PRODUCT MONOGRAPH

NorLevo®

Levonorgestrel Tablets

0.75 mg

Manufacturer's Standard

EMERGENCY CONTRACEPTION

Manufacturer :
Laboratoire HRA Pharma
15, rue Béranger
75003, Paris, France

Distributor :
Bayer Inc
77 Belfield Road
Toronto, Ontario, M9W 1G6
Canada

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NORLEVO®

Levonorgestrel

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 0.75 mg	Lactose monohydrate, maize starch, povidone *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NorLevo® (levonorgestrel 0.75 mg tablets) is an emergency contraceptive intended to be used within 72 hours following known or suspected contraceptive failure or unprotected intercourse such as:

- ruptured or forgotten condom;
- missed oral contraceptive pill;
- expelled intrauterine device;
- early removal or dislodgment of a vaginal diaphragm or of a contraceptive cap;
- failure of the coitus interruptus method;
- sexual intercourse during the supposedly fertile period when relying on periodic abstinence (temperature method);
- rape.

Treatment should not be delayed as efficacy declines with an increased interval between intercourse and the start of the treatment. In clinical trials, the proportion of pregnancies avoided after the use of levonorgestrel varied from 52 % (36) to 85 % (5) of expected pregnancies. Efficacy appears to decline with time after intercourse.

In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more and levonorgestrel was not effective in women who weighed more than 80 kg.

The pregnancy rate of levonorgestrel 0.75 mg tablets is calculated for a single use. If NorLevo® is used on more than one occasion, the cumulative pregnancy rate may be higher. NorLevo® is not recommended for routine use as a contraceptive.

NorLevo® 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 judge that a woman is a repeat user of Emergency Contraception (defined as use more than once a month on a regular basis) or that NorLevo® 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 care provider for contraceptive counselling services and advise on other methods of contraception and prevention of sexually transmitted infections. NorLevo® should be dispensed if indicated.

Geriatrics: NorLevo® has not been studied in this population

Pediatrics: NorLevo® has not been studied in this population

CONTRAINDICATIONS

- NorLevo® is contraindicated in women with hypersensitivity to the active substance levonorgestrel or any of the excipients. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- NorLevo® (levonorgestrel tablets) 0.75 mg is contraindicated in women with known or suspected pregnancy. If there is a doubt regarding pregnancy following a previous act of intercourse, especially if there is recent abnormal bleeding, a pregnancy test should be performed before taking NorLevo®.

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 tumors, known or suspected carcinoma of the breast and undiagnosed abnormal vaginal bleeding). It is not known whether these same conditions apply to the NorLevo® regimen consisting of the emergency use of two progestin pills, but these risks should be considered if NorLevo® needs to be administered several times.

WARNINGS AND PRECAUTIONS

General

NorLevo® is not effective in terminating an existing pregnancy.

Emergency contraception is an **occasional** method. It should in no instance replace a regular contraceptive method. Repeated administration within a menstrual cycle is not advisable, because of an undesirable high load of hormones for the patient and the possibility of severe disturbances of the cycle. Emergency contraception does not prevent a pregnancy from occurring in every instance, especially if uncertain about the timing of the unprotected intercourse.

The use of NorLevo® does not protect against HIV infections (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 hepatic neoplasia and gallbladder disease. NorLevo® does not contain estrogen. While these conditions have not been associated with the routine use of progestin-only oral contraceptives, it is unknown if the use of short-term high-dose progestin-only contraceptives (a single 1.5 mg dose of levonorgestrel) would accentuate the risk.

Concomitant use of NorLevo® and drugs containing ulipristal acetate is not recommended (see *Drug-Drug Interactions* section).

Cardiovascular

The use of cyclic combination oral contraceptives containing estrogen and progestin is also associated with increased risks of thromboembolic and cardiovascular disorders (e.g. thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis).

NorLevo® does not contain estrogen. These conditions have not been associated with the routine use of progestin-only oral contraceptives, but whether short-term use of high-dose progestin-only contraceptives (2 doses of 0.75mg levonorgestrel, taken at once) would accentuate the risk is unknown. Controlled clinical trials using levonorgestrel for postcoital and emergency contraception have not identified any serious cardiovascular adverse reactions. There have been reports of thrombotic events during the postmarketing period, however a causal relationship with NorLevo® treatment has not been determined.

Sexual Function/Reproduction

Effects on Menses: Some women may experience spotting a few days after taking levonorgestrel as an emergency contraceptive. At the time of expected menses, approximately 75% of women using levonorgestrel had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. Approximately 75 % of women had their next menstrual period earlier than expected, on time, or just slightly later than expected. However, in 19.9 % of women, menses was delayed by more than 7 days. **If there is a delay in the onset of menses beyond 5-7 days, a pregnancy test is recommended.**

Ectopic Pregnancy: Ectopic pregnancies account for approximately 2% of reported pregnancies. It is not known to what extent NorLevo® prevents implantation of an ectopic pregnancy and one cannot exclude that an ectopic pregnancy continues to develop despite the occurrence of uterine bleeding. Therefore, NorLevo® is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy). Physicians should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking NorLevo®.

Suspected Pregnancy: A pregnancy test and/or a physical examination are warranted if pregnancy is suspected (see Effect on Menses). Women should be counselled to abstain from sexual intercourse or use an alternative contraceptive method until the onset of their next normal menstrual period after NorLevo® intake. If a normal menstrual period is delayed by more than 5-7 days of its expected date, after NorLevo® has been used, a pregnancy test should be performed. Counseling on routine contraception for future use should be provided as appropriate.

Special Populations

Pregnant Women: This medicinal product is not indicated in case of pre-existing pregnancy and cannot interrupt it. Several epidemiological studies have shown no increase in congenital malformation risk after failure of regular contraceptive pills, some of which contained levonorgestrel. In case of failure of this treatment with persisting pregnancy, only few pregnancies brought to term and documented were available and no increased risk of congenital abnormalities was observed.

Nursing Women: Levonorgestrel is secreted into breast milk. Therefore, it is suggested to breastfeed immediately before taking the NorLevo® tablets and to skip the nursing following NorLevo® administration for at least 8 hours. Discard the extracted milk during this period.

Body weight 75 kg and more:

In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more, and levonorgestrel was not effective in women who weighed more than 80 kg (see *Clinical Trials* section).

Pediatrics: NorLevo® has not been studied in this population.

Geriatrics: NorLevo® has not been studied in this population.

Monitoring and Laboratory Tests

Pathologists should be advised about recent oral contraceptive therapy when specimens obtained from Pap smears are submitted for examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequent undesirable effects are nausea, low abdominal pain, headache, fatigue and dizziness. Vomiting is reported in less than 8 percent of women. These effects usually disappear within 48 hours after levonorgestrel intake. Breast tenderness is reported in 5 to 21 percent of patients, bleeding (including spotting) is reported in 28 to 31 percent of patients; both can last until the next menstrual period. Delayed menses (greater than 7 days) is reported in up to 24 % of patients.

Hypersensitivity reactions, such as pharyngeal/face oedema and cutaneous reactions have been reported after the intake of NorLevo®.

Clinical Trial Adverse Drug Reactions

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

The following table gives the frequency of undesirable effects reported in four clinical trials and two post-marketing observational (Actual Use) studies.

