PRODUCT MONOGRAPH

CONTINGENCY ONE™

Levonorgestrel Tablet

1.5 mg

Manufacturer's Standard

EMERGENCY CONTRACEPTION

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, ON
M8Z 2S6

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PART I: HEALTH CARE PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet 1.5 mg	Colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate and polyvinyl pyrrolidone K-25.

INDICATIONS AND CLINICAL USE

CONTINGENCY ONE™ (levonorgestrel 1.5 mg tablet) is an emergency contraceptive that can prevent pregnancy and is intended to be used within 72 hours (three days) following known or suspected contraceptive failure or unprotected intercourse such as:

- 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
  - expelled intrauterine device
  - 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

Treatment should not be delayed as efficacy may decline with an increased interval between intercourse and the start of the treatment. Efficacy is greatest when treatment is taken within 24 hours of unprotected intercourse, decreasing somewhat during each subsequent 24-hour period.

The pregnancy rate of CONTINGENCY ONE™ (levonorgestrel 1.5 mg tablet) is calculated for a single use. If CONTINGENCY ONE™ is used on more than one occasion, the cumulative

pregnancy rate will be higher. CONTINGENCY ONE™ is not recommended for routine use as a contraceptive.

CONTINGENCY ONE™ 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.

Note to Pharmacist: If you determine that a woman is a repeat user of Emergency Contraception (defined as use more than once a month on a regular basis) or that CONTINGENCY ONE™ has been used within the past cycle, you should consider discussing other, more effective contraceptive methods with the woman, as well as encouraging her to see her physician or other health professional for contraceptive counselling services and advise on other methods of contraception and prevention of sexually transmitted infections. CONTINGENCY ONE™ should still be dispensed, if indicated.

Geriatrics: Levonorgestrel tablet 1.5 mg has not been studied in this population.

Pediatrics: Levonorgestrel tablet 1.5 mg has not been studied in this population.

CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance levonorgestrel or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- 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, especially if there is recent abnormal bleeding, a pregnancy test should be performed before taking CONTINGENCY ONE™.
- Patients with undiagnosed abnormal vaginal bleeding, a pregnancy test should be performed before taking CONTINGENCY ONE™.

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 CONTINGENCY ONE™ regimen consisting of the emergency use of one progestin pill, but these risks should be considered if CONTINGENCY ONE™ needs to be administered several times.

WARNINGS AND PRECAUTIONS

General

CONTINGENCY ONE™ is not an abortifacient and should not be taken by pregnant women, as it will not be effective.

Patients should be advised that CONTINGENCY ONE™ provides no protection against HIV infection (AIDS) and other sexually transmitted diseases.

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 (single dose) use of high-dose progestin-only contraceptives would accentuate the risk is unknown. CONTINGENCY ONE™ does not contain estrogen. Controlled clinical trials using levonorgestrel tablets and post-market experience with levonorgestrel for postcoital and emergency contraception have not so far identified any serious adverse events.

CONTINGENCY ONE™ **is not recommended for routine use as a contraceptive.** The pregnancy rate of CONTINGENCY ONE™ (levonorgestrel 1.5 mg tablet) is calculated for a single use. If CONTINGENCY ONE™ is used on more than one occasion, the cumulative pregnancy rate will be higher.

Migraine and Headache: During the use of CONTINGENCY ONE™, 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 re-evaluation of a future use of emergency contraceptive pills.

Concomitant use of CONTINGENCY ONE™ and drugs containing ulipristal acetate is not recommended (see Drug-Drug Interactions section).

Carcinogenesis and Mutagenesis

See Toxicology section in Part II: Scientific Information.

Cardiovascular

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.

Endocrine and Metabolism

Diabetes: The effects of CONTINGENCY ONE™ 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 CONTINGENCY ONE™.

Hepatic

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

Sexual Function/Reproduction

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 CONTINGENCY ONE™. At the time of expected menses, approximately 77% of women using levonorgestrel tablet had vaginal bleeding similar to their normal menses, 11-12% bled more than usual, and 11% bled less than usual. The majority of women (78%) had their next menstrual period at the expected time or within 5 days, while only 4.5% 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.** However, there appears to be no increase in the rate of ectopic pregnancy after use of levonorgestrel for emergency contraception. 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 CONTINGENCY ONE™.

Suspected Pregnancy: A pregnancy test is 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 is delayed beyond 1 week, the patient's pregnancy status should be confirmed with a pregnancy test and follow-up with a health professional. Counseling on routine contraception for future use should be provided as appropriate.

Special Populations

Pregnant Women: CONTINGENCY ONE™ is not an abortifacient and 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 CONTINGENCY ONE™ (levonorgestrel 1.5 mg tablet) 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 CONTINGENCY ONE™ is used after a woman is already pregnant or in cases of method failure.

Nursing Women: Administration of combined oral contraceptives and progestin-only contraceptives to breastfeeding women has been reviewed in the literature[13]. 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[13, 14]. 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.

Pediatrics: No data is available.

Geriatrics: No data is available.

Body weight: Limited and inconclusive data suggest that there may be reduced efficacy of levonorgestrel with increasing body weight or body mass index (BMI). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the women's body weight or BMI.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

There are in general no serious adverse drug reactions to report following the use of levonorgestrel tablets 0.75 mg, either in clinical trials or post-market surveillance. Most commonly observed adverse drug reactions are presented in the following sections.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be

compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Levonorgestrel Tablets 0.75 mg, divided dose regimen

The most common adverse events reported in the Pivotal Study (Study 92908) of levonorgestrel tablet 0.75 mg when administered as two doses of 0.75 mg at a 12-hour interval 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 levonorgestrel tablets. 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 excluded. Women who take levonorgestrel tablets frequently are likely to experience disruptions of the menstrual cycle.
- *Other:* breast tenderness, dizziness and diarrhea have been reported in women using levonorgestrel tablets 0.75 mg 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 levonorgestrel tablets than for women receiving the Yuzpe regimen. Adverse events reported in the other controlled clinical trial of the levonorgestrel tablets regimen by Ho and Kwan [10] were consistent with those in the Pivotal Study (Study 92908) (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/MedDRA Preferred Term	WHO/HRP 1998 - Study 92908		Ho and Kwan, 1993	
	Levonorgestrel N = 977 (%)	Yuzpe N = 979 (%)	Levonorgestrel N = 410 (%)	Yuzpe N = 424 (%)
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, $P < 0.001$

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/ MedDRA 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)

