

plan B™ (LEVONORGESTREL)

NAME OF DRUG

Plan B™ (Levonorgestrel Tablets) 0.75mg

THERAPEUTIC CLASSIFICATION

Emergency Contraception

This product is intended to prevent pregnancy. It does not protect against sexually transmitted diseases, including HIV/AIDS.

ACTION AND CLINICAL PHARMACOLOGY

Emergency contraceptives are intended to be used after known or suspected contraceptive failure or unprotected intercourse. They are not effective if a woman is already pregnant. **Plan B™** (levonorgestrel) is believed to act as an emergency contraceptive principally by preventing ovulation or by inhibiting fertilization (by altering tubal transport of sperm and/or ova). It may also prevent implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

The absolute bioavailability of **Plan B™** in humans has not been specifically investigated. However, levonorgestrel is reported in the literature to be rapidly and completely absorbed following oral administration and does not undergo first pass metabolism.

Plan B™ reaches a maximum serum concentration of 14.1 ± 7.7 ng/mL at an average of 1.6 ± 0.7 hours after a single dose (0.75 mg) under fasting conditions. It has a mean terminal elimination half-life of 24.4 ± 5.3 hours. Orally administered levonorgestrel is found in breast milk at levels approximating a plasma/milk ratio of 100:15.

INDICATIONS AND CLINICAL USE

Plan B™ (levonorgestrel 0.75 mg tablets) is an emergency contraceptive that can prevent pregnancy if the first tablet is taken within 72 hours (three days) following unprotected intercourse or a contraceptive accident, and the second tablet is taken 12 hours later.

As an emergency contraceptive, **Plan B™** is indicated following any unprotected act of sexual intercourse, including:

- when no contraceptive has been used
- when a contraceptive method may have failed, including:
 - condom rupture, slippage, or misuse
 - diaphragm or cap dislodgment, breakage or early removal
 - failed coitus interruptus
 - miscalculation of periodic abstinence method
 - IUD expulsion
 - missed oral contraceptive
 - a delay in starting a new packet of oral contraceptives
 - a delay in getting a scheduled contraceptive injection
- in cases of sexual assault

Plan B™ is more effective than two tablets containing 0.1 mg of ethinyl estradiol and 0.5 mg of levonorgestrel (the Yuzpe regimen). In a double-blind comparative clinical study of 1955 evaluable women, the relative risk of pregnancy following the use of the Yuzpe regimen was 2.8 times higher than that of **Plan B™**. In this study, **Plan B™** prevented 89% of expected pregnancies when used according to the instructions by the 976 evaluable women on this regimen. After a single act of intercourse the pregnancy rate was less than 1% for women who started treatment within 72 hours of intercourse. With no contraception, the expected pregnancy rate is 8% after a single act of intercourse.

Treatment should not be delayed as efficacy may decline with an increased interval between intercourse and the start of treatment. Efficacy is greatest when treatment is taken within 24 hours of unprotected intercourse (95% of expected pregnancies prevented), decreasing somewhat during each subsequent 24 hour period (prevents 61% of expected pregnancies when taken during the 48 to 72 hour period).

The pregnancy rate of **Plan B™** (levonorgestrel 0.75 mg tablets) is calculated for a single use. If **Plan B™** is used on more than one occasion, the cumulative pregnancy rate will be higher. **Plan B™** is not recommended for routine use as a contraceptive.

Plan B™ will not prevent pregnancy from future acts of unprotected intercourse.

Following use of this product, the woman should either abstain or use an alternative contraceptive method until her next menstrual cycle.

CONTRAINDICATIONS

Plan B™ (levonorgestrel 0.75 mg tablets) is contraindicated in women with known or suspected pregnancy. The method is not to be used by a woman who is pregnant due to a previous act of intercourse.

Plan B™ is not recommended for use in patients with undiagnosed abnormal vaginal bleeding.

Women with hypersensitivity to any component of these tablets should not use **Plan B™**.

Progestin-only oral contraceptives are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions (acute liver disease or history of or actual benign or malignant liver tumours, known or suspected carcinoma of the breast, and undiagnosed abnormal vaginal bleeding). It is not known whether these same conditions apply to the **Plan B™** regimen consisting of the emergency use of two progestin pills, but these risks should be considered if **Plan B™** needs to be administered several times.