Table 1: Percent of women with ≥ 1% undesirable effects after the intake of 1.5 mg of levonorgestrel as a single dose of 0.75 mg and a second dose of 0.75 mg 12 hours later or a single dose of 1.5 mg

	Clinical Trials				Post-marketing observational studies	
Effect	**Trial 1 (1) n=544[1]**	**Trial 2 (2) n=1359[2]**	**Trial 3 HRA2914-507 (35) N= 840[3]**	**Trial 4 HRA2914-513 (36) N=1117[4]**	**Observational Study 1 (3) n= 242[5]**	**Observational Study 2 (4) n=299[6]**
Nausea	24.3 %	14 %	26 %	11.3%	19 %	13 %
Low abdominal pain	15.6 %	14 %	8 %	3.1% (6.7%)[2]	29 %	17 %
Fatigue	NR	14 %	36 %	3.9 %	28 %	20 %
Headache	21.3 %	10 %	33 %	18.9 %	22 %	25 %
Dizziness	12.6 %	10 %	18 %	4.9 %	NR	NR
Breast tenderness	12.9 %	8 %	17 %	1.7 %	21 %	5 %
Vomiting	7.8 %	1 %	2 %	1.1%	NR	2 %
Heavy menses	15.5 %	NR		NR	NR	NR
Diarrhea	NR	4 %	12 %	1.5%	NR	7 %
Bleeding	NR	31 %	NR	NR	28 %	28 %
Delay of menses	19.9[1] %	5 %	NR	NR	18 %	24 %
Sun sensitivity	NR	NR	NR	NR	3 %	NR
Paresthesia of the lower limbs	NR	NR	NR	NR	4 %	5 %
Uterine pain	NR	NR	19 %	NR	NR	NR
Dysmenorrhea	NR	NR	7 %	14.3%	NR	NR
Nasopharyngitis pain	NR	NR	4 %	2.9%	NR	NR
Gastrointestinal pain	NR	NR	2 %	NR	NR	NR
Upper abdominal pain	NR	NR	NR	4.1 %	NR	NR
Abdominal distension	NR	NR	NR	1.3 %	NR	NR

[1] 1062 women have been evaluated for the adverse events, of these 1062 women, 544 received a single dose of 1.5 mg of levonorgestrel and 518 received a divided dose (0.75mg levonorgestrel separated by 12 hours).
[2] 4071 women participated in this study, of these 4071 women, 1359 women received a single dose of 1.5 mg of levonorgestrel and 1361 received a divided dose (0.75mg levonorgestrel separated by 12 hours)

[3] 840 women received a divided dose (0,75 mg levonorgestrel separated by 12 hours)
[4] 1117 women received a single dose of 1,5 mg levonorgestrel
[5] 528 women were interviewed (data from pharmacies), of these 528 women, 242 women received two doses of 0,75 mg levonorgestrel in a single intake and 282 women received two divided doses; 4 women received only one dose and were excluded from the table.
[6]409 women were interviewed (data from family planning organisations), of these 409 women, 299 women received two divided doses of 0,75 mg levonorgestrel in a single intake.

	Clinical Trials				Post-marketing observational studies	
Effect	**Trial 1 (1) n=544[1]**	**Trial 2 (2) n=1359[2]**	**Trial 3 HRA2914-507 (35) N= 840[3]**	**Trial 4 HRA2914-513 (36) N=1117[4]**	**Observational Study 1 (3) n= 242[5]**	**Observational Study 2 (4) n=299[6]**
Somnolence	NR	NR	NR	1.1%	NR	NR
Pharyngolaryngeal pain	NR	NR	NR	1.4%	NR	NR
Migraine	NR	NR	NR	1.3%	NR	NR
Back pain	NR	NR	NR	2.4%	NR	NR
Vaginal discharge	NR	NR	NR	1.5%	NR	NR

NR: Not record

[1] Delay defined as more than 7 days

[2] Abdominal pain (unspecified)

The safety data analysis of reported side effects from the efficacy studies indicates that levonorgestrel is safe with an acceptable number of mild to moderate undesirable experiences. The most frequent adverse experiences were nausea, vomiting, dizziness, fatigue and headache. The incidence of adverse events was lower in the levonorgestrel groups than in the Yuzpe regimen groups. However, some adverse events such as breast tenderness and inter-menstrual bleeding or spotting were found with similar incidence in both groups. In the Grimes 1998 WHO study (5), one case of fatal meningitis was reported without any relationship to levonorgestrel.

In the WHO study (6) comparing the two regimens of levonorgestrel (second intake 12 hours and 24 hours after the first intake), the occurrence of diarrhoea and breast tenderness was more frequent in the 12-hour group ($p<0.05$). The incidence of the other side effects was otherwise similar between the two groups.

An open labelled study was performed in Edinburg (UK) (7). The primary end-point was the tolerance to NorLevo® when used in regular clinical settings. Women were eligible as long as they requested an Emergency Contraception, and were not pregnant. After treatment with NorLevo® (one 0.75 mg tablet to be repeated 12 hours later) women were asked to fill a diary card during the 7 days post treatment. They were asked to attend a control visit after the expected date of the next menstrual periods.

Of the 400 enrolled, 286 women accepted to fill the diary card (7). The frequency range of the reported symptoms during the first 4 days were: nausea (4.2-21%), fatigue (6.6-17.5%), headache (4.9-11.5%), tender breast (4.9-7.3%), dizziness (0.7-5.9%) and spotting (2.4-4.2%). The incidence of vomiting was very low. The mean length of the cycle was 28 days. In only 15 percent of the women, the onset of menstrual periods was delayed by more than 5 days. No other specific side effect was reported during this study.

In a double-blind study (1), the two-dose regimen levonorgestrel 0.75 mg taken 12 h apart (group A) and levonorgestrel 1.5 mg taken in a single dose administration (group B) were studied in 1118 volunteers for emergency contraception. From the 1118 women analyzed, only 1062 subjects (518 in group A and 544 in group B) provided enough information to be assessed for side effects and timing of next menses. The side effects observed after treatment were nausea, vomiting, headache, breast tenderness, lower abdominal pain, and menorrhagia. Women in group A had more frequent vomiting, dizziness and lower abdominal pain and less nausea, headache, breast tenderness, and increased menstrual flow than those in group B.

In a double-blind WHO study (2) compared the efficacy and safety of a single 10 mg dose of mifepristone (group A), two 0.75 mg doses of levonorgestrel 12 hours apart (group B) and a single dose of 1.5 mg levonorgestrel (group C) in 4136 healthy women. There are no significant difference between the side-effects observed in group B and C.

Study HRA2914-507 (35) was a prospective, randomized, double-blind multicenter study carried out in the United States to compare the efficacy, safety and tolerability of ulipristal acetate, 50mg unmicronized, with levonorgestrel (1.5mg) as oral emergency contraception (EC) within 72 hours of unprotected intercourse. Levonorgestrel was administered as two 0.75 mg tablets, 12h apart, and served as the control group in the trial; to ensure the double-blind design, administration of ulipristal was followed by a matching placebo 12h later. The medications and placebos were placed in an opaque capsule and were administered to patients in this form.

Overall, 76% of subjects who received levonorgestrel experienced an adverse event. The most frequently reported adverse event was fatigue (36%), followed by headache (33%) and nausea (26%). Relative to the average cycle length reported by subjects on study entry, the cycle length was about 2 days shorter following treatment with levonorgestrel. No Serious Adverse Events were reported in women treated with levonorgestrel. Safety profiles yielded no significant safety findings and indicate that the treatment was well tolerated.

Study HRA2914-513 (36) was a prospective, randomized, single-blind multicenter study carried out in the United Kingdom, Ireland, and the United States to compare the efficacy, safety and tolerability of ulipristal acetate, 30mg with levonorgestrel (1.5mg) as oral emergency contraception (EC). Levonorgestrel was administered as a single 1.5 mg tablet and served as the control group in the trial.

Overall, 56% of subjects who received levonorgestrel experienced at least one adverse event. The most frequently reported adverse event was headache (18.9%), followed by dysmenorrhea (14.3%) and nausea (11.3%). Relative to the average cycle length reported by subjects on study entry, the cycle length was 1.2 days shorter following treatment with levonorgestrel than the average cycle length reported by subjects on study entry. Post-treatment, 117 (10.5%) levonorgestrel-treated subjects experienced inter-menstrual bleeding other than menses, the majority of which was described as spotting.

Four SAEs were reported in women who received levonorgestrel: vomiting blood stained fluid, molar pregnancy, ruptured ovarian cyst, and kidney stones. The case of molar pregnancy was the only one considered possibly related to the study drug; all others were assessed as unrelated. Safety profiles yielded no significant safety findings and indicate that the treatment was otherwise well tolerated.

From all of these studies, no embryo or fetal disorders were reported in the women who continued their pregnancy and for whom follow-up information was available.