*Significantly different, $P < 0.001$

The levonorgestrel tablets 0.75 mg OTC Label Comprehension Study[18] was conducted to evaluate whether levonorgestrel tablets 0.75 mg can be used safely and effectively without oversight by a licensed medical practitioner. A total of 540 women used the study product. No

serious adverse events were reported. The findings of the study, compared to those of the Pivotal study, indicate that the pattern of adverse events does not change when the product is provided in a non-prescription setting. (Table 3)

Table 3: Adverse Events in OTC Actual Use Study and WHO Pivotal Clinical Trial

	% Subjects Reporting Adverse Events	
Adverse Event	**OTC Actual Use Study WCC/FHI 2002 N = 540**	**WHO/HRP 1998 Study 92908 N = 979**
Abdominal Pain	14.3	17.6
Asthenia (Fatigue)	8.0	16.9
Headache	11.3	5.6
Nausea	12.4	23.1
Vomiting	1.2	5.6
Metrorrhagia	4.3	--
Dizziness	3.7	11.2
All other	29.6	13.5

Levonorgestrel 1.5 mg tablet single dose administration

In a double-blind pivotal trial, the safety profile of levonorgestrel was compared following the administration of a single dose of 1.5 mg or two doses of 0.75 mg at a 12-hour interval (Study 97902). A total of 2,756 women used the study product. There was no statistically significant difference in the incidence of the adverse events between the two levonorgestrel groups.

Table 4: Frequency of Adverse Experiences by Body System Reported in ≥1% of Subjects for Emergency Contraception: Subjects in Study 97902

Adverse Event	**Levonorgestrel One dose of 1.5 mg N = 1379 (%)**	**Levonorgestrel two tablets of 0.75 mg Administered at a 12-hour interval N = 1377 (%)**
Lower abdominal pain	183 (13.3)	198 (14.4)
Fatigue	184 (13.3)	182 (13.2)
Diarrhea	53 (3.8)	44 (3.2)
Nausea	189 (13.7)	199 (14.5)
Vomiting	19 (1.4)	19 (1.4)
Dizziness	132 (9.6)	126 (9.2)
Headache	142 (10.3)	130 (9.4)
Breast tenderness	113 (8.2)	115 (8.4)
Bleeding more	426 (30.9)	426 (30.9)
Delay of menses more than 7 days*	61 (4.5)	61 (4.5)

* The denominator for "Delay of menses more than 7 days" is 1359 and 1353, compared to 1379 and 1377 for the other adverse experiences listed in the table.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body as a whole: Back muscular pain, influenza, light headedness, numbness in lower extremities, migraine NOS, redness arms, redness of the chest, tiredness

Cardiovascular: Palpitations

Ear and Nose: Otitis

Gastrointestinal: Acute appendicitis, air in stomach, constipation, polydipsia

Hematology: High platelets counts, low haemoglobin (anaemia hypochromic)

Immunology: Acute tonsillitis, otitis, pharyngitis

Metabolic: Blood glucose increased

Musculoskeletal: Muscle twitching, leg cramps

Psychiatric: Weeping

Reproductive: Corpus luteum cyst or haematoma, ectopic pregnancy termination, late menses, vaginal mycosis

Respiratory: Coughing, rhinitis, sinusitis NOS

Skin and appendages: Acne, acne aggravated, chapped lips, rash

Urinary: Blood in urine, cystitis, ketone positive in urine, urinary protein increased, white blood cells positive in urine

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of Levonorgestrel Tablets, 0.75 mg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: Abdominal distension, abdominal pain, diarrhoea, nausea, vomiting

General disorders and administration site conditions: Fatigue

Musculoskeletal and connective tissue disorders: Back pain

Nervous system disorders: Dizziness, headache

Pregnancy, puerperium and perinatal conditions: Unintended pregnancy

Reproductive system and breast disorders: Breast tenderness, dysmenorrhoea, menorrhagia, menstruation delayed, menstruation irregular, oligomenorrhoea, pelvic pain, uterine hemorrhage, vaginal discharge, vaginal hemorrhage.

DRUG INTERACTIONS

Overview

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 [3]. As the efficacy of CONTINGENCY ONE™ may be decreased in cases of concomitant intake of these drugs, it is recommended that patients perform a pregnancy test if menses is delayed beyond 1 week.

Drug-Drug Interactions

Anti-HIV Drugs: The metabolism of levonorgestrel is enhanced by the concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%[24,25,26]. A similar reduction is suspected with the concomitant administration of ritonavir.

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)[5]. 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, primidone and phenobarbital.

Antibiotics (see below for rifampicin and rifabutin): No consistent effect has been found in formal pharmacokinetic studies[3] 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/Rifabutin: 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 progestin levels have been shown in subjects being treated simultaneously with oral contraceptives and rifampicin[13]. The metabolism of levonorgestrel is enhanced by the concomitant use of rifabutin.

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[15].

Ulipristal acetate: Ulipristal acetate is a progesterone receptor modulator that may interact with the progestational activity of levonorgestrel. Therefore the concomitant use of levonorgestrel and drugs containing ulipristal acetate is not recommended.

Drug-Food 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.

Drug-Herb Interactions

The concomitant use of *Hypericum perforatum* (St. John's wort) can decrease the efficacy of CONTINGENCY ONE™.

Interactions with other herbal products have not been established.

Drug-Laboratory Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CONTINGENCY ONE™ can be administered at any time during the menstrual cycle.

Recommended Dose and Dosage Adjustment

One tablet of CONTINGENCY ONE™ (levonorgestrel 1.5 mg) should be taken orally as soon as possible but within 72 hours after unprotected intercourse. The total dosage for one complete regimen of CONTINGENCY ONE™ consists in a single dose of 1.5 mg levonorgestrel.

The patient should be instructed to contact her health care professional if she vomits in the first two hours after taking the dose of medication. An additional dose may be administered, based on the judgment of the health care professional. In clinical studies, of the 55 women who vomited as a result of taking levonorgestrel tablets 0.75 mg, 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 CONTINGENCY ONE™, 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 of or use an alternative method of contraception (e.g., diaphragm or condom) until the next menstrual cycle. Most patients will have their next menstrual period at the expected time or within a week of the expected time. If a normal period is delayed beyond 1 week, the patient's pregnancy status should be confirmed with a pregnancy test and follow-up with a health professional.

OVERDOSAGE

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

There are no data on overdosage of CONTINGENCY ONE™; 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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. CONTINGENCY ONE™ (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.