WARNINGS

General: The use of cyclic combination oral contraceptives containing estrogen and progestin is associated with increased risks of several serious conditions, including thromboembolic and cardiovascular disorders (e.g. thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis,

retinal thrombosis), hepatic neoplasia and gallbladder disease. These conditions have not been associated with the routine use of progestin-only oral contraceptives, but whether short-term (12 hour) use of high-dose progestin-only contraceptives would accentuate the risk is unknown. **Plan B™** does not contain estrogen. Controlled clinical trials using **Plan B™** and postmarket experience with levonorgestrel for postcoital and emergency contraception have not so far identified any serious adverse events.

Plan B™ is not recommended for routine use as a contraceptive. The pregnancy rate of **Plan B™** (levonorgestrel 0.75 mg tablets) is calculated for a single use. If **Plan B™** is used on more than one occasion, the cumulative pregnancy rate will be higher.

Plan B™ is not effective in terminating an existing pregnancy.

Effects on Menses: Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking **Plan B™**. At the time of expected menses, approximately 75% of women using **Plan B™** had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within ± 7 days, while only 13% had a delay of more than 7 days beyond the anticipated onset of menses. **If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.**

Ectopic pregnancy: Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). **Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only oral contraceptives are ectopic.** A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. However, physicians should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking **Plan B™**.

PRECAUTIONS

General: Patients should be advised that Plan B™ provides no protection against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up: Before **Plan B™** is used, a brief medical and menstrual history should be obtained and the risks of pregnancy and risks associated with progestin-only oral contraceptives should be reviewed with the woman. A pregnancy test and/or a physical examination are warranted if pregnancy is suspected. Women should be counseled to abstain from sexual intercourse or use an alternative contraceptive method until the onset of their next normal menstrual period. If a normal menstrual period has not occurred within 3 to 4 weeks after **Plan B™** has been used, the woman's pregnancy status should be confirmed with a pregnancy test at the time of the follow-up visit or contact with the health care provider. Counselling on routine contraception for future use should be provided as appropriate.

Pregnancy: **Plan B™** should not be taken by pregnant women as it will not be effective. Studies involving women who have taken combined oral contraceptives containing levonorgestrel inadvertently during early pregnancy do not suggest that these drugs have an adverse effect on the fetus and there is no evidence that **Plan B™** (levonorgestrel 0.75 mg tablets) taken as an emergency contraceptive would have an adverse effect on an established pregnancy. However, there are insufficient data to rule out the possibility of adverse effects on the fetus if **Plan B™** is used after a woman is already pregnant or in cases of method failure.

Nursing Mothers: Administration of combined oral contraceptives and progestin-only contraceptives to breastfeeding women has been reviewed in the literature. Seven studies were reviewed that analyzed the transmission of progestins in breast milk. Data were obtained as early as one week post-partum up to approximately six months post-partum. Very small amounts of progestin have been measured in the milk of breastfeeding mothers who are taking progestin-only contraceptives. Levonorgestrel is transferred from maternal breast milk to infants, with infant plasma levels approximately 40% of those in breast milk and approximately 1% to 6% of maternal plasma. No adverse effects due to progestin-only oral contraceptives have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth, or development of the infant.

Hepatic Function: Following a single oral dose, levonorgestrel 0.75 mg does not appear to be significantly metabolized by the liver. The risks of **Plan B™** to women with a history of liver disease is unknown. Women with a history of liver disease should be given **Plan B™** under medical supervision especially if the method needs to be administered more than once.

Hypertension: Patients with essential hypertension whose blood pressure is well-controlled may be given combined oral contraceptives containing estrogen and progestin, but only under close supervision. Progestin-only oral contraceptives are not contraindicated for such patients.

Migraine and Headache: During the use of **Plan B™**, the onset or exacerbation of migraine or the development of a new pattern that is recurrent, persistent or severe requires evaluation of the cause and may require discontinuation of the second dose of and/or future use of emergency contraceptive pills.

Diabetes: The effects of **Plan B™** on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use progestin-only oral contraceptives do not generally experience changes in their insulin requirements. Nevertheless, diabetic women should be monitored while taking **Plan B™**.