Post-Market Adverse Drug Reactions

The safety profile of Norlevo®, based on the post-marketing spontaneous reports, does not differ from the one observed in the clinical trials. In the last periodic safety update reports (PSUR 16, 17 and 18; covering period April 16, 2011- October 15, 2012), the most commonly spontaneously reported adverse drug reactions were: unintended pregnancy, vaginal/genital haemorrhage, menstruation delayed, metrorrhagia, nausea, abdominal pain, headache, vomiting, diarrhoea, dizziness, and fatigue.

There have been reports of thrombotic events (e.g. venous thromboembolism, pulmonary embolism) during the postmarketing period, however a causal relationship with NorLevo® treatment has not been determined.

DRUG INTERACTIONS

Overview

The metabolism of levonorgestrel is enhanced by the concomitant use of liver enzyme inducers: anticonvulsant (phenobarbital, phenytoin, primidone, carbamazepine); rifabutin; rifampicin; griseofulvin; ritonavir; Hypericum perforatum (St. John's wort)**.** As the efficacy of NorLevo® may be decreased in cases of concomitant intake of these drugs, it is recommended that patients perform a pregnancy test 2 to 3 weeks after NorLevo® intake.

Drug-Drug Interactions

As mentioned in the overview above, the metabolism of levonorgestrel is enhanced by the concomitant use of certain drugs such as anticonvulsant (phenobarbital, phenytoin, primidone, carbamazepine), rifabutin, rifampicin (8), griseofulvin and ritonavir. Acetaminophen was tested for potential interactions but none were observed with levonorgestrel (9).

As the efficacy of NorLevo® may be decreased in case of concomitant intake of these drugs, it is recommended that patients perform a pregnancy test 2 to 3 weeks after NorLevo® intake.

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

Drug-Food Interactions

No formal pharmacokinetic studies of the effects of food have been performed. Efficacy is presumed to be independent of the timing of meals.

Drug-Herb Interactions

The concomitant use of *Hypericum perforatum* (St. John's wort) can decrease the efficacy of NorLevo®.

As the efficacy of NorLevo® may be decreased in case of concomitant intake of these drugs, it is recommended that patients perform a pregnancy test if there is a delay in the onset of menses beyond 5-7 days.

Drug-Laboratory Interactions

Interactions between laboratory tests and levonorgestrel have not been established.

Use of oral contraceptives can modify the results of laboratory tests. Laboratory test 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

NorLevo® can be taken at any moment during the menstrual cycle.

Recommended Dose and Dosage Adjustment

Two tablets of NorLevo® (0.75 mg levonorgestrel) should be taken simultaneously for a total dose of 1.5 mg levonorgestrel. The efficacy of the treatment is higher the sooner after the unprotected intercourse it is initiated. Therefore, the tablets must be taken **as soon as possible, preferably within 12 hours, after the unprotected intercourse** and no longer than 72 hours (3 days) after the intercourse.

In case of vomiting taking place within three hours after intake of NorLevo®, the patient should make sure that the two tablets are found in the content of the vomit. If this is the case, and only then, it is recommended that an additional dose (2 tablets) be taken immediately.

After using an emergency contraception, it is recommended to use a barrier contraceptive method (condom, spermicide, cervical cap) until the next menstrual period resumes (See Warnings and Precautions). The use of NorLevo® does not contraindicate the continuation of regular hormonal contraception**.**

OVERDOSAGE

Serious effects have not been reported following acute ingestion of large doses of oral contraceptives. Overdose may cause nausea and withdrawal bleeding may occur. There are no specific antidotes and treatment should be symptomatic.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary mechanism of action of levonorgestrel has been shown to involve blockade and/or delay of ovulation via suppression of the luteinizing hormone (LH) peak. The ability of levonorgestrel to interfere with the ovulatory process is limited to its administration during the period preceding the onset of the LH surge. Levonorgestrel has no emergency contraceptive effect when administered later in the cycle. Levonorgestrel intake is able to disrupt the ovulatory process in 93% of cycles if the diameter of the dominant follicle is between 12 and 17 mm (37). Furthermore, in two clinical studies, the effectiveness of levonorgestrel EC was studied when the cycle day was determined by hormonal analysis (while other studies have used less precise self-reported cycle dates). In these studies, no pregnancies occurred in the women who took EC before ovulation, while pregnancies occurred only in women who took EC on or after the day of ovulation, providing evidence that EC were unable to prevent implantation (38, 39).

Pharmacokinetics

The absolute bioavailability of levonorgestrel 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. In the plasma, it is strongly bound to SHBG. Levonorgestrel is hydroxylated in the liver, and its metabolites are excreted as glucuronide and sulphate conjugates eliminated mostly in urine and, to a lesser extent, in feces.

A pharmacokinetic study with levonorgestrel (10) was performed to compare its plasma profile relative to different dosing regimen. This open observer-blind randomized study was performed on 24 healthy Caucasian female volunteers. The latter were randomized into three groups of eight women taking either a single 0.75 mg levonorgestrel tablet (Group B) or two 0.75 mg levonorgestrel tablets 12 hours (Group A) or 24 hours apart (Group C). Plasma levels of

levonorgestrel were measured from the time of intake up to 36 hours after this initial intake. Plasma sampling began at the time of intake.

The results showed T_{max} and C_{max} values of 2.50hr, 2.30hr, 2.06hr and 33.1 nmol/L, 30.7 nmol/L, 27.2 nmol/L, for groups A, B and C, respectively. The results of this study also indicated that the absorption, distribution and elimination profiles of levonorgestrel between the different treatments were similar. The maximal concentration of all groups combined was reached within 2.27 hours (± 1.17hr). The plasma half-life was estimated to be approximately 22 hours. The mean plasma concentration of levonorgestrel 24 hours after the first tablet intake was 6.2 nmol/L ± 5.46 (in both groups B and C combined). Also it indicates that 12 or 24 hours after administration, levonorgestrel plasma levels remain significant.

In another similar pharmacokinetic study (11), five healthy women received NorLevo® tablets in a cross-over fashion according to different schemes. Each woman participated in the three arms of the study with a washout period between treatments of 27-28 days. The treatments were:

A: two doses of 0.75 mg levonorgestrel given 12 hours apart;
B: two doses of 0.75 mg levonorgestrel given 24 hours apart;
C: a single dose of 1.5 mg levonorgestrel (two 0.75 mg tablets).

Maximum concentration levels of approximately 27 nmol/L (for group A and B) and 40 nmol/L (for group C) of levonorgestrel were reached between 1.54 and 1.8 hours (for group A and B) and 2.6 hours (for group C). The peak plasma concentration observed following the second dose, 12 or 24 hours later, was slightly higher than that following first dose (32.8 vs 29.5 nmol/L and 30.0 vs 27.2 nmol/L respectively). By 48 hours, all treatment arms had very similar levonorgestrel levels (6.2-7.4 nmol/L). The total area under the curve (AUC_{total}) was similar for treatment A and B (443.6 vs 432.5 nmol/h) and significantly higher for treatment C (925.0 nmol/h) (p=0.0003).

Lactation

A pharmacokinetic study was performed in healthy lactating women volunteers to assay levonorgestrel concentrations in plasma and milk following the intake of NorLevo® (single tablet containing 1.5 mg levonorgestrel) (12).

Twelve healthy lactating women volunteers on average 25 years old and 11 weeks post-partum participated in the study. Following a screening visit, they pumped breast milk (450 ml per kilogram infant bodyweight) and conserved it frozen to use to feed their babies during the first 72 hours after dosing. Women reported to the clinic with their infants at 08.00 – 10.00 am the day of the scheduled treatment phase. After collection of pre-dose blood and milk samples, women received one tablet of Norlevo (1.5 mg levonorgestrel) with 240 ml water. Milk and plasma levonorgestrel levels were measured at 1 (plasma only), 2, 4, 6, 8, 24, 48, 72, 96 and 120 hours after dosing. Plasma sex hormone binding globulin (SHBG) was performed prior to dosing and at 1, 24, 48, 72, 96 and 120 hours post-dosing.