Pharmacokinetics

Absorption and Distribution:
The absolute bioavailability of levonorgestrel tablets 0.75 mg 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.

Single dose Studies:
In WCC-PK 001, investigators administered single doses of 0.75 mg tablets to 16 healthy young women. The same subjects received levonorgestrel 0.75 mg as an oral suspension, prepared immediately prior to dosing. The rate and extent of absorption following administration of the suspension were lower than those measured following administration of the tablet (mean C_{max} of 7.52 ± 4.14 ng /mL occurring on average 2.8 ± 1.1 hours post-dose for

the suspension versus 14.1± 7.7 ng /mL and 1.6 ± 0.7 hours post-dose for the tablets). This pattern was observed in 14 of 16 subjects. (The lower bioavailability of the oral suspension is attributed to the larger particle size in the micronized drug substance as compared with that in the tablet.)

The volume of distribution (Vd) was estimated to be 260.0 L. Serum levels declined with a mean terminal half-life of 24.4 ± 5.3 hours following administration as a tablet and 27.3 ± 6.3 hours following administration as a suspension.

Results for the three published studies were similar to one another and also to results for the tablet in the WCC-sponsored study (Table 5). Reported half-lives were shorter in the published single dose studies, approximately 13 to 14 hours. The duration of sampling was shorter.

Table 5: Summary of Pharmacokinetic Parameter Values for Studies

Study	N	Dose	Mean (± S.D.)						
			C_{max} (ng/mL)	T_{max} (h)	T_{α} (h)	T_{β} (h)	Vd (L)	CL (L/h)	$AUC_{0-\infty}$ (ng/mL/h)
WCC-Sponsored Study of Proposed Commercial Formulation									
WCC-PK 001	16	0.75 mg	14.1 ± 7.7	1.6 ± 0.7	–	24.4 ± 5.3	260.0	7.7 ± 2.7	123.1 ± 50.1
Other Studies Performed with Gedeon Richter Formulation									
He 1990	10	0.75 mg	11.2 ± 3.4	1.9 ± 0.6	1.3 ± 0.6	13.3 ± 3.7	115 ± 41	6.1 ± 1.9	124 ± 43
Landgren 1989	10	0.75 mg	16.0	–	–	14.5	–	–	–
Shi 1988	6	0.75 mg	9.0 ± 2.2	2 ± 4	–	8.9 ± 1.9	88.6 ± 25.6	7.2 ± 2.7	116 ± 41

Multiple Dose Study:
One study[16], also provided results for seven-day dosing of six healthy young women. Serum levels on Day 7 were found to be somewhat lower than Day 1 levels (mean C_{max} value of 9.0 ng/mL for Day 1; 5.3 ng/mL mean C_{max} for Day 7 corrected values), and a longer half-life was reported (mean 12.6 hours on Day 7). Steady state was obtained on the fourth day, with no unanticipated accumulation.

Orally administered levonorgestrel is found in breast milk at levels approximating a plasma/milk ratio of 100:15.

Metabolism: Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3a,5b- and 3a,5a-tetrahydrolevonorgestrel with 16b-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2a and 16b positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Special Populations and Conditions

Age Effects: Due to the age range of women participating in these studies (19-44 years), and given that the target population for levonorgestrel emergency contraception is comparable, age effects have not been evaluated.

Race: Pharmacokinetic parameters have been summarized separately by ethnicity (Table 6). Ethnicity was not stated in the three published studies. Two studies were conducted in China, and presumably, all 16 subjects were Chinese. Similarly, the ten subjects participating in Sweden are all assumed to be Caucasian. There is a suggestion of lower concentrations in Asian subjects. These observations should be interpreted with caution, however, as in the U.S.-based study, there was only one Asian subject, and the assay methodology in the other studies differed.

Table 6: Summary of Levonorgestrel 0.75 mg Single Dose Tablet Pharmacokinetic Parameter Values by Ethnicity

Parameters	WCC-PK 001			Landgren, 1989	He, 1990	Shi, 1988
	Caucasian (U.S.) (N=9)	Black (U.S.) (N=6)	Asian/Pacific Islander (U.S.) (N=1)	— (Sweden) (N=10)	— (China) (N=10)	— (China) (N=6)
C_{max} (ng/mL)	15.9	12.2	9.4	16.0	11.2 ± 3.4	9.0 ± 2.2
T_{max} (h)	1.8	1.4	1.3	—	1.9 ± 0.6	2-4
$AUC_{0-\infty}$ (ng/mL/h)	131.5	120.7	62.5	—	124 ± 43	116 ± 41
Half life (h)	24.6	24.5	22.9	14.5	13.3 ± 3.7	8.9 ± 1.9
CL (L/hr)	6.4	7.2	12.0	—	6.1 ± 1.9	7.2 ± 2.7

Hepatic and Renal Insufficiency: No formal pharmacokinetic studies have been conducted in patients with renal or hepatic impairment. Since the product is administered as a single course of treatment there is no concern about the potential accumulation that might occur with chronic dosing in patients with hepatic or renal impairment.

STORAGE AND STABILITY

Store CONTINGENCY ONE™ tablet between 15°C and 30°C (59-86°F). Protect from high humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

How Supplied: Round, white to off-white, uncoated, flat tablet debossed with 251 on one side and plain on the other side.

Packaging: CONTINGENCY ONE™ tablet (1.5 mg of levonorgestrel) are available in Alu foil/PVC coated with PVdC, blister pack of one tablet each.

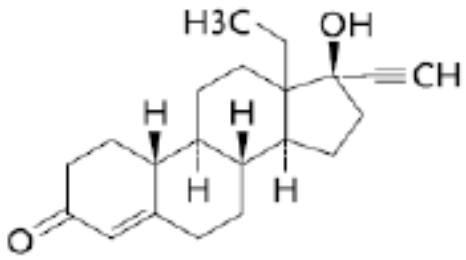
Composition: Each CONTINGENCY ONE™ tablet contains 1.5 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy–(17α)-(-)-], a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate and polyvinyl pyrrolidone K-25.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Levonorgestrel (USAN), Progestin (INN, BAN)
Chemical Name:	18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-(17α)-(-)-
Molecular Formula:	$C_{21}H_{28}O_2$
Molecular Mass:	312.45 g/mol
Structural Formula:	



Physicochemical properties:

Description:	White to off-white crystalline powder.
Solubility:	Practically insoluble in water and n-hexane, slightly soluble in acetone and ethanol, sparingly soluble in dichloromethane and soluble in chloroform.
Melting Point:	232°C - 239°C.

