

NEW ZEALAND DATASHEET

NAME OF MEDICINE

LEVONELLE-1

PRESENTATION

Each round white tablet contains 1.5 mg of levonorgestrel.
Tablet cannot be halved.

INDICATIONS

LEVONELLE-1 is an oral emergency contraceptive indicated for use within 72 hours of unprotected intercourse. It should be used only as an emergency measure.

Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

DOSAGE AND ADMINISTRATION

For oral administration: One tablet should be taken as soon as possible, preferably within 12 hours and no later than 72 hours after unprotected intercourse.

The highest efficacy is achieved if the tablet is taken as early as possible. Therefore treatment should not be delayed as efficacy declines with time.

Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

If the patient vomits within three hours of taking the tablet, she should return to her pharmacist, doctor or clinic where an additional tablet may be given.
LEVONELLE-1 can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

Children

LEVONELLE-1 is not recommended in children. Very limited data are available in women under 16 years of age.

CONTRAINDICATIONS

Hypersensitivity to the active substance levonorgestrel or any of the excipients.

LEVONELLE-1 should not be given to pregnant women. If menstrual bleeding is overdue, if the last menstrual period was abnormal in timing or character, or if pregnancy is suspected for any other reason, pregnancy should be excluded (by pregnancy testing or pelvic examination) before treatment is given.

If a woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle conception may have already occurred. Treatment with LEVONELLE-1 following the second act of intercourse may therefore be ineffective in preventing pregnancy. While the consensus is that levonorgestrel is not teratogenic, no guarantee can be given that pregnancy will result in a normal baby.

Progestogen-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not

known whether these same conditions apply to the LEVONELLE-1 regimen consisting of the emergency use of one 1.5 mg tablet.

Traditionally many of the contraindications to combined hormonal contraception have been applied to progestogen-only contraception. Since the contraindications largely apply to oestrogen this is inappropriate. In their Medical Eligibility Criteria, the World Health Organisation advises that the only absolute contraindications to high dose progestogen-only contraception are unexplained vaginal bleeding, current breast cancer, pregnancy or hypersensitivity to any of the ingredients of the preparation

WARNINGS AND PRECAUTIONS

LEVONELLE-1 is not as effective as a conventional regular method of contraception and is suitable only as an emergency measure. Emergency contraception does not prevent a pregnancy in every instance. If menstrual periods are delayed by more than 5 days or abnormal bleeding occurs at the expected date of menstrual periods or pregnancy is suspected for any other reason, pregnancy should be excluded.

If pregnancy occurs after treatment with levonorgestrel, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as levonorgestrel prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding. Therefore, levonorgestrel is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).

Repeated administration within a menstrual cycle is not advisable. Women who present for repeated courses of emergency contraception should be advised to consider a long-term method of contraception.

The use of emergency contraception does not replace the precautions necessary to prevent sexually transmitted diseases.

Only limited data are available in young women of child-bearing potential aged 14 to 16 years. No data are available about use in young women aged less than 14 years or in children (see also 'Use in children' and Dosage and administration").

LEVONELLE-1 contains 142.5 mg lactose. This should be taken into account in women with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

LEVONELLE-1 is not recommended in patients with severe hepatic dysfunction. Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of LEVONELLE-1.

Conditions which are considered relative contraindications include severe hypertension (BP>180+/110+), diabetes mellitus with nephropathy, retinopathy, neuropathy or vascular disease, ischaemic heart disease, stroke, or a past history of breast cancer. However, since exposure to levonorgestrel with LEVONELLE-1 is brief, the risks of pregnancy in all women, including those with pre-existing medical conditions, are almost certainly greater than those associated with LEVONELLE-1.

In individual cases the risk-benefit ratio should be assessed by the practitioner in discussion with the patient.

Precautions before use

- Exclude pregnancy if suspected clinically
- Breast or pelvic examinations are not routinely necessary. Perform such examinations only if indicated by the patient's history
- Blood pressure may be measured before prescribing LEVONELLE-1. An elevated BP is not a contraindication to treatment but indicates the need for further investigation
- No routine laboratory testing is required
- Possibility of an early or late onset of the next menstrual period to the patient.

