina or cervix in her teens or young adulthood. Abnormalities of the urinary tract and sex organs have been reported in male offspring so exposed. It is possible, although this has not been demonstrated, that other estrogens such as those in oral contraceptives could have the same effect in the child if the mother takes them during pregnancy.

There is also no conclusive evidence that the use of birth control pills immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking birth control pills to become pregnant, however, her doctor may recommend a different method of contraception until she has a period on her own. In this way, the pregnancy can be more accurately dated.

5. Gallbladder disease and liver tumours

Users of birth control pills 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.

The short and long-term use of birth control pills also has been linked with the growth of benign or malignant liver tumours. Such tumours are **extremely** rare. Benign tumours do not spread but they may rupture and produce internal bleeding which may cause death.

6. Use during pregnancy

Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing and may interfere with the normal development of the baby.

7. Pregnancy after stopping taking birth control pills

You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternate methods of contraception during this time.

8. Use after pregnancy, miscarriage or abortion

Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.

9. Use while breastfeeding

If you are breast feeding, consult your doctor before starting the birth control pill. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. The long-term effects on the developing child are not known. However, cases of breast enlargement have been reported in breast-fed infants. You should use another method of contraception and only consider starting the birth control pill once you have weaned your child completely.

INTERACTIONS WITH THIS MEDICATION

The concurrent administration of DEMULEN with other drugs may result in an altered effectiveness of either drug. It is important to advise your doctor of any drug you are taking, both prescription and non-prescription, before you take DEMULEN.

Drugs that may interact with DEMULEN include:

- Anticonvulsants (carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, topiramate, lamotrigine)
- Antibiotics (ampicillin, cotrimoxazole, penicillin, rifampin, chloramphenicol, metronidazole, neomycin, nitrofurantoin, sulfonamides, tetracyclines, troleandomycin, rifabutin)
- Antifungals (griseofulvin, fluconazole)
- Cholesterol Lowering Agents (clofibrate, atorvastatin)
- Sedatives and Hypnotics (benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate, chlordiazepoxide, lorazepam, oxazepam, diazepam)
- Antacids
- Alpha-II Adrenoreceptor Agents (clonidine)
- Antidiabetic Drugs (oral hypoglycemics and insulin)
- Antihypertensive Agents (guanethidine, methyldopa and beta blockers)
- Antipyretics (acetaminophen, antipyrine, ASA)
- Betamimetic Agents (isoproterenol)
- Corticosteroids (prednisone, dexamethasone)
- Phenothiazine Tranquilizers (all phenothiazines, reserpine and similar drugs)
- HIV infection (ritonavir, indinavir)
- Bronchodilator (theophylline)
- Stimulants (modafinil)
- Tricyclic antidepressants (clomipramine)
- Others: pheylbutazone, antihistamines, analgesics, antimigraine preparations, anticoagulants, aminocaproic acid, vitamin E, vitamin B12, vitamin C, cyclosporine, folic acid, meperidine, St John's wort, flunarizine

Caffeine and alcohol may also affect the efficacy of Oral Contraceptives.

During concomitant use of DEMULEN and substances that may affect its effectiveness, it is recommended that you use a non-hormonal back-up method of birth control in addition to the regular intake of DEMULEN. In the case of prolonged use of such substances, oral contraceptive should not be considered the primary contraceptive. After discontinuation of substances that interact with DEMULEN, use of a non-hormonal back-up method is recommended for at least 7 days.

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

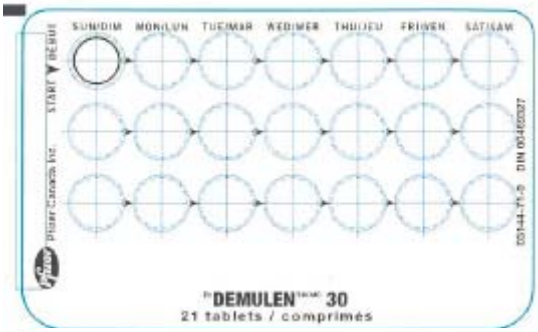
PROPER USE OF THIS MEDICATION

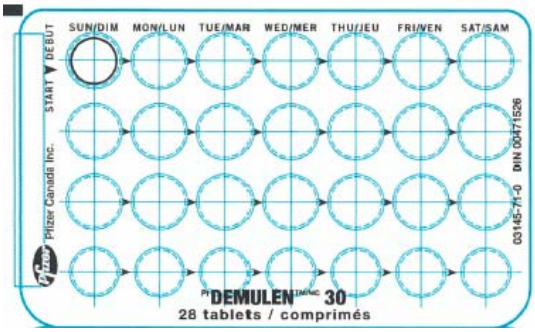
Usual dose:

1. Read these directions
   - Before you start taking your pills, **and**
   - Any time you are not sure what to do.

2. **Look at your pill pack** to see if it has 21 or 28 pills:
   - 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then 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. It is recommended that you use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle

of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.

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

5. **Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months on the pill.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

7. **If you miss pills at any time, you could get pregnant. The greatest risks for pregnancy are:**
   - When you start a pack late, or
   - When you miss pills at the beginning or at the very end of the pack.

8. **Always be sure you have ready:**
   - **Another kind of birth control** (such as latex condoms and spermicidal foam or gel) to use as back-up 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**, such as antibiotics, you pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

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

11. **If your questions are not answered here, call your doctor or clinic.**

There is no need to stop taking birth control pills for a rest period.

When to start the first pack of DEMULEN pills:

Be sure to read these instructions;

- before you start taking your pills, and
- any time you are not sure what to do.