CLINICAL TRIALS

Levonorgestrel tablets 0.75 mg divided dose regimen

Study demographics and trial design

Two well-controlled studies have evaluated a two tablet regimen of levonorgestrel 0.75 mg tablets specifically for emergency contraception. Both were randomized trials comparing the levonorgestrel regimen to the standard Yuzpe regimen of combined high-dose oral contraceptives.

Pivotal Study (Study 92908)
The Pivotal Study was conducted between 1995 and 1997 at 21 clinical sites in 14 countries on 5 continents. The earlier controlled clinical trial by Ho and Kwan showed that levonorgestrel alone was at least as effective as a regimen combining ethinyl estradiol and levonorgestrel (the Yuzpe regimen), and was associated with significantly lower incidence of nausea, vomiting, and other side effects. The sample size on the Ho and Kwan study of 834 women was too small, however, to detect a difference in efficacy of levonorgestrel and hence the pivotal trial was commenced.

In the Pivotal Study, a total of 1,998 women were recruited, including 1,001 in the levonorgestrel group and 997 in the Yuzpe group; between 42 and 200 women were enrolled at each site. Of the enrolled women, the final pregnancy status was unknown in 43 women who were lost to follow-up. The 100 protocol violations included 4 women who were found after discontinuation to have been pregnant at admission (1 in the levonorgestrel group and 3 in the Yuzpe group) and 5 who were pregnant at discontinuation but whose pregnancy status at admission was unknown (two in the levonorgestrel group and 3 in the Yuzpe group). These latter 5 women were excluded from the primary efficacy analysis population, which thus included 976 women in the levonorgestrel group and 979 women in the Yuzpe group. Among these 1,995 women, an additional 698 used the treatment imperfectly.

Ho and Kwan Study
In the Ho and Kwan study, 440 women were recruited into each group. Of these, 46 never returned after admission and were excluded from the analysis. No women were found to have been pregnant at admission.

OTC Actual Use Study
An OTC (over-the-counter) Actual Use study[18] was also conducted to evaluate whether levonorgestrel tablets 0.75 mg can be used safely and effectively without oversight by a licensed medical practitioner. The study was conducted in the year 2000 at five affiliates of Planned Parenthood Federation of America located in geographically diverse regions of the United States and at five pharmacies in the US state of Washington.

Study results

Pivotal and Ho and Kwan Studies

No differences in baseline characteristics were detected between groups in the primary efficacy analysis population in either study. In both studies, the average age was about 27 years, and many women had previously been pregnant. The ethnic background of the women in the two studies differed substantially owing to the locations of the study centres. In both studies, about half of the participants requested emergency contraception because of failure to use a method during intercourse, and the rest requested it because of method failure (such as a ruptured condom). Distribution of the day of intercourse relative to ovulations was similar between groups within each study. In both studies, the distribution was skewed such that more women had intercourse before ovulation than after. In each study, the two groups were also similar in the timing of intercourse and treatment received. In the Pivotal Study, just under half started treatment within 24 hours after intercourse, whereas in the Ho and Kwan study, almost two-thirds did so.

In the Pivotal Study, 31 women (3.2%) became pregnant in the Yuzpe group and 11 (1.1%) became pregnant in the levonorgestrel group. The relative risk of pregnancy in the Yuzpe group was 2.8 times higher than that of the levonorgestrel tablets 0.75 mg group, with a lower one-sided 95% confidence bound of 1.53. Since the lower confidence bound was greater than 0.5, the levonorgestrel regimen was deemed to be as effective as the Yuzpe regimen. The fact that this bound was greater than 1 was considered strong evidence that the levonorgestrel regimen was more effective than the Yuzpe regimen.

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).

In the Ho and Kwan study, 12 women (2.9%) became pregnant in the levonorgestrel group and 15 (3.5%) became pregnant in the Yuzpe group.

Ectopic Pregnancy

Ectopic pregnancy is a potential risk of progestin-only contraception; however, the reports of ectopic pregnancies are sparse. They do not appear to occur more in women using emergency contraception than in the untreated population. The controlled and uncontrolled trials have been reviewed for possible ectopic pregnancies. If ectopic pregnancies occurred in up to 10% of pregnancies as predicted by the literature[13], 3 ectopic pregnancies would have been seen in the five studies conducted by WHO/HRP. None were observed. Among the 30 pregnancies reported in the 30 other small studies of levonorgestrel 0.75 mg reviewed, no ectopic pregnancies were reported. One ectopic pregnancy is noted in the literature. There appears to be no increase in the rate of ectopic pregnancy after use of levonorgestrel for emergency contraception. There were also no reports of congenital anomalies in any of the clinical studies.

OTC Actual Use Study

In the OTC Actual Use study, 665 women were screened, 585 were enrolled in the study, and 540 are known to have used the product at least once. The primary objective was to estimate the frequency of contraindicated and incorrect uses of levonorgestrel tablets 0.75 mg when dispensed under simulated OTC conditions. Secondary objectives were to estimate the incidence of repeat use, pregnancy and adverse events. The label was written to be understood by women of low literacy. Women received no medical screening or counselling prior to receiving the product.

The reproductive and contraceptive histories were similar across the study populations and consisted of a wide range of demographic characteristics representative of the female population of the USA. About 68% of the enrolled population had never been pregnant before their first screening and more than 80% had no living children. A total of 92% reported having used a contraceptive method in the month before admission and 60% indicated that they had had sex without contraception at least once in that month. About 16% reported irregular menstrual cycles.

Contraindicated use occurred in 1.3% and incorrect use occurred in 7% of users. Eight subjects used the product twice and two used it three times during the course of the study; the reason for each repeat use was consistent with the indications for use described on the product label. Ten of the product users (1.9%) were noted to be pregnant during the study. Adverse events reported by more than 5% of the subjects were abdominal pain, headache, nausea, and asthenia. These findings were consistent across subgroups of the study populations defined by age, race, ethnicity, and education level. No serious adverse events occurred.

Under simulated OTC conditions, the incidence of contraindicated use was extremely low, the incidence of incorrect use was also very low, and repeat use was very low. The pregnancy rate and pattern of adverse events were consistent with the findings of previous studies of the product.

<u>Levonorgestrel 1.5 mg tablet single dose regimen</u>

Study Demographics and Trial Design

Pivotal Study (Study 97902)
Study Demographics and Trial Design

A double blind, randomized, multicenter study evaluated and compared the efficacy and safety of levonorgestrel for emergency contraception following the administration of one single dose of 1.5 mg, as well as when two doses of 0.75 mg each were given at a 12-hour interval. This study was done in 15 family-planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the UK between 1998 and 2001. Each centre recruited between 41 and 149 subjects.