Advise the practice of abstinence or careful use of a barrier method (e.g. condom, diaphragm, spermicide, cervical cap) until the onset of the next period. Follow-up should be offered 3 weeks after administration of therapy to assess the effectiveness of the method, to discuss future management if a period has not occurred, and to counsel the patient about future contraception. The use of levonorgestrel does not contraindicate the continuation of regular hormonal contraception.

Women should be warned that if pregnancy occurs after treatment with LEVONELLE-1, there is a possibility of an ectopic pregnancy.

Precautions after use

If pregnancy occurs after treatment with LEVONELLE-1, the possibility of an ectopic pregnancy should be considered.

Vomiting, severe diarrhoea or other causes of malabsorption, such as Crohn's disease, might impair the efficacy of LEVONELLE-1. Women suffering from conditions associated with possible malabsorption should be referred for medical consultation as consideration should be given to the taking of another tablet. If the patient vomits within three hours of taking the tablet, she should return to her pharmacist, doctor or clinic where an additional tablet may be given (see also Dosage and Administration).

EFFECT ON ABILITY TO DRIVE AND USE MACHINES

No effect is known.

CARCINOGENESIS AND MUTAGENESIS

No studies of the carcinogenic or mutagenic potential of levonorgestrel have been performed. Numerous epidemiological studies have been performed to determine the incidence of breast, endometrial, ovarian and cervical cancer in women using combination oral contraceptives. Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

Evidence in the literature suggests that use of combination oral contraceptives is not associated with an increased risk of developing breast cancer in the overall population of users. However, some of these same studies have shown an increased relative risk of

breast cancer in certain subgroups of combination-oral contraceptive users, although no consistent pattern of findings has been identified. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing levonorgestrel. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

USE IN PREGNANCY

LEVONELLE-1 should not be given to pregnant women and it will not interrupt the pregnancy. In the case of failure of emergency contraception, epidemiological studies indicate no adverse effects of progestogens on the foetus. It is generally considered that known teratogens will not produce malformations before organogenesis starts, which is later than 72 hours after fertilisation.

USE IN LACTATION

Progestogens do not appear to affect the quantity or quality of breast milk. However, levonorgestrel has been identified in the breast milk following oral administration to lactating women. Women should be advised not to breast-feed within 3 days after taking LEVONELLE-1.

EFFECT ON FERTILITY

Levonorgestrel increases the possibility of cycle disturbances which can sometimes lead to earlier or later ovulation date. These changes can result in modified fertility date; however there are no long term fertility data.

USE IN CHILDREN

LEVONELLE-1 is not indicated for use in children.

ADVERSE EFFECTS

The most commonly reported undesirable effect was nausea.

System Organ Class MedDRA 13.1	Frequency of adverse reactions	
	Very common (≥10 %)	Common (≥1 % to < 10 %)
Nervous System Disorders	Headache	Dizziness
Gastrointestinal disorders	Nausea Abdominal pain lower	Diarrhoea Vomiting
Reproductive system and breast disorders	Bleeding not related to menses*	Delay of menses more than 7 days Menstruation irregular Breast tenderness
General disorders and administration site conditions	Fatigue	

Bleeding patterns may be temporarily disturbed, but most women will have their next menstrual period within 5-7 days of the expected time. If the next menstrual period is more than 5 days overdue, pregnancy should be excluded.

From Post-marketing surveillance additionally, the following adverse events have been reported:

Skin and subcutaneous disorders
Very rare (<1/10000): rash, urticarial, pruritus

Reproductive system and breast disorders
Very rare (<1/10000): pelvic pain, dysmenorrhoea

General disorders and administration site reactions
Very rare (<1/10000): face oedema

INTERACTIONS

The metabolism of levonorgestrel can be enhanced by concomitant use of drugs which induce CYP3A4, one of the family of liver enzymes. This may reduce the effectiveness of LEVONELLE-1 in preventing pregnancy.

Drugs suspected of having the capacity to reduce the efficacy of levonorgestrel-containing medications includes: barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing *Hypericum perforatum* (St John's Wort), rifampicin, ritonavir, rifabutin, griseofulvin and efavirenz.

Medicines containing levonorgestrel may increase the risk of cyclosporin toxicity due to possible inhibition of cyclosporin metabolism.

Levonorgestrel has the ability to decrease glucose tolerance when it is used in the longer term. However, use of levonorgestrel as an emergency contraceptive is not thought to induce significant modification of carbohydrate metabolism.