Laboratory Tests and Tissue Specimens: Use of oral contraceptives can modify the results of laboratory tests. Lab tests should therefore be done prior to dosing or more than 3 days after dosing to avoid misinterpretation of the results. Pathologists should be advised about oral contraceptive therapy when specimens obtained from Pap smears are submitted for examination.

Food and Drug Interactions: No formal pharmacokinetic studies of the effect of food have been performed. Efficacy is presumed to be independent of the timing of meals since no instruction on timing of dosing relative to meals was provided to the participants in the primary clinical trials supporting the indication. There are no published drug interaction

studies of levonorgestrel. Contraceptive steroids are known to be sensitive to anticonvulsants, griseofulvin, rifampicin, and certain other antibiotics (decreased efficacy) and acetaminophen.

Anticonvulsant Drugs: There was a marked decrease in the AUC of levonorgestrel following 12 weeks of treatment with phenytoin and carbamazepine (42% and 40%, respectively). In contrast, sodium valproate had no detectable effect. These results are consistent with the known effects of the drugs on liver enzyme induction. A number of reports exist in the literature on oral contraceptive failures in women using certain anticonvulsants, most commonly phenytoin.

Antibiotics (see below for Rifampicin): No consistent effect has been found in formal pharmacokinetic studies of a number of antibiotics (including ampicillin, cotrimoxazole, tetracycline, the quinolone temafloxacin, and the macrolide clarithromycin) on plasma concentrations of steroids, in particular ethinyl estradiol. It is impossible at the present time to evaluate fully the potential impact of antibiotics on efficacy based on the literature.

Rifampicin: Rifampicin is a potent enzyme inducer and, as with anticonvulsant drugs, there is a molecular basis for expecting an interaction with contraceptive steroid efficacy. Oral contraceptive failures, menstrual abnormalities, and low progesterone levels have been shown in subjects being treated simultaneously with oral contraceptives and rifampicin.

Acetaminophen: Paracetamol is metabolized primarily by conjugation with sulfuric and glucuronic acids and hence has the potential for interfering with ethinyl estradiol metabolism. However, a similar effect on levonorgestrel was not shown in the same study.

ADVERSE REACTIONS

The most common adverse events reported in the Pivotal Study of **Plan B™** (Study 1) (levonorgestrel 0.75 mg tablets) included:

- Nausea: 23%
- Abdominal pain: 18%
- Fatigue: 17%
- Headache: 17%
- Vomiting: 6%
- Intermenstrual bleeding and altered menstrual cycles: Some women may experience spotting a few days after taking **Plan B™**. The majority of women (58%) will have their next menstrual period at about the expected time or a few days early or late; if there is a delay in the onset of menses of more than one week, the possibility of pregnancy should be considered. Women who take **Plan B™** frequently are likely to experience disruptions of the menstrual cycle.
- Other: Breast tenderness, dizziness and diarrhea have been reported in women using **Plan B™** and may be drug related.

In this comparative clinical study involving 1,955 evaluable women, the incidence of nausea and vomiting, were significantly ($P < 0.01$) less for women using **Plan B™** than for women receiving the Yuzpe regimen. Adverse events reported in the other controlled clinical trial of the **Plan B™** regimen by Ho and Kwan (Study 2) were consistent with those in the Pivotal Study (Study 1) (Table 1).

In the combined controlled clinical trials, the proportion of women receiving levonorgestrel who reported nausea was less than half of the proportion in the Yuzpe group (Table 2). The proportion that reported vomiting in the levonorgestrel group was only one-fourth that in the Yuzpe group.

TABLE 1.
Frequency of Adverse Experiences by Body System Reported in 1% of Subjects for Emergency Contraception: Subjects in Controlled Clinical Trials (June 1998)

Body System/ Preferred Term	Study 1 (WHO/HRP 1998 - Study 92908)		Study 2 Ho and Kwan, 1993	
	Levonorgestrel N = 977 (%)	Yuzpe N = 979 (%)	Levonorgestrel N = 977 (%)	Yuzpe N = 979 (%)
Body, Whole				
Abdominal pain	172 (17.6)	205 (20.9)	—	—
Fatigue	165 (16.9)	279 (28.5)	98 (23.9)*	156 (36.8)
Flu syndrome	10 (1.0)	9 (0.9)	—	—
Digestive				
Diarrhea	49 (5.0)	64 (6.5)	—	—
Nausea	226 (23.1)*	494 (50.5)	66 (16.1)*	197 (46.5)
Vomiting	55 (5.6)*	184 (18.8)	11 (2.7)*	95 (22.4)
Nervous				
Dizziness	109 (11.2)	163 (16.6)	76 (18.5)	98 (23.1)
Headache	164 (16.8)	198 (20.2)	—	—
Urogenital				
Breast tenderness	105 (10.7)	118 (12.1)	65 (15.9)	88 (20.8)
Bleeding more	133 (15.6)	116 (11.8)	—	—
Vaginal hemorrhage	10 (1.0)	12 (1.2)	14 (3.4)	18 (4.2)