A total of 2,756 healthy women, who needed emergency contraception were randomly allocated into one of the two dose groups, with 1379 to receive a single dose of 1.5 mg levonorgestrel and 1377 to receive two doses of 0.75 mg levonorgestrel. Overall, 41 subjects (1.5%) were lost to follow-up and the outcome of treatment was unknown. Of these, 22 were in the single dose levonorgestrel group and 19 were in the two-dose levonorgestrel group. Three women (0.1%) were found to have had unprotected intercourse after the expected date of menses were considered withdrawn as they had been erroneously treated (i.e., they had no need for EC). Of these 3 subjects, 1 was in the two-dose levonorgestrel group and 2 were in the single dose levonorgestrel group. The intent to treat population was therefore 1356, in both groups.

There were 156 protocol violations among 144 subjects. These were primarily further acts of unprotected intercourse (31 in the single dose group and 30 in the two-dose group) and use of rhythm methods in current cycle (23 in the single dose group and 37 in the two-dose group).

Study Results
Baseline characteristics were similar for subjects randomized for each group. The mean age was 27, the mean weight was 56 kg, the mean height was 163 cm, and the mean duration of menstrual flow was 5 days. The mean cycle length was 29.2 days in the single dose group and 29.3 days in the two-dose group. In both groups 54% were Chinese, 34% were Caucasian and 12% were Asian or Black.

In the single dose group 53.5% of subjects requested emergency contraception because of failure to use a method during intercourse, and 36.4% requested it because of method failure. Corresponding figures for the two-dose group were 50.6% and 39.5%, respectively.

In the single dose group 45.9% of subjects requested treatment within 24 hr, 27.8% within 48 hr, 14.7% within 72 hr, 6.4% within 96 hr and 4.6% requested treatment after 97 hrs. Corresponding figures for the two-dose group were 42.2%, 26.6%, 18.4%, 7.4% and 4.6%, respectively.

The fraction of prevented pregnancies was 81.9% (CI: 72.1% to 88.9%) in the levonorgestrel single group and 77.3% (CI: 66.3% to 85.5%) in the 0.75 mg two-dose group, with a relative risk of pregnancy of 0.83 (CI: 0.46 to 1.50) for the levonorgestrel single dose group over the 0.75 mg two-dose group.

The two levonorgestrel regimens studied are highly effective for emergency contraception. The study showed that the 1.5 mg levonorgestrel single dose regimen had a similar effectiveness with the two doses of 0.75 mg levonorgestrel. There was no significant difference between the two levonorgestrel groups ($p>0.6$).

When comparing the efficacy of treatment in women starting the treatment within 3 days of unprotected intercourse and those starting treatment within a delay of 4 or 5 days, there was a decreasing trend of efficacy found, although the difference in efficacy was not statistically significant.

For all treatment groups combined, there was a significant trend in pregnancy rates in the 5 successive days from the time of unprotected intercourse in each efficacy set, showing an increase in pregnancy rates by days elapsed from unprotected intercourse. A similar trend was found when the two levonorgestrel regimens were combined.

Post-hoc analysis of efficacy by weight:

In clinical trials of products similar to Levonorgestrel 0.75 mg, a post-hoc analysis[20] of data from two published papers[21, 22] on the efficacy of levonorgestel 1.5 mg (single dose) and 0.75 mg (two doses 12 hours apart) raised questions concerning the efficacy of single ingredient levonorgestrel emergency contraceptives in women with higher body weights.

There is limited and inconclusive data on the effect of high body weight/high BMI in the contraceptive efficacy. In three WHO studies[1, 19, 23, 27] no trend for a reduced efficacy with increasing body weight/BMI was observed (Table 7), whereas in the two other studies [21, 22, 28] a reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 8). Both meta-analyses excluded intake later than 72 hours after unprotected intercourse and women who had further acts of unprotected intercourse.

Table 7: Meta-analyses on three WHO studies [1, 19, 23, 27]

BMI (kg/m^2)	**Underweight 0 – 18.5**	**Normal 18.5 - 25**	**Overweight 25 - 30**	**Obese ≥ 30**
N total	600	3952	1051	256
N pregnancies	11	39	6	3
Pregnancy rate	1.83%	0.99%	0.57%	1.17%
Confidence Interval	0.92 – 3.26	0.70 – 1.35	0.21 – 1.24	0.24 – 3.39

Table 8: Meta-analyses on two studies [21, 22, 28]

BMI (kg/m^2)	**Underweight 0 – 18.5**	**Normal 18.5 - 25**	**Overweight 25 - 30**	**Obese ≥ 30**
N total	64	933	339	212
N pregnancies	1	9	8	11
Pregnancy rate	1.56%	0.96%	2.36%	5.19%
Confidence Interval	0.04 – 8.40	0.44 – 1.82	1.02 – 4.60	2.62 – 9.09

Comparative Bioavailability Studies

A two-way blinded, single dose, randomized, two-period, two-treatment, crossover bioequivalence study of 1 x (0.75 mg) CONTINGENCY (levonorgestrel) (Jai Pharma Limited) and 1 x (0.75 mg) Plan B® (levonorgestrel) (Manufactured by Duramed Pharmaceuticals Inc.)

was performed in healthy, adults, Indian Asian female subjects (n= 30) under fasting conditions.

Table 9: Mean Levonorgestrel pharmacokinetic parameter are tabulated below

Levonorgestrel (1 x 0.75 mg) From measured data Geometric Least Square Means Arithmetic Mean (CV %)				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng*hr/mL)	198.6 213.9 (42.15)	201.8 216.9 (44.18)	0.98	91.53% – 105.87%
C_{max} (ng/mL)	13.46 14.20 (33.98)	13.48 13.97 (30.44)	1.00	91.24% – 109.29%
T_{max}§ (h)	2.47 (67.95)	2.42 (51.28)		

* CONTINGENCY (Levonorgestrel) 0.75 mg Manufactured by Jai Pharma Limited for Mylan Pharmaceuticals ULC

† Plan B® 0.75 mg, (Manufactured by Duramed Pharmaceutical Inc.) was purchased in Canada.

§Arithmetic mean (%CV) presented only.

AUC_I and $T_{1/2}$ could not be reliably characterized due to the long terminal elimination half-life of Levonorgestrel.