OVERDOSAGE

Serious undesirable 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.

FURTHER INFORMATION

EFFICACY

From earlier studies where two LEVONELLE-2 tablets (each 750 micrograms) have been taken 12 hours apart, it has been estimated that LEVONELLE-2 prevents 85% of expected pregnancies. Efficacy appears to decline with time after intercourse (95% within 24 hours, 85% 24-48 hours, 58% if used between 48 and 72 hours).

In an additional study to compare taking the two tablets 12 hours apart versus taking a total dose of 1.5 mg after unprotected intercourse, similar rates of prevention of pregnancy were observed when taken within 72 hours. In this study, it was also observed that efficacy declined with increasing time of taking the medication after intercourse.

In further studies to compare the bioavailability of the single 1.5 mg tablet to two 750 microgram tablets, it has been determined that the efficacy would be similar.

PHARMACODYNAMICS

The precise mode of action of LEVONELLE-1 is not known. Emergency hormonal contraception is thought to work mainly by preventing ovulation and fertilisation by

altering tubal transport of sperm and/or ova. Levonorgestrel is not effective once the process of implantation has begun.

At the recommended regimen, levonorgestrel is not expected to induce significant modification of blood clotting factors, and lipid and carbohydrate metabolism.

PHARMACOKINETICS

Absorption and Distribution

The absolute bioavailability of levonorgestrel was determined to be almost 100% of the dose administered.

A study compared the pharmacokinetics of LEVONELLE-1 (a 1.5 mg levonorgestrel tablet taken as a single dose) with that of two 750 microgram tablets taken 12 hours apart. Following ingestion of one 1.5 mg tablet, maximum plasma drug levels of 18.5 ng/mL were found at 2 hours. Thereafter, levonorgestrel plasma levels decreased with a half life of approximately 26 hours. In this study, the C_{max} was higher for the single 1.5 mg tablet, but plasma levels over a 24 hour period were similar, as were the T_{max} and half life.

In another study, a comparison of the pharmacokinetics with two 750 microgram tablets taken together (as a single dose) or 12 hours apart showed similar levels of serum levonorgestrel over a 24 hour period, and similar terminal half lives (43.7 versus 43.3 hours). The C_{max} was about 50% higher when the two tablets were taken together than when they were taken 12 hours apart (12.3 versus 7.9 ng/mL, $p=0.03$), and this occurred at 2.5 and 1.8 hours, respectively, after the (first) dose.

When the bioavailability of a single 1.5 mg LEVONELLE-1 tablet was compared to two 750 microgram tablets taken at the same time, AUC and C_{max} were found to be the same with both treatments. In this study, maximum plasma drug levels of 19.1 ng/mL were found at 1.7 hours following the ingestion of one 1.5 mg tablet. Thereafter, levonorgestrel plasma levels decreased with a half life of approximately 27 hours.

In general, it is recognised that the pharmacokinetics of levonorgestrel can be variable.

Levonorgestrel is bound to serum albumin and sex hormone binding globulin (SHBG). Only about 1.5% of the total serum levels are present as free steroid, but 65% are specifically bound to SHBG.

About 0.1% of the maternal dose can be transferred via milk to the breast-fed infant.

Metabolism and Excretion

Levonorgestrel is not excreted in unchanged form but as metabolites.

Levonorgestrel metabolites are excreted in about equal proportions in urine and faeces. The biotransformation follows the known pathways of steroid metabolism, with levonorgestrel being hydroxylated in the liver and the metabolites then excreted as glucuronide conjugates. No pharmacologically active metabolites are known.

CLINICAL TRIALS

Two large controlled studies of levonorgestrel using 750 microgram tablets (two tablets taken 12 hours apart), for emergency contraception have been undertaken. The first of these is referred to as the Ho and Kwan study and the second, which included larger

numbers, as the Pivotal study. Both studies compared this treatment regime to the Yuzpe regimen (ethinylloestradiol 100 micrograms plus levonorgestrel 500 micrograms, repeated 12 hours later).