Levonorgestrel milk concentrations paralleled those of plasma but were lower than plasma concentrations, with an overall mean milk-to-plasma ratio of 0.23 ± 0.09. LNG concentrations increased after dosing to reach a peak between 1 and 4h in plasma and between 2 and 4h in milk. The mean levonorgestrel concentrations were 15.4 and 6.9 ng/mL in plasma and milk, respectively. The mean terminal half-life of levonorgestrel was 29h in plasma and 26h in milk. At 120h after dosing, plasma concentrations (mean ± SD) of levonorgestrel were still above the lower limit of quantification for all subjects (0.23 ± 0.07 ng/mL), while milk concentrations were very low (0.06 ± 0.4 ng/mL) and reached undetectable levels for two subjects out of twelve.

The amount of levonorgestrel excreted in milk over the first 24h was 0.09% of the dose administered. This amount decreased rapidly with time, with only 0.01% of the given dose recovered in milk over the 49 -72h interval. The concentration of levonorgestrel (mean ± SD) measured in pooled milk samples was 1.56 ± 0.41 ng/mL on the first day, decreasing to 0.34 ± 0.20 ng/mL on the second day and to 0.20 ± 0.13 ng/mL on the third day. Based on AUC per 24-hour interval, the estimated mean amount of progestin potentially absorbed by an infant suckling about 800 mL of milk per day was 1.6 µg in the 0-24 h interval after dosing (1.0 µg in the first eight hours and 0.6 µg in the interval 8 to 24 hours after dosing), 0.3 µg in the 24-48h interval and 0.2 µg in the 48-72h interval. The mean total amount of levonorgestrel excreted in milk was 1830 ± 522 ng over the three days following the administration of 1.5 mg levonorgestrel.

On average, plasma SHBG concentrations remained essentially unchanged 1h after levonorgestrel dosing (56.3±21.5 nmol/L to 57.5±23.0 nmol/L) and then decreased consistently for all subjects over the 120h sampling time period to a mean of 35.9±12.8 nmol/L at the 120h time-point, which corresponds to a mean of 64% of pre-dose values.

These suggest that to limit infant exposure to the period of maximum levonorgestrel excretion in milk, mothers should discontinue nursing for at least 8 h, but not more than 24h, after emergency contraception.

Special Populations and Conditions

Pediatrics: Due to the nature of the product, no studies have been performed on pediatrics population.

Geriatrics: Due to the nature of the product, no studies have been performed on geriatrics population.

Gender: Studies have been performed with women only.

Race: No differences in safety or efficacy relative to ethnicity have been observed.

Hepatic and Renal Insufficiency: No formal studies have been conducted in patients with hepatic or renal insufficiency. Due to the sporadic administration of NorLevo® there are no concerns about the potential accumulation that may occur in patients with hepatic or renal insufficiency.

Body weight 75 kg and more: In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more, and levonorgestrel was not effective in women who weighed more than 80 kg (see section *Clinical Trials*).

STORAGE AND STABILITY

NorLevo® is stable at room temperature (15-30°C) for the period indicated on the label. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NorLevo® tablets are white, round, biconvex with no marking. Each tablet contains 0.75 mg levonorgestrel and the following non-medicinal ingredients: anhydrous colloidal silica, lactose monohydrate, magnesium stearate, maize starch and povidone.

NorLevo® is packaged in PVC/PE/PVDC/Aluminum blisters of 2 tablets. Pack sizes of 10, 20, 50 or 100 tablets presented in blisters of 2 tablets are available for hospital use.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

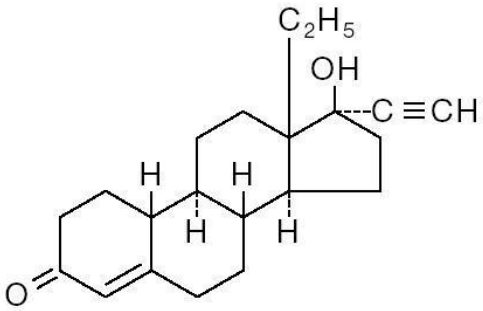
Drug Substance

Proper name: Levonorgestrel

Chemical name: (-)-13b-ethyl-17β-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one.

Molecular formula and molecular mass: $C_{21}H_{28}O_2$, 312.45 g/mol

Structural formula:



Physicochemical properties

Description: White to almost white crystalline powder, odorless.

Solubilities:		
	Water:	Practically insoluble
	Ethanol:	Slightly soluble
	Methylene Chloride:	Sparingly soluble
	Chloroform:	Sparingly soluble
	Dimethylformamide:	Soluble
	Dimethylsulfoxide:	Soluble

Melting point: 235°C

Particle size distribution: 100 % inferior to 30µm
80 % minimum inferior to 5µm
35 % maximum inferior to 1µm

CLINICAL TRIALS

Study demographics and trial design

Table 2- Summary of patient demographics for clinical trials in specific indication

Study Identifier;	Study Design	Test Product(s); Dosage Regimen;	Number of Subjects; Age and sex	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Arowojolu A.O. et al, 2002 (1)	Double-blind, placebo controlled trial	A: two dose of 0.75 mg levonorgestrel 12 h apart. B: single dose of 1.5 mg levonorgestrel;	1160 women, mean age: 27 years of age	Healthy noncontracepting women	Two doses treatment, 12 hours apart (Group A) One treatment (Group B)
WHO study Von Hertzen H. et al, 2002 (2)	Randomized, double-blind trial.	A: single dose of 10 mg of mifepristone B: single dose of 1.5 mg levonorgestrel C: two separate doses of 0.75 mg levonorgestrel given 12 h apart;	4136 women, mean 27.23 years old	Healthy women needed emergency contraception	One treatment (Group A and B); Two doses treatment, 12 hours apart (Group C)
WHO Study Ho. PC and al. 1993 (13)	Prospective, Randomized trial	A: two separate doses of 0.75 mg levonorgestrel given 12 hours apart; B: two separate doses of Yuzpe regimen given 12 hours apart	834 women, mean 26.8 years old.	Healthy women needed emergency contraception	Two doses treatment, 12 hours apart
WHO Study Grimes D. et al. 1998 (5)	Double-blind, Randomized, controlled trial.	A: two separate doses of 0.75 mg LNG given 12 hours apart; B: two separate doses of Yuzpe regimen given 12 hours apart	1955 women, mean 27.25 years old	Healthy women needed emergency contraception	Two doses treatment, 12 hours apart

Study Identifier;	Study Design	Test Product(s); Dosage Regimen;	Number of Subjects; Age and sex	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
WHO Study Ngai et al. 2005 (6)	Double-blind, Randomized trial	A: two doses of 0.75 mg levonorgestrel given 12 hours apart; B: two doses of 0.75 mg levonorgestrel given 24 hours apart	2071 women; mean 27 years old.	Healthy women needed emergency contraception	Two dose treatment, 12 or 24 hours apart
HRA2914-507 Creinin, 2006 (35)	Randomized, double-blind, multicenter, noninferiority trial	A: 50 mg unmicronized CDB-2914 (ulipristal) plus a placebo B: 2x0.75 mg tablets of levonorgestrel (12 h apart)	1672 women (832 in CDB-2914 group and 840 in the levonorgestrel group),	Healthy women needed emergency contraception	Two dose treatments, 0.75 mg 12 hours apart
HRA2914-513 Glasier, 2010 (36)	Randomized, multicenter, single-blind, non-inferiority trial	A: 30 mg CDB-2914 (ulipristal) B: 1.5 mg levonorgestrel	2221 women (1104 in CDB-2914 group and 1117 in the levonorgestrel group).	Healthy women needed emergency contraception	One dose treatment (levonorgestrel 1.5 mg)

Efficacy:

The primary outcome of the clinical studies investigating efficacy were pregnancy rates: the number of pregnancies divided by the number of subjects in a study, expressed as a percentage. An emergency contraceptive is considered as effective if the pregnancy rate and entire confidence interval is below 4%. These statistical criteria were agreed upon in consultation with the FDA and EMA to assess whether an EC method was sufficiently effective and in the absence of a negative control (placebo). This pregnancy rate represents a reduction of about 50% from a conception probability of 8% following a single act of intercourse.