DETAILED PHARMACOLOGY

Pharmacodynamics

Animal in vivo studies

Levonorgestrel is active in standard tests for progesterone activity, acts like a true progestin when tested for pregnancy maintenance, and is neither estrogenic by itself nor metabolically converted to an estrogen. Non-clinical studies conducted on the use of levonorgestrel or norgestrel have shown that levonorgestrel administered subcutaneously or orally mimics the primary properties of progesterone in that it binds to the progesterone receptor and produces glandular transformation of the endometrium. In addition, levonorgestrel maintains pregnancy in the appropriate animal model and delays implantation of the blastocysts. Levonorgestrel also inhibits ovulation, gonadotropin secretion, and shows contraceptive activity as demonstrated in a number of biological systems. The qualitative and quantitative parameters for the reproductive pharmacology of levonorgestrel have been established through extensive studies using rabbits, rats, and mice.

Levonorgestrel can increase uterine weight but does not bind to the estrogenic receptor and does not lead to keratinization of the vaginal epithelium. Anti-estrogenic activity against the vaginal and uterine effects of estrone and estradiol have been demonstrated following parenteral administration of levonorgestrel. This estrogenic antagonism suggests levonorgestrel acts like progesterone. However, there is no evidence to support antagonism of estrogen-induced mammary tumours, uterine overstimulation, or cataracts. Levonorgestrel can bind to the androgenic receptor and has anabolic androgenic effects such as protecting bone mass from

osteopenia in an animal model. However, levonorgestrel inhibits ovulation at much lower dosages than were needed to produce androgenic and anabolic effects on suitable target tissues. In a number of other standard evaluations of endocrine activity, levonorgestrel was devoid of detectable glucocorticoid, mineralocorticoid, and anti-mineralocorticoid activity *in vivo*, even though it binds to the glucocorticoid (aldosterone) receptor.

The qualitative profile of levonorgestrel with respect to sexual function is summarized in Table 10.

Table 10: Qualitative Non-clinical Pharmacological Profile of Levonorgestrel with Respect to Sexual Functions

Test	Activity
Progestin-like activity	
In vivo	Active
Receptor binding	Active
Contraception	
In vivo	Active
Inhibition of fertility	
Inhibition of the gonadotropins	Active
Inhibition of ovulation	Active
Change in the estrous cycle	Active
Androgen-like/anabolic activity	
In vivo	Some active/some inactive
Receptor binding	Some active/some inactive
Antiandrogenic activity	
In vivo	Inactive
Estrogenic activity	
In vivo	Inactive
Receptor binding	Inactive
Estrogen antagonism	
In vivo	Active
Receptor binding	Inactive

Pharmacokinetics

The nonclinical pharmacokinetics of levonorgestrel have been investigated pertaining to its development as a low-dose oral contraceptive. These data indicate low oral bioavailability of levonorgestrel in animals as compared to man, urinary and biliary excretion of an absorbed dose, and the formation of conjugated metabolites. The pharmacokinetics of a single elevated dose have not been investigated in animals.

TOXICOLOGY

The nonclinical toxicology of levonorgestrel or norgestrel has been investigated in a number of studies in rodents, dogs, and monkeys, including a 7-year repeat administration study in

monkeys and numerous reproductive toxicity studies and mutagenicity studies. All of these studies were conducted as part of the nonclinical development of norgestrel as a traditional oral contraceptive or contraceptive implant. This large body of evidence was used to support the approval of oral contraceptives containing up to 500 µg of norgestrel in combination with ethinyl estradiol or 75 µg alone, where the intended use required chronic administration.

The Toxicology Review Panel of the Special Programme (WHO) has reviewed the available animal data on levonorgestrel and has concluded that the toxicological and teratological data from animal studies on levonorgestrel provide a sufficient indication that levonorgestrel may be considered safe for use as an implantable contraceptive. Toxicity studies are summarized in Table 11.

Table 11: Previously Reviewed FDA Toxicity Studies

Title	Date	Dose of Wy-3707	Duration
Studies in Rodents			
Toxicity Study of Norgestrel in Combination with Ethinyl Estradiol in Mice (10: and 20:1 ratios)		0.0002 and 0.0004% of diet	81-83 weeks
Toxicity Studies in Rodents	6/12/62	0.0125, 0.025 mg/kg	7.5 weeks
Sub-acute Toxicity of Wy-3707 Alone, Mixtures of Wy-3707 with Ethinyl Estradiol, Ethinyl Estradiol Alone in Rats	6/12/64	0.01, 0.1, 0.2 mg/kg	7-10 weeks
Toxicity Study of Wy-3707 in Combination with Ethinyl Estradiol in Rats (Radios of 2:1and 5:1)	7/1/66	0.0001 - 0.0025 mg/kg	36-38.5 weeks
Toxicity Study of Wy-3707 in Combination with Ethinyl Estradiol in Rats (Radios of 25:1, 20:1, and 2:1)	7/1/66	0.00025, 0.005, 0.001 mg/kg	56 weeks
Chronic Toxicity Study of Wy-3707 in Rats	7/1/66	0.001, 0.01, 0.05, 0.1 mg/kg	62.5-80 weeks
Toxicity Studies of Wy-3707 and Ethinyl Estradiol in Rats	7/1/66	0.0001 - 0.001 mg/kg	99.5-100 weeks
Toxicity Studies of Wy-3707 in Combination with Ethinyl Estradiol in Rats (Ratio of 10:1)	7/1/66	0.000-0.01 mg/kg	99-100 weeks
Studies in Dogs			
Sub-acute Toxicity in Dogs	6/2/64	1, 10, 50 mg/kg	6 weeks
Sub-acute Toxicity Studies of Wy-3707 Alone and Mixtures of Wy-3707 and Ethinyl Estradiol Alone in Dogs	6/17/64	1, 10, 50 mg/kg	6 weeks
Chronic Toxicity Study of Wy-3707 in Dogs	10/14/65	1, 10, 20 mg/kg	52-52.5 weeks
Toxicity Studies of Wy-3707 in Combination with Ethinyl Estradiol in Dogs (Ratio of 10:1)	7/1/66	1 or 2 mg/kg	54 and 104 weeks
Toxicity Studies of Wy-3703 and Wy-3707 in Combination With Ethinyl Estradiol in Dogs (Ratio of 20:1)	7/1/66	2 or 4 mg/kg	25-36 weeks
Toxicity Studies of Wy-3707 and Ethinyl Estradiol	7/1/66	0.01, 0.1, 0.2,	54, 64 and

in Dogs		1.0 mg/kg	100/104 weeks
Toxicity Studies of Norgestrel in Dogs	~1977	0.1, 0.25 mg/kg	7 years
Study in Primates			
Toxicity Study of Norgestrel in Rhesus Monkeys	~1977	0.02, 0.1, 0.5 mg/kg	7 years

Acute Toxicity Studies: In single dose studies, the LD_{50} for norgestrel was > 5000 mg/kg dosed orally in rodents and dogs. Multiple dose studies in mice for 18 months had no effect. In rats, other than exaggerated physiological effects expected with high doses of estrogens, there was little evidence of drug toxicity. Findings included decreased pituitary weights, secretory changes in the cervix and vagina, and endometrial hyperplastic changes. Growth rate and food consumption were depressed among norgestrel-treated animals at high doses.