The Ho and Kwan study was a single centre and open-label (age range 18-45 years) while the Pivotal study was multi centre, randomised and double-blind (age range 14-47 years), with both including women requiring emergency contraception resulting from no contraception used during intercourse or contraception method failure. The regimens were similar with two exceptions:-

- The Ho and Kwan study allowed treatment to be initiated up to 48 hours post intercourse whereas the Pivotal study allowed a 72 hour gap between treatment initiation and intercourse.
- The treatment regimen in both studies used two tablets, the second taken 12 hours after the first. In the Pivotal study only, women in each of the two groups were provided with replacement medication to take should vomiting occur within four hours of either dose.

The efficacy results from the efficacy population analysis from the two studies are summarised in the following table:

Parameter	Ho and Kwan Study		Pivotal Study	
	LNG ^a	Yuzpe	LNG ^a	Yuzpe
Number of women	410	424	976	979
Number of pregnancies	12	15	11	31
Pregnancy rate (%)	2.9	3.5	1.1	3.2
Number of Observed/Expected Pregnancies	8/19.8 ^b	9/22.0 ^b	11/76.3	31/74.2
Prevented fraction (%)	60	59	86 ^c	58

a LNG = Levonorgestrel

b Among 331 (LNG) and 341 (Yuzpe) women who had reliable menstrual dates.

c Significantly greater than in the Yuzpe group

The relative risk of pregnancy in the Pivotal study for the Yuzpe versus levonorgestrel regimens was 2.8 with a lower one-sided 95% confidence bound of 1.53.

Stratified analyses of the data showed no significant effect for age or ethnicity. For interval between intercourse and initiation of treatment, shorter intervals were associated with lower pregnancy rates.

Two further studies have been conducted in order to determine whether taking two 750 microgram tablets at the same time (as a single dose) was as efficacious as taking the two tablets 12 hours apart.

The pivotal study for this comparison was a double blind, randomised, double dummy multicentre study, conducted by the WHO/HRP across 10 countries. This study included women ranging in age from 14 to 52 years, and allowed for enrolment up to 120 hours after intercourse.

A supporting study (Arowojolu et al, 2002) for this comparison was conducted in Nigeria at a single centre. A total of 1118 women were assessed for efficacy in this study.

The efficacy results from the data analysis for the two treatment regimes from both studies are summarised in the following table:

Parameter	Pivotal study		Arowojolu et al, 2002	
	Two 750 microgram tablets taken as a single dose	Two 750 microgram tablets taken 12 hours apart	Two 750 microgram tablets taken as a single dose	Two 750 microgram tablets taken 12 hours apart
Number of women	1356	1356	545	573
Number of pregnancies	20	24	4	7
Pregnancy rate (%)	1.5	1.8	0.7	1.3
Number of Observed/ Expected Pregnancies	20/111	24/106		
Prevented fraction (%)	81.9 ¹	77.3 ¹	93.4 ²	87.5 ²

¹Prevented fraction over 5 days – calculated from Number of Observed / Expected Pregnancies (Pivotal study)

²Prevented fraction calculated using British conception probabilities (Arowojolu et al study)

There was no significant difference in efficacy between the two levonorgestrel treatment groups in the pivotal study. Shorter intervals between intercourse and treatment were associated with lower pregnancy rates in both groups.

The authors of the supporting study (Arowojolu et al, 2002) concluded that both treatment regimes were effective – the single two tablet dose appeared to be more effective than when the two tablets were taken 12 hours apart and that the earlier the medication is taken after unprotected intercourse, the better the efficacy.

Adverse events reported in these two studies were similar for both treatment groups (see 'Adverse Effects').

No specific clinical trials investigating pregnancy outcome have been conducted on the single 1.5 mg tablet. Evidence for its efficacy is based on the 1.5 mg tablet and two 750 microgram tablets taken at the same time having the same pharmacokinetic profile.

INSTRUCTIONS FOR USE/HANDLING

Keep out of reach of children.

OTHER

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in

acetone, and in ether; soluble in chloroform; sparingly soluble in methylene chloride.

LIST OF EXCIPIENTS

Potato starch, maize starch, colloidal silica anhydrous, magnesium stearate, purified talc, lactose monohydrate.

PHARMACEUTICAL PRECAUTIONS

Shelf-life: 3 years

Special precautions for storage: Store at or below 25°C in the original container.

MEDICINE CLASSIFICATION

Pharmacist Only Medicine

PACKAGE QUANTITIES

LEVONELLE-1 contains one blister aluminium/PVC blister sheet containing one tablet.

NAME AND ADDRESS

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