Divided Dose Regimen

Two major studies, sponsored by the World Health Organization (5, 13), have shown that levonorgestrel alone, orally administered at the dose of 0.75 mg twice, 12 hours apart, within 72 hours following a supposedly fertilizing intercourse, is at least as efficient and better tolerated than the Yuzpe regimen (combined high dose estrogen and progestin). A third study, also sponsored by the WHO (6) compared a 24-hour versus a 12-hour interval between the two levonorgestrel intakes for emergency contraception and allowed to conclude that the 24-hour interval is as effective as the 12-hour interval up to 120 hours after unprotected intercourse.

The first WHO study (13) was conducted on 834 evaluable women, between 18 and 45 years old, with cycle lengths ranging from 21 to 35 days and who had a single act of intercourse 48 hours before the study entry. The subjects were randomised in two groups with no difference in baseline characteristics: The Yuzpe regimen group, n = 424 and the levonorgestrel group, n = 410 women. Regarding the primary efficacy results, this study showed an overall crude pregnancy rate (i.e. failure rate) of 3.5% in the Yuzpe regimen group and 2.9% in the levonorgestrel group. After excluding the patients who had further acts of intercourse, the crude pregnancy rates were 2.7 % (95% CI: 1.0 – 4.1%) in the Yuzpe regimen group and 2.4% (95% CI: 0.8 – 4.1%) in the levonorgestrel group. The difference observed was not statistically significant. In both groups, pregnancy rates were lower in women who took the study drug within 24 hours than in subjects who took it later, although this difference was not statistically significant. The study showed that post-treatment menstrual periods occurred in most women at the expected time or slightly earlier (88.5% of women in the Yuzpe regimen group versus 85.1% in the levonorgestrel group, difference not significant).

The second WHO study (5) was a large-scale double-blind randomized trial, conducted in 14 countries which compared the Yuzpe regimen and levonorgestrel for emergency contraception. A total of 1,998 women were found eligible, i.e. had regular menstrual cycles (24 – 42 days) and had a single unprotected intercourse 72 hours before taking the study medication. The eligible women were randomly given the Yuzpe regimen (4 tablets) or levonorgestrel (0.75 mg twice) in a double-blind fashion.

Efficacy was measured by assessing the number of unintended pregnancies, expressed as both crude and adjusted rates as well as the estimated reduction in expected pregnancies. The primary analysis was done in all randomised women with outcome information (n = 979 in the Yuzpe regimen group and n = 976 in the levonorgestrel group). The results showed that in both groups the earlier the treatment was started, the higher was the efficacy. When initiated within 24 hours of unprotected intercourse NorLevo® prevents 95% of expected pregnancies. When initiated within 24-48 or 48-72 hours, it prevents 85 % and 58% of expected pregnancies, respectively. At each time point, the efficacy of levonorgestrel was higher than in the Yuzpe regimen, but the difference was not statistically significant (p = 0.58).

The secondary analysis was performed in all subjects who used the assigned method correctly, as follows:

- first dose of treatment within 72 hours of unprotected intercourse,
- the interval to the second dose of less than 24 hours,
- no further acts of coitus and,
- no hormonal contraception during the rest of the cycle.

In this subgroup of 1,157 women, the crude pregnancy rates were found to be 1.9% (1.0 – 3.4) and 0.9% (0.3 – 2.0) with the Yuzpe regimen and levonorgestrel, respectively. In addition, the time of resumption of menses was similar in both groups (p = 0.67): in 13% of women menses returned later than 7 days after the expected date; in 15% menses was delayed by 3 to 7 days; in 57% menses was delayed by less than 3 days and in 15% menses returned earlier than expected.

In the third and most recent double-blind, randomized trial sponsored by the WHO (6), conducted from 1997 to 2003 in China, a total of 2,071 women were enrolled for emergency contraception within 120 hours of unprotected intercourse. The study compared women in whom the first levonorgestrel dose (0.75 mg) was given up to 120 hours and the second dose (0.75 mg) was administered 12 hours after the first dose (group 1), to women in whom the first levonorgestrel dose (0.75 mg) was given up to 120 hours and the second dose (0.75 mg) was administered 24 hours after the first dose (group 2). The analysis of the 2,018 subjects, who completed the follow-up, showed a crude pregnancy rate of 2.0% in group 1 (95% CI: 1.19 – 2.99) and of 1.9% in group 2 (95% CI: 1.17 – 2.94); the proportion of pregnancies prevented was estimated to be 75% in group 1 (95% CI: 59.0 – 83.7) and to 72% in group 2 (95% CI: 56.7 – 82.7).

In the HRA2914-507 study (35) which compared the efficacy, safety and tolerability of CDB-2914 (ulipristal acetate, 50mg) with levonorgestrel (1.5mg) as oral emergency contraception (EC) within 72 hours of unprotected intercourse. Levonorgestrel was administered twice at a 0.75mg dose, separated by 12 hours.

Overall, 1672 subjects were enrolled and randomized (832 to ulipristal, 840 to levonorgestrel); a total of 1578 subjects completed the study with a post-treatment pregnancy evaluation (792 ulipristal, 786 levonorgestrel, comprising the modified ITT population) of whom 1549 were evaluable for efficacy purposes (775 ulipristal, 774 levonorgestrel).

A total of 26 pregnancies were observed in the modified ITT population: 12 in subjects who received ulipristal (1.5%; 95% CI 0.7-2.4%) and 14 in subjects who received levonorgestrel (1.8%; 95% CI 0.9-2.7%). Following exclusion of off-treatment pregnancies (subjects who were subsequently found to have been pregnant prior to taking levonorgestrel or ulipristal acetate), a total of 20 pregnancies were observed (7 (0.9% [0.2-1.6%]) for ulipristal, 13 (1.7% [0.8-2.6%]) for levonorgestrel), confirming the non-inferiority of the two regimens. Ulipristal users experienced an 85% reduction in the number of expected pregnancies compared to 69% for levonorgestrel users. No statistical correlation between time to treatment (0-24h, >24-48h, >48-72h) and effectiveness was observed in either treatment group, although beyond 48h after intercourse, the effectiveness of levonorgestrel dropped considerably.

Single Dose Regimen

In a double-blind WHO study (2) the efficacy of 1.5 mg levonorgestrel was evaluated when given as two 0.75 mg tablets in a single intake, or given as two 0.75 mg tablets separated by 12 hours and compared to a single 10 mg dose of another product (mifepristone) on 4136 healthy women. Of the 3897 evaluable women enrolled in the trial (after exclusion), 1.5 % became pregnant in the single dose levonorgestrel group (20/1356) compared to 1.7% in the two-dose levonorgestrel group (24/1356; p = 0.83). In comparison with the estimated number of expected pregnancies in the absence of treatment, single dose levonorgestrel prevented 82% of expected pregnancies. For the three regimen combined, women who were treated after 72 hours had higher pregnancy rates, 2.4 % than those treated within 72 hours, 1.5 %, but the difference was not significant (p = 0.16).

In a double-blind study (1), the efficacy and safety of two-dose regimen of levonorgestrel 0.75 mg taken 12 h apart (group A) and levonorgestrel 1.5 mg (two 0.75 mg tablet) taken in a single administration (group B) were studied in 1062 evaluable women. Eleven pregnancies (1.0 %) were reported (7 in group A and 4 in group B). The crude relative risk of pregnancies was similar within the two groups (RR= 0.71 (0.32-1.55) (95 % C.I.); p>0.05). The estimated effectiveness rate of 86.80 % in group A was significantly lower than the 92.99 % for group B (p < 0.05).

The HRA2914-513 study (36) compared the efficacy, safety and tolerability of CDB-2914 (ulipristal acetate, 30mg) with levonorgestrel (1.5mg) as oral emergency contraception (EC). Levonorgestrel was administered as a single 1.5 mg tablet and served as the control group in the trial.