Chronic Toxicity Studies: Data from the first seven years of a ten-year repeat administration study in Rhesus monkeys with d,l-norgestrel was collected to support clinical use as an oral contraceptive. Sixty-four female Rhesus monkeys (16/group) were administered norgestrel 0 mg, 0.02 mg, 0.1 mg, and 0.5 mg/kg/day as a dietary admixture for 21 consecutive days followed by seven days of a non-dosing period (28-day cycle). There were no norgestrel-related effects on mortality, behaviour, mean body weights, endocrine function, or ophthalmoscopic exams. A number of minor dose related changes were noted in hematocrit, Stypven Times, activated partial thromboplastin times, fibrinogen concentrations, and urinary output of 17-hydroxycorticosteroids. There were no findings in gross or histopathologic evaluations indicative of toxicity, and microscopic examination of cervical smears did not reveal any evidence of neoplasia. No mammary nodules were palpable at the end of the first, third, sixth, and seventh years, none of the monkeys had palpable mammary nodules at the end of the sixth and seventh years, and there was no effect on the number of palpable mammary nodules or the month when the first mammary nodule was found over the course of seven years. The conclusion of the U.S. FDA review of this study indicated that administration of norgestrel to female monkeys for ten years caused essentially no untoward effects.

Carcinogenicity Studies: In CF-LP (MTV^+) mice administered doses described as low (2-5 times clinical), mid (50-150 times clinical), and high (200-400 times clinical) for 80 weeks, there was no effect on incidence of tumours in any tissues. In castrated C3HxRIII (MTV^+) mice administered 0.5 mg/kg d-norgestrel or 1 mg/kg dl-norgestrel in the diet, the incidence of mammary tumours was slightly raised in the absence of any effect on latency. In the rat, administration of norgestrel in the diet (doses not described) for 104 weeks had no effect on the incidence of tumours.

Genotoxicity: Levonorgestrel revealed no potential for genotoxicity in a standard Ames Salmonella/Microsome Mutagenicity Test.

Reproductive Toxicity: A large number of reproductive toxicity studies were performed by repeat dose administration to evaluate the effects on mating fertility, fecundity, post-treatment recovery of fertility, effects on the estrous cycle, claudogenic effects as well as classic Segment I, II, and III reproductive studies. Of greatest possible relevance to emergency contraception are the studies of recovery of fertility and birth defects. In a study in mice treated with up to 50x the human contraceptive dose, no irreversible impairment of fertility was noted.

Segment II studies were given by repeat dose during organogenesis. At the levels required to maintain pregnancy, virilizing effects were noted and were considerably greater than those of progesterone. Two of 439 fetuses from dams treated at these levels of norgestrel were deformed; one fetus from a dam treated with norgestrel 3 mg subcutaneously had incomplete spinal closure and one fetus from a dam treated with norgestrel 3 mg orally had a poorly developed cranium. The 88 control fetuses were normal. Occasional deformities appeared in the other progestogen groups, and were more frequent from spayed mothers. In a study where norgestrel was given subcutaneously from Days 16 to 19 of gestation, potency in producing virilization in female fetuses was found to be nearly equal to testosterone propionate and three times greater than norethindrone acetate. Histological examination showed that norgestrel 0.1 mg/day subcutaneously was effective, while 10 mg/day orally was ineffective. For a macroscopically detectable increase in ano-genital distance, 3 mg/day subcutaneously was required.

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PART III: CONSUMER INFORMATION

CONTINGENCY ONE™

Levonorgestrel Tablet

Tablet, 1.5 mg

Manufacturer's Standard

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

ABOUT THIS MEDICATION

What the medication is used for:

CONTINGENCY ONE™ is an emergency or backup contraceptive.

CONTINGENCY ONE™ can prevent pregnancy after a contraceptive accident (such as a broken condom) or when no form of birth control was used. Treatment is **most** effective if used in the first 72 hours (3 days) following unprotected sex.

CONTINGENCY ONE™ cannot terminate an existing pregnancy. Although there is no scientific evidence that CONTINGENCY ONE would harm a developing embryo, women who are already pregnant should not use this product.

CONTINGENCY ONE™ should not be used in place of regular contraception. It does not work as well as most other contraceptives used correctly.

What it does:

CONTINGENCY ONE™ acts as an emergency contraceptive by preventing the release of an egg from the ovary, or preventing sperm and egg from uniting. In addition, CONTINGENCY ONE™ may prevent the fertilized egg from attaching to the wall of the uterus. CONTINGENCY ONE™ is not effective once a pregnancy has started, that is once the fertilized egg has attached to the wall of the uterus. CONTINGENCY ONE™ does not cause an abortion.

CONTINGENCY ONE™ can be used 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
  - Failure to withdraw before ejaculation
  - Miscalculation of the fertile period by women practising periodic abstinence
  - IUD expulsion
  - Missed oral contraceptives
  - A delay in starting a new packet of oral contraceptives
  - A delay in getting a scheduled contraceptive injection
- In cases of sexual assault (rape)

When it should not be used:

Do not use CONTINGENCY ONE™ if:

- you have a confirmed or suspected pregnancy
- you are allergic to Levonorgestrel, or to any ingredient in the formulation (see list of non-medicinal ingredients below)
- you have abnormal vaginal bleeding

What the medicinal ingredient is:

Levonorgestrel

What the non-medicinal ingredients are:

Colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate and polyvinyl pyrrolidone K-25.