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

A. 21-day combination:

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 doctor may advise you to start taking the pills 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.

2. Label your pack correctly before starting. The pack is pre-printed with a Sunday starting day. If you are starting on a day other than a Sunday, use the sticker labels provided. Peel off the label with the chosen starting day and apply over the pre-printed days on top of the card.

3. Take one pill at approximately the same time every day for 21 days. T**hen take no pills for seven days.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period).

B. 28-day combination

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

1. **The first day of your menstrual period (bleeding) is day 1 of your cycle.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. Label your pack correctly before starting. The pack is pre-printed with a Sunday starting day. If you are starting on a day other than a Sunday, use the sticker labels provided. Peel off the label with the chosen starting day and apply over the pre-printed days on top of the card.

3. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **not missing any days.** Your period should occur during the last seven days of using the pills

What to do during the month

1. **Take a pill at approximately the same time every day until the pack is empty.**
   - Try to associate taking your pill with some regular activity 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**
   - **21 Pills: Wait seven days** to start the next pack. You will have your period during that week.
   - **28 Pills:** Start the next pack **on the next day.** Take one pill every day. Do not wait any days between packs.

Overdose:

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.

Numerous cases of the ingestion, by children, of estrogen progestogen combinations have been reported. Although mild nausea may occur, there appears to be no other reaction. Treatment should be limited to a laxative such as citrate of magnesia with the aim of removing unabsorbed material as rapidly as possible

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

SUNDAY START	OTHER THAN SUNDAY START
MISS ONE PILL Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	**MISS ONE PILL** Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
MISS TWO PILLS IN A ROW **First two Weeks:** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week:** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**MISS TWO PILLS IN A ROW** **First two Weeks:** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week:** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**
MISS THREE OR MORE PILLS IN A ROW **Anytime in the Cycle:** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**MISS THREE OR MORE PILLS IN A ROW** **Anytime in the Cycle:** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**

NOTE: 28-DAY PACK: If you forget any of the seven reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You

do not need to use a back-up method.

Always be sure you have on hand:
- A back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- An extra, full pack of pills.

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

NON-CONTRACEPTIVE BENEFITS OF BIRTH CONTROL PILLS

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

- Effects of menses: increased menstrual cycle regularity; decreased menstrual blood loss; decreased incidence of iron deficiency anemia secondary to reduced menstrual blood loss; decreased incidence of dysmenorrhea (painful periods) and premenstrual syndrome (PMS)
- Effects related to ovulation inhibition: decreased incidence of functional ovarian cysts; decreased incidence of ectopic pregnancy
- Effects on other organs of the reproductive tract: decreased incidence of acute uterine tube inflammation; decreased incidence of endometrial cancer (50 per cent); decreased incidence of ovarian cancer (40 per cent); potential beneficial effects on endometriosis; decreased incidence of acne, excessive hair growth and other male hormone-related disorders
- Effects on breasts: decreased incidence of benign (non-cancerous) breast disease; decreased incidence of breast biopsies

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some users of birth control pills have unpleasant side effects. These side effects are temporary and are not hazardous to health. There may be tenderness of the breasts, nausea, and vomiting. Some users will experience weight gain or loss. Many of these side effects occurred with high dose combination birth control pills. These side effects are less common with the low dose pills prescribed today.

Unexpected vaginal bleeding or spotting and changes in the usual menstrual period also may occur. These side effects usually disappear after the first few cycles. They are NOT an indication to stop taking birth control pills. Unless more significant complications occur, a decision to stop using the pill or to change the brand of pill should be made only after three consecutive months of use.

Occasionally, users develop high blood pressure that may require stopping the use of birth control pills. High blood pressure may persist after stopping the pill and may lead to serious disease of the kidney and circulatory system.

Other side effects may include:
- growth of pre-existing fibroid tumours of the uterus
- mental depression
- liver problems with jaundice (yellowing of the skin)
- an increase or decrease in hair growth (hirsutism, loss of scalp hair), sex drive and appetite
- skin pigmentation
- headaches
- migraines
- rash
- vaginal infections

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

A woman's menstrual period may be delayed after stopping birth control pills. There is no evidence that the use of the pill leads to a decrease in fertility. As mentioned, it is wise to delay starting a pregnancy for one menstrual period after stopping birth control pills.

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Abdominal pain, nausea or vomiting or lump in the abdomen		√	
Sharp pain in the chest, coughing blood, or sudden shortness of breath (These symptoms could indicate a possible blood clot in the lung)			√
Pain or swelling in the leg (this symptom could indicate a possible blood clot in the leg)			√
Crushing chest pain or heaviness (this symptom could indicate a possible heart attack).			√
Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg, or numbness in the face (these symptoms could indicate a possible stroke)			√
Sudden partial or complete loss of vision, double vision (this symptom could indicate a possible blood clot in the eye)			√
Severe pain or lump in the abdomen (these symptoms could indicate a possible tumor of the liver)		√	
Persistent sad mood		√	
Yellowing of the skin (jaundice)			√
Unexpected vaginal bleeding		√	
Unusual swelling of the extremities		√	
Breast lumps		√	

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

HOW TO STORE IT

Store DEMULEN between 15°C and 25°C.
Keep DEMULEN and all medication out of 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 www.healthcanada.gc.ca/medeffect**
- **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 0701D
    Ottawa, Ontario
    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.healthcanada.gc.ca/medeffect.

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 plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001

This leaflet was prepared by Pfizer Canada Inc.

Last revised: 17 February 2014