A total of 2,221 women were enrolled and treated in this study. The results in the levonorgestrel treatment arm show an observed pregnancy rate of 2.59% (95% CI; 1.68%, 3.94%). With respect to effectiveness, treatment with levonorgestrel prevented 52.2% (95% CI; 25.12%, 69.45%) of expected pregnancies when unprotected intercourse was within 72 hours of EC intake (mITT population).

Analysis of the effect of body weight on the efficacy of levonorgestrel

Utilizing the datasets from the two prospective randomized controlled trials (HRA2914-507 and HRA2914-513) carried out in the course of the development of ulipristal that included a levonorgestrel control group, a series of analyses was performed to assess the statistical significance and clinical relevance of the effect of weight on the efficacy of levonorgestrel for emergency contraception.

The analyses were conducted on the primary efficacy populations as specified in each study protocol; one thousand seven hundred and thirty one (1731) subjects randomized to receive levonorgestrel in the two studies were included in the analyses:

- 773 subjects in study HRA2914-507, in which 13 pregnancies were reported;
- 958 subjects in study HRA2914-513, in which 25 pregnancies were reported;

Mean (SD) weight of the overall analysis population was 66.6 (15.3) kg.

Weight of pregnant and non-pregnant women: women who became pregnant despite levonorgestrel intake for EC weighed significantly more than women who did not become pregnant (mean difference of 10 kg, p<0.0001 and median difference of 14 kg; p=0.001).

Pregnancy rates according to weight categories: in the first three weight categories, the pregnancy rate is below 2% and the upper limit of its 95% confidence interval remains within the 4% limit of clinical interest. Starting from the category of 75 kg, the pregnancy rate increases significantly and crosses well above the 4% clinical interest limit (Table 3).

Table 3: Pregnancy rate (95% CI) according to weight categories

Weight (kg)	**< 55**	**[55-65]**	**[65-75]**	**[75-85]**	**≥ 85**
N total	349	608	426	155	193
N pregnancies	3	8	6	10	11
Pregnancy rate	0.9%	1.3%	1.4%	6.4%	5.7%
Confidence interval	[0.2-2.5]	[0.6-2.6]	[0.5-3.0]	[3.1-11.5]	[2.9-10.0]

DETAILED PHARMACOLOGY

Animal:

Pharmacodynamics:

Levonorgestrel is the active enantiomer of the racemate mixture of which norgestrel is constituted, the dextrorotatory enantiomer being essentially inactive. Jones et al, 1979 (14) provides a comparison of the activity of levonorgestrel and the norgestrel racemate in a number of test systems which shows that levonorgestrel is consistently twice as active as the racemate.

Levonorgestrel was active in the Clauberg test in the rabbit (dose: 5-150 µg/day) and in maintaining pregnancy in the spayed rat (dose: 100-1000 µg/day). It inhibited the compensatory growth of the left ovary in rats following removal of the right ovary (dose: 500-1000 µg/day). Whilst having no uterotrophic effect in the immature mouse (dose: 5-500 µg/day), levonorgestrel did increase uterine weight in the ovariectomised adult rat (500-5000 µg/day). Levonorgestrel also inhibited estrone-induced vaginal cornification in the ovariectomised rat, which confirms its anti-estrogenic activity (15-500 µg/day). In general, levonorgestrel was active at lower doses in the tests of its progestational activity (Clauberg, pregnancy maintenance) than those of its estrogen-like activity (uterotrophic effects). Levonorgestrel was also shown to be devoid of androgenic activity by a lack of effect on the weights of prostate, seminal vesicles or levator ani in castrated male rats administered oral doses up to 1500 µg/day for 7 days.

Van der Vies and de Visser (15) show comparative data on the activity of levonorgestrel. The data shows levonorgestrel to be more active than norethisterone but less active than progesterone in the one Clauberg test, in which the two compounds were compared (oral dose: 15-125 µg; intra-uterine dose: 5-20 µg). Comparison of these data with those reported by Jones et al (14) for the Clauberg test show similar activity for levonorgestrel, despite the different dosing regimens employed in the two studies. Although it is difficult to compare the anti-estrogenic activity of levonorgestrel and norethisterone because of the different dose ranges at which the two were administered by van der Vies and de Visser (15), levonorgestrel does again appear to be the more active.

The studies of Van der Vies and de Visser (15) also investigated potential effects on fertility. When orally administered to rats twice daily for 5 days at dose levels of 2000, 4000 and 8000 µg/day, levonorgestrel did not suppress ovulation. Ovulation in rabbits was also investigated. All control animals ovulated, but levonorgestrel inhibited ovulation (100 % ovulation at 125 µg, 50% at 250 µg and 0% at 1000 µg).

Levonorgestrel slightly decreased the total number of ova and was also shown to decrease the number of fertilised ova in artificially inseminated rabbits, presumably through inhibition of sperm migration through the uterine cervix. The percentages of fertilised ova are summarized as follows: control 96%, 250 µg 94 %, 1000 µg 59% (15).

Oettel et al (16) also investigated the effect on deciduoma formation in rats (in combination with progesterone) and in maintaining pregnancy in ovariectomised rats, confirming the results of Van der Vies and de Visser (15) and Jones et al (14). In addition, the activity of levonorgestrel in blocking pregnancy was investigated in the mouse, rat and baboon when given immediately or shortly after mating. **Table 4** summarises the results obtained in mice and rats.

Table 4: Effect of levonorgestrel on pregnancy in the mouse and rat when administered after mating (Oettel 1980)

Species	Treatment (mg/day)	Group size	Number pregnant	Average number of implantations
Mouse	Control	13	13	9.3
	Levo, 0.0125	13	12	9.2
	0.125	12	10	7.9
	1.25	13	9	3.4
Rat	Control	12	12	13.2
	Levo, 0.125	12	12	12.2
	1.25	12	12	12.5
	12.5	11	11	8.1

Subcutaneous dosing started on the first day of pregnancy (defined as the presence of sperm in vaginal smears) and continued daily for a total of four doses; animals were sacrificed on day 10 (rats) or 14 (mice) to determine the number of pregnant animals and the number of implant sites - animals with at least one normal implantation site were assessed as pregnant.

Dasgupta et al, 1973 (17) studied the contraceptive effect of norgestrel, the racemate, in rats administering 2 µg orally on days 1-7 of gestation, on days 6-8 or as single doses on day 6, 7 or 8. Seven days administration terminated 100% of pregnancies; a single dose was effective only when given on day 6, terminating 57 % of pregnancies, whilst dosing on days 6-8 terminated 50%.

In contrast to the only weak activity in blocking pregnancy in mice and rats reported by Oettel et al (16), they showed levonorgestrel to be very effective in the baboon. A single oral administration of 400 µg of levonorgestrel within 6 hours of mating blocked pregnancies in 2 of 13 animals, as compared to pregnancies in 11 of 12 control animals.

Pharmacokinetics:

Dusterberg and coworkers (18, 19) studied the pharmacokinetics of levonorgestrel after oral, intravenous and subcutaneous administration in the rat, dog and rhesus monkey. Dusterberg et al, (18) provides data only on bioavailability after oral administration and terminal half-life after intravenous administration which is summarized in **Table 5**.

Table 5: Oral bioavailability and intravenous terminal half-life of levonorgestrel in the rat, dog and rhesus monkey

Species	Oral bioavailability (%)	Intravenous terminal half-life (h)	Oral dose (mg/kg)	Intravenous dose (mg/kg)
Rat	9	0.5 (0.17 - 7)[1]	6.7	0.07
Dog	22 ± 6	1.2 ± 0.3 (3 - 9)[1]	0.8	0.008
Rhesus monkey	9 ± 4	4.4 ± 0.5 (2 - 30)[1]	1.5	0.015

[1] range of values determined

A study in rhesus monkeys by Sisenwine et al (20) provided a half-life of 7 hours after oral administration of 0.5 mg/kg of levonorgestrel. More complete pharmacokinetic data are available after subcutaneous administration of levonorgestrel, as summarised in **Table 6** (18).