What dosage forms it comes in:

The package contains one tablet, containing 1.5 mg of levonorgestrel. The tablet is round, white to off-white, uncoated, flat faced beveled edge debossed with 251 on one side and other side plain.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **CONTINGENCY ONE™ provides no protection against HIV/AIDS and other sexually transmitted diseases (STDs), such as syphilis, gonorrhoea, chlamydia, and herpes.** If you are worried about whether you may have been infected with HIV/AIDS, or other sexually transmitted diseases, talk to your

health professional about your concerns and ask how you can protect yourself in the future.
- **If your period is delayed more than 1 week, you should contact your doctor and have a pregnancy test done.**

CONTINGENCY ONE™ is for Emergency Contraceptive Use Only and should not be used on a regular basis. CONTINGENCY ONE™ is not as effective in preventing pregnancy as most other birth control methods (e.g. oral contraceptive pills, IUDs, implants or condoms, etc.). It should not be relied on for routine birth control by sexually active women.

CONTINGENCY ONE™ provides only short-term protection against pregnancy. Sexual activity that takes place later can still result in pregnancy if no contraceptive is used. You must abstain from sex or use another barrier method of birth control until your next normal period to make sure you do not get pregnant.

In all women, emergency contraception should be taken as soon as possible after unprotected intercourse. There is some data that levonorgestrel may be less effective with increasing body weight or body mass index (BMI), but these data were limited and inconclusive. If you have any questions regarding this, please consult with a health care professional.

BEFORE you use CONTINGENCY ONE™, talk to your doctor or pharmacist if you have now or have previously had any of the following conditions:
- Unusual vaginal bleeding that has not yet been diagnosed
- Known or suspected breast cancer
- Active liver disease or tumour
- You have diabetes
- You have high blood pressure
- You are pregnant or breast feeding

INTERACTIONS WITH THIS MEDICATION

Before you use CONTINGENCY ONE™, talk to your doctor or pharmacist if you are taking any of the following drugs:

Drugs that may decrease the efficacy of CONTINGENCY ONE™ include:
- anti-HIV drugs (efavirenz, ritonavir)
- anticonvulsant drugs (phenytoin, carbamazepine, primidone, phenobarbital)
- antibiotics (ampicillin, cotrimoxazole, tetracycline, temafloxacin, clarithromycin)
- rifampicin
- rifabutin
- griseofulvin
- *Hypericum perforatum* (St. John's wort)
- ulipristal acetate

If your period is delayed more than 1 week and you were taking any of these medications, you should contact your doctor or pharmacist and have a pregnancy test done.

Tell your doctor if you have taken CONTINGENCY ONE™ within 3 days of a Pap test, as it may affect your results.

PROPER USE OF THIS MEDICATION

Usual dose:

CONTINGENCY ONE™ can prevent pregnancy if the tablet is taken within 72 hours (3 days) and preferably within 12 hours after a contraceptive accident or unprotected sex (sex without birth control). Do not delay starting treatment. CONTINGENCY ONE™ is more effective the sooner you start after unprotected intercourse.

CONTINGENCY ONE™ can be taken with a glass of water.

If you vomit within 2 hours of taking CONTINGENCY ONE™, call your doctor or pharmacist as you might need another dose.

Important: If more than 72 hours (3 days) have passed since unprotected sex occurred, CONTINGENCY ONE™ may not be effective. See your health professional as soon as possible to discuss other options.

Although the risk of pregnancy is highest in the middle of the menstrual cycle (possibly as early as day 10 after the beginning of your last period), pregnancy can occur at other times during the menstrual cycle. CONTINGENCY ONE™ can be administered anytime during your monthly cycle if you are worried about an unwanted pregnancy.

The treatment does not bring on menstruation. You may experience spotting a few days after taking CONTINGENCY ONE™, but this is not a period. Your next menstrual period should come on time (or a few days early or late). If your period is delayed more than a week or if you have any other cause for concern, talk to a health professional. More than occasional use (more than once in a menstrual cycle or more than once a month) may upset your menstrual cycle (period).

If you are sexually active and do not wish to become pregnant, you should use a reliable method of contraception on a regular basis. If you want more

information about regular contraceptives or if you are having trouble using a method, ask your health professional for help in choosing a method that works for you.

Overdose:

If you think you have taken too much CONTINGENCY ONE™, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Symptoms of overdose may include nausea, vomiting, vaginal bleeding, and may lead to menstrual cycle disturbances.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

CONTINGENCY ONE™ can cause temporary side effects in some women. These side effects generally do not last more than 24 hours.

Common side effects include:

- **Nausea:** This occurs in about 14 to 23% of women taking levonorgestrel tablets.
- **Abdominal pain:** This occurs in about 18% of women taking levonorgestrel tablets.
- **Fatigue:** This occurs in about 17% of women taking levonorgestrel tablets.
- **Headache:** This occurs in about 17% of women taking levonorgestrel tablets.
- **Dizziness:** This occurs in about 11% of women taking levonorgestrel tablets.
- **Breast tenderness:** This occurs in about 11% of women taking levonorgestrel tablets.
- **Vomiting:** This occurs in about 6% of women taking levonorgestrel tablets.
- **Diarrhea:** This occurs in about 5% of women taking levonorgestrel tablets.
- **Irregular menstrual bleeding:** Some women may experience spotting after taking CONTINGENCY ONE™. The majority of women will have their next menstrual period at the expected time or early. When CONTINGENCY ONE™ is used repeatedly (more than once in a menstrual cycle, or more than occasional once a month use), menstrual changes may occur, including a shorter or longer cycle and a heavier or lighter period than normal.

Less common side effects: Migraine or severe headache, lower abdominal pain, painful menstruation and vaginal discharge. If the symptoms continue for more than 48 hours or are severe, see your health professional.

Delayed menstrual period: If your period is delayed more than 1 week, you should contact your doctor or pharmacist and have a pregnancy test done.

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

Call your doctor immediately if the following symptoms and signs of serious adverse effects occur:

- Itching and rash
- Cramping or severe pain in your stomach or belly prior to your next normal period, since this can be a warning sign of tubal (ectopic) pregnancy – a serious medical problem
- Uterine hemorrhage
- Vaginal hemorrhage

HOW TO STORE IT

Store CONTINGENCY ONE™ tablet between 15°C and 30°C (59-86 °F). Protect from high humidity.

Keep out of reach of children.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to:
    Canada Vigilance Program
    Health Canada,
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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

MORE INFORMATION

This document can be found at: www.mylan.ca.

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

This leaflet was prepared by Mylan Pharmaceuticals ULC
Etobicoke, Ontario M8Z 2S6

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Mylan Pharmaceuticals ULC
Etobicoke, ON M8Z 2S6
1-844-596-9526
www.mylan.ca