*significantly different

TABLE 2.
Frequency of Adverse Experiences by Body System Reported in 1% of Subjects for Emergency Contraception: Subjects in Controlled Clinical Trials (Pooled), March 1999

Body System/Preferred Term	Levonorgestrel N = 1387 (%)	Yuzpe N = 1403 (%)
Body, Whole		
Fatigue	263 (19.0)	435 (31.0)
Digestive		
Nausea	292 (21.1)	691 (49.3)
Vomiting	66 (4.8)	279 (19.9)
Nervous		
Dizziness	185 (13.3)	261 (18.7)
Urogenital		
Breast tenderness	170 (12.3)	206 (14.7)
Spotting/bleeding	24 (1.7)	30 (2.1)

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There are no data on overdosage of **Plan B™**; however, it is anticipated that the incidence and severity of nausea and vomiting and of menstrual cycle disturbances may be increased. In case of overdose or accidental ingestion by children, treatment is generally not required, but the patient should be closely observed by the physician and gastric lavage may be employed if considered necessary.

DOSAGE AND ADMINISTRATION

One tablet of **Plan B™** (levonorgestrel 0.75 mg tablets) should be taken orally as soon as possible but within 72 hours after unprotected intercourse. The second tablet must be taken at 12 hours after the first dose. The total dosage for one complete regimen of **Plan B™** is 1.50 mg levonorgestrel.

Plan B™ can be administered at any time during the menstrual cycle.

The patient should be instructed to contact her health care provider if she vomits in the first hour after taking either dose of medication. An additional dose may be administered, based on the judgement of the physician. In clinical studies, of the 55 women who vomited as a result of taking **Plan B™**, 40 took a replacement dose. Statistical analysis showed that the replacement dose did not increase efficacy significantly. If vomiting occurs as a result of taking **Plan B™**, it is possible that sufficient quantities of the hormone have been absorbed, as the maximum blood level after oral consumption is reached in about 1.6 hours. If vomiting occurs, for other reasons (such as the flu), or if the pills are visible in the emesis, a replacement dose may be warranted.

The patient should be counselled to abstain or utilize an alternative method of contraception (e.g., diaphragm or condom) until the next menstrual cycle. A menstrual period usually begins within 2-3 weeks after medication administration.

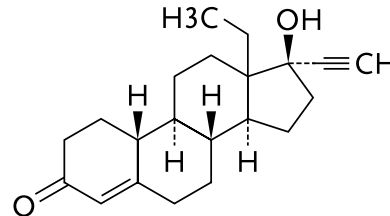
PHARMACEUTICAL INFORMATION

Trade Name: **Plan B™**

Proper Name: Levonorgestrel (USAN), Progestin (INN, BAN)

Chemical Name: 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-(17)-(-)-

Structural Formula:



Molecular Formula: C₂₁H₂₆O₂

Molecular Weight: 312.45 grams/mole

Description: White or almost white crystalline powder.

Solubility: Practically insoluble in water, soluble in chloroform, sparingly soluble in ethanol and methylene chloride.

Melting Point: 232 – 239°C

Composition: Each 100 mg **Plan B™** tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-(17)-(-)-], a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate.

AVAILABILITY

How Supplied: Almost white, flat, rimmed tablets of about 6 mm diameter with an impressed mark of "INOR" on one side. **Plan B™** tablets (0.75 mg of levonorgestrel) are available in PVC/aluminum foil blister packages of two tablets each, which are permanently sealed in a double-layer, six panel outer package.

Storage: Store **Plan B™** tablets between 15°C and 30°C (59-86°F). Protect from high humidity.

Product Monograph is available upon request from Paladin Labs Inc.

 **paladin**

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