Table 6: Pharmacokinetics of levonorgestrel after subcutaneous administration in the rat, dog and rhesus monkey

Species	Dose (mg/kg)	C_{max} (µg/mL)[1]	t_{max} (hours)	$t_{1/2}$ (hours)	AUC (ng.d/mL)[1]
Rat	6.7	6.3 ± 2	1	24 (1 - 120)[2]	5.3
Dog	0.08	58 ± 20	4 - 24	16 ± 3 (24 - 96)[2]	94
Rhesus monkey	0.15	246 ± 20	4 - 12	22 ± 2 (8 - 96)[2]	444

[1] values normalised to a dose of 1 mg/kg
[2] range of values determined

Naqvi et al (21) analysed the pharmacokinetics of levonorgestrel after intravenous administration in the rat for fit to two- or three-compartment models and concluded that a tri-exponential equation provided a better fit to the data. Half-lives for the ∀, ∃ and (phases were, respectively, 10.1 minutes, 42.7 minutes and 23.1 hours. Corresponding values determined after intravenous dosing in the rabbit are 1.0, 3.8 and 37.5 hours for the ∀, ∃ and (phases respectively (21).

Protein binding:

Serum or plasma protein binding in rat, rabbit, dog, monkey and man has been studied by Qi-Gui and Humpel (22); human samples were of plasma whilst serum was obtained for the animal species. Protein binding was high in all species, 92 to 98%, when binding to undiluted plasma/serum was assessed. With human plasma diluted 1 in 30, it was possible to observe a contribution of sex hormone binding globulin (SHBG) to the binding. Total binding capacity was measured across species with a concentration of 100 ng/mL of levonorgestrel; capacity was lowest in the monkey and highest in rat - values were 58, 76, 76, 116 and 291 pmol/mg of protein for monkey, dog, human, rabbit and rat, respectively.

Tissue distribution:

A study in rabbits with ^{14}C-norgestrel (23) showed that up to 5 hours after intravenous dosing, large amounts of radioactivity were found in liver, kidney, intestine and bile. Although the concentration in fat and muscle was relatively low, because of the quantity of these tissues present in the body, the total amount found in these tissues may approach 5% of the dose. The uterus contained a high concentration of radioactivity. By 24 hours after dosing, the amount of radioactivity in the tissues had markedly decreased. Small amounts of radioactivity crossed the placenta of near-term pregnant animals and small amounts were found in the foetus and amniotic fluid.

Metabolism:

Levonorgestrel and its dextrorotatory enantiomer are metabolised differently in the African green monkey with the principal metabolite of levonorgestrel being 3∀, 5∃-tetrahydro-*d*-norgestrel (24), the same as found in women (25), where it occurs mainly as glucuronide and sulphate conjugates, and in the rhesus monkey (20).

Excretion:

Data on norgestrel are available after intravenous injection of ^{14}C-labelled compound in the rabbit are available; over the 7-day period following dosing 57.4% of administered radioactivity was excreted in the urine, the majority within the first 24 hours (23). Following oral dosing of 0.5 mg/kg of ^{14}C-levonorgestrel to female rhesus monkeys, 29.5 and 57.1%, respectively, of administered radioactivity was excreted in urine and faeces; for norgestrel, the urinary route was confirmed as more important (20).

TOXICOLOGY

Single dose toxicity

Levonorgestrel was not acutely toxic in mice or rats after oral or subcutaneous dosing, with the highest dose administered, 5000 mg/kg, failing to cause any deaths. After intraperitoneal dosing, LD_{50} values were >5000 and 2500-5000 mg/kg in male and female mice respectively with corresponding figures in rats of 2880 and 1470 mg/kg. Only slightly decreased physical activity was observed in animals dosed orally or subcutaneously whilst decreased activity, abnormal gait, lacrimation and sustained prone posture were observed after intraperitoneal dosing (26). The racemate, norgestrel, is similarly non-toxic in mice, rats and dogs with LD_{50} values >5000 mg/kg after oral dosing (26, 27).

Repeated-dose toxicity

A one-year repeated-dose toxicity study of levonorgestrel was conducted in rats and monkeys. Levonorgestrel was given at doses of: 0, 0.0005, 0.01, 0.5 and 25.0 mg/kg/day in rats and 0, 0.00025, 0.025, 0.25 and 2.5 mg/kg/day in monkeys. The findings of this study were basically the consequences of the pharmacological activity of levonorgestrel and, apart from the alterations in neutrophils and clotting time seen only at the end of dosing in the rat and of questionable relation to treatment, were reversible during the recovery periods at the end of dosing. The no effect levels were concluded to be 0.01 and 0.00025 mg/kg/day in the rat and monkey, respectively (28, 29).

Hillesheim et al (30) investigated the toxicity of a novel progestagen, STS 557, in a 6-month oral study in the dog and included a single dose level of levonorgestrel, 1.0 mg/kg/day, as a comparator. Four male and four female animals received levonorgestrel for six months, at the end of which time one animal of each sex was observed for a 2-month recovery period. Ovulation was completely suppressed and circulating estradiol levels tended to be lower than in control animals. Levonorgestrel did not affect circulating levels of testosterone in female animals but did so in male animals. Androgenic signs were however seen in females, the authors suggesting that this may have been due to displacement of testosterone from SHBG. Total cholesterol was lowered in male dogs.

The World Health Organisation (27) reviewed the toxicity data on levonorgestrel as part of an analysis of the risk associated with an implantable contraceptive releasing levonorgestrel. In this, they refer to long-term studies in the dog and monkey conducted by Wyeth Laboratories and submitted by them to regulatory authorities. These involved cyclic administration of levonorgestrel (regimen not specified) to dogs for 7 years at dose levels up to 0.125 and 0.5 mg/kg/day (two studies) and a 10-year study in monkeys at doses up to 1.0 mg/kg/day. The WHO panel concluded that the dog studies did not show any adverse events relevant to human use, although emphasising the now-recognised opinion that the dog is not a suitable model; no toxic effects attributable to treatment were seen in the monkey.

Reproductive toxicity

As discussed in the pharmacodynamics section, levonorgestrel administered soon after mating prevents pregnancy. Three publications address the reproductive toxicity during pregnancy.

In the study by Klaus (31), pregnant mice were treated with either 0.1, 1 or 10 mg/kg/day of levonorgestrel on days 3 to 7 post-coitum, or 1, 10 or 100 mg/kg/day on days 8 to 12 or 13 to 17 post-coitum; each dosing period had a contemporary control group. Foetuses were examined following hysterectomy on day 18; in order to assess possible effects on the fertility of offspring, some animals treated on days 3 to 7 and 8 to 12 with 1 and 10 mg/kg/day were allowed to deliver normally and the 11-week old pups were mated.

Levonorgestrel administration on days 8 to 12 at the highest dose level of 100 mg/kg/day increased foetal mortality and slightly reduced mean foetal body weight; a slight effect on foetal body weight was also apparent at 10 mg/kg/day on days 3 to 7. There was no effect on the fertility of pups.

Table 7 summarises the data on malformations from this study.

Table 7: **Malformations and skeletal retardations observed in an embryotoxicity study of levonorgestrel in the mouse**

Treatment	Total foetus examined	% gross malformation	% skeletal retardation	Type of malformation
Day 3 to 7				
Control	78	1.3	2.2	IM ectopia (liver & intestine)
0.1 mg/kg/day	29	0.0	0.0	Not Applicable
1.0	66	1.8	0.0	IF dwarf + excencephalia
10.0	107	8.4	20.7	6M + IF skeletal delay + small body mass + haemorrhage; IF hernia unbilica; IM dwarf
Days 8 to 12				
Control	76	0.0	2.6	Not Applicable
1.0 mg/kg/day	68	1.5	0.0	IF dwarf
10.0	92	3.3	0.0	IM missing vertebra
100.0	31	3.2	6.7	IM dwarf
Days 13 to 17				
Control	83	1.2	2.1	IM dwarf
1.0 mg/kg/day	112	0.9	0.0	IF dwarf
10.0	86	3.5	0.0	IM + IF dwarf; IM hernia unbilica
100.0	24	0.0	0.0	Not Applicable

A preliminary embryotoxicity study in the rabbit (32) studied a single dose level of 0.5 mg/kg/day of levonorgestrel in 10 rabbits, as compared to a control group of 12 animals. Treatment with levonorgestrel had no effect on litter parameters and did not increase the number of malformations.

A more recent study has examined the quality of oocytes recovered from mice implanted subdermally with levonorgestrel-releasing implants (33). The implants released 25 or 50 µg/day for 2 months or 55 µg/day for 3 months. After this time, mice were injected with gonadotropin to stimulate ovulation and oocytes were recovered, inseminated and cultivated, some in medium supplemented with levonorgestrel. Levonorgestrel had no adverse effect on fertilisation or development to the preimplantation stage.

Genotoxicity:

Lang and Reimann (34) studied the mutagenic potential of a series of hormonally active steroids, including levonorgestrel, in the Ames test. It was evaluated in five strains of *Salmonella typhimurium* - TA 1535, TA 100, TA 1537, TA 1538, TA 98 - at concentrations in the range 5 to 2500 µg per plate. No increase in mutagenic response was seen in any strain, in the absence or presence of metabolic activation.

Carcinogenicity:

The potential carcinogenic effect of levonorgestrel has been reviewed by the IARC (17), based partly on data submitted to the United Kingdom Committee on Safety of Medicines (CSM). On the basis of the information submitted to the CSM, the IARC review concludes that there was no alteration in the incidence of tumours in CF-LP (MTV^-) mice after administration of doses of norgestrel described as low dose (2-5 times human contraceptive dose), mid dose (50-150 times human contraceptive dose) and high dose (200-400 times human contraceptive dose) for 80 weeks. In the rat, administration of norgestrel in the diet (doses not described) for 104 weeks had no effect on the incidence of tumours.

Also reviewed by IARC (17) is a study in which castrated C3HxRIII (MTV^+) mice were fed norgestrel, 1.0 mg/kg/day, or levonorgestrel, 0.5 mg/kg/day, in the diet. The duration of dosing is not given. Both agents slightly raised the incidence of mammary tumours (females: control 17/29 mice, norgestrel 22/31, levonorgestrel 27/34; males: control 10/61, norgestrel 9/32, levonorgestrel 10/32); latencies were unchanged.

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PART III: CONSUMER INFORMATION

NorLevo®
Levonorgestrel Tablets
0.75 mg

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

ABOUT THIS MEDICATION

What the medication is used for:

NorLevo® is an emergency or backup contraceptive.

NorLevo® 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.

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

NorLevo® should not be used in place of regular contraception.

What it does:

NorLevo® acts as an emergency contraceptive by stopping or delaying the release of an egg from the ovary, thus preventing sperm and egg from uniting (fertilization). NorLevo® is not effective once a pregnancy has started, that is once the fertilized egg has attached to the wall of the uterus. It cannot stop a fertilized egg from attaching to the womb.

NorLevo® can be used following any unprotected act of sexual intercourse, including:

- when no contraceptive method has been used,
- when a contraceptive method may have failed, such as:
  - forgotten, ruptured, misuse or slippage of condom;
  - missed oral contraceptive pill;
  - expelled intrauterine device (IUD);
  - early removal, breakage or dislodgment of a vaginal diaphragm or of a contraceptive cap;
  - failure to withdraw before ejaculation ;
  - sexual intercourse during the supposedly fertile period when relying on periodic abstinence (temperature method);
  - in cases of sexual assault (rape);
  - a delay in starting a new packet of oral contraceptives;
  - a delay in getting a scheduled contraceptive injection.

NorLevo® is not as effective in preventing pregnancy as the use of most other birth control methods (e.g. oral contraceptive pills, IUS's, IUD's).

When it should not be used:

Do not use NorLevo® if:

- you have a confirmed or suspected pregnancy;
- you are allergic to it, or to any of the components of its formulation (for list of components, see the section "What the nonmedicinal ingredients are");
- you have abnormal vaginal bleeding.

What the medicinal ingredient is:

Levonorgestrel

What the nonmedicinal ingredients are:

Anhydrous colloidal silica, lactose monohydrate, magnesium stearate, maize starch, povidone.

What dosage form it comes in:

NorLevo® tablets are supplied in a blister package containing 2 tablets of 0.75 mg levonorgestrel. The tablet is round and white with no marking.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

NorLevo 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 care provider about your concerns and ask how you can protect yourself in the future.

If your period is delayed by more than 5 to 7 days, you should contact your doctor and have a pregnancy test done.

NorLevo® is for Emergency Contraceptive Use Only and should not be used on regular basis.

NorLevo® provides only short-term protection against pregnancy. Sexual activity that takes place after taking NorLevo 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.

BEFORE you use NorLevo® talk to your doctor or pharmacist if:

- you are allergic to levonorgestrel or any component of NorLevo® tablet;
- you are pregnant or breast-feeding;
- you have recent unusual vaginal bleeding (during your last cycle);
- known or suspected breast cancer;
- you have active liver disease or tumor
- you weigh 75 kg (165 lbs) or more.

INTERACTIONS WITH THIS MEDICATION

Drugs that decrease the efficacy of NorLevo® include:

- Anticonvulsants (phenobarbital, phenytoin, primidone, carbamazepine)
- Rifubutin
- Rifampicin
- Griseofulvin
- Ritonavir
- Hypericum perforatum (St. John wort)
- Ulipristal acetate

If you are taking one of the above medications, and your period is delayed by more than 5 to 7 days after using NorLevo®, you should contact your doctor and/or have a pregnancy test done.

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

PROPER USE OF THIS MEDICATION

Usual Dose:

NorLevo® may prevent pregnancy if the two tablets are taken together within 72 hours (3 days) and preferably with 12 hours, after a contraceptive accident or other unprotected sexual intercourse. You should not delay starting treatment. NorLevo® is more effective the sooner you start taking the tablets after unprotected intercourse.

Tablets should be taken with a glass of water.

If you vomit within three (3) hours after swallowing the tablets:

- If you can see the tablets in the vomit, you should purchase and take a second dose as soon as possible.
- If the tablets are not visible in the vomit, call you doctor or pharmacist as you might need another dose.

NorLevo® can be taken at any time during your menstrual cycle.

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.

NorLevo® is less effective in women weighing 75 kg (165 lbs) or more and not effective in women weighing more than 80 kg (176 lbs). If your weight is 75 kg or more, ask your health professional for advice on alternative methods of emergency contraception.

Nursing mothers:
You should discontinue nursing for at least 8 h, but not more than 24h, after emergency contraception. Any milk expressed during this period should be discarded.

Important:

If more than 72 hours (3 days) have passed since unprotected sex occurred, NorLevo® may not be effective. See your health care provider as soon as possible to discuss other options.

NorLevo® is not as effective in preventing pregnancy as the use of most other birth control methods (e.g. oral contraceptive pills, IUS's, IUD's or condoms, etc.). It should not be relied on for routine birth control by sexually active women.

Overdose:

Contact your local poison control center or emergency room immediately. Symptoms of overdose may include nausea, vomiting, vaginal bleeding and may lead to menstrual cycle disturbances.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

NorLevo® can cause temporary side effects in some women. These side effects generally do not last more than 24 hours. If the symptoms persist (for more than 48 hours) or are severe, see your doctor.
Common side effects include:

- Nausea, vomiting and diarrhea,
- Dizziness, fatigue, headache,
- Abdominal pain,
- Breast tenderness,
- Delayed menstrual period,
- Spotting,
- Irregular bleeding
- Painful menses;
- Uterine pain.

Delayed menstrual period: If your period is delayed by more than 5 to 7 days after using NorLevo®, you should contact your doctor and/or have a pregnancy test done.

Inform your doctor or pharmacist of any unwanted effect which is not mentioned in this insert.

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	
Uncommon	– Itching and/or redness all over your body			√
	– Mouth or throat swelling			√
	– Cramping or severe pain in your stomach or belly			√
	– Unusual vaginal bleeding prior or at your next normal period			√

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

HOW TO STORE IT

Keep out of reach of children.

Store at room temperature (15-30°C) and protect from light. Keep container in outer carton.

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 0701E
    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.bayer.ca

or by contacting the distributor Bayer Inc., at:
1-800-265-7382

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