NEW ZEALAND DATA SHEET

1 NAME OF THE MEDICINE

Levonorgestrel-1

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levonorgestrel-1 tablet contains 1.5 mg of levonorgestrel.

List of excipients with known effect: lactose monohydrate (see **Section 4.4 Special Warnings and Precautions for Use - Excipients)**.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

Tablet, uncoated

Levonorgestrel-1 is a white to off-white, round shaped tablet debossed with 'LV1' on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

4.2 Dose and Method of Administration

Dosage

One tablet should be taken, as soon as possible, preferably within 12 hours, and no later than 72 hours after unprotected intercourse (see section 'Efficacy').

If vomiting occurs within three hours of taking the tablet, another tablet should be taken immediately. Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal EC, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. 2 tablets of 1500 micrograms taken together) for those women unable or unwilling to use Cu-IUD (see section 'Interactions').

Levonorgestrel can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

After using emergency contraception, it is recommended to use a local barrier method (e.g. condom, diaphragm, spermicide, cervical cap) until the next menstrual period starts. The use of levonorgestrel does not contraindicate the continuation of regular hormonal contraception.

Paediatric population
There is no relevant use of levonorgestrel for children of pre-pubertal age in the indication emergency contraception.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in **Section 6.1 List of Excipients**.

Levonorgestrel should not be given to pregnant women.

4.4 Special Warnings and Precautions for Use

Pregnancy
Pregnancy should be excluded before treatment.

If a woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, or there is uncertainty about the timing of unprotected intercourse, conception may have already occurred.

If menstrual bleeding is delayed by more than 5 days, or if abnormal bleeding occurs at the expected date of menstrual period, or if the last menstrual period was abnormal in timing or character, or if pregnancy is suspected for any reason, pregnancy should be excluded (be pregnancy testing or pelvic examination) before treatment is given.

Emergency contraception does not prevent a pregnancy in every instance. Treatment with levonorgestrel following the second act of intercourse during the same menstrual cycle may therefore be ineffective in preventing pregnancy.

If pregnancy occurs or there are complaints of severe lower abdominal pain 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 occurrent 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).

Precautions before use
Vomiting, severe diarrhoea or other causes of malabsorption, such as Crohn's disease, might impair the efficacy of Levonorgestrel-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.

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

Precautions after use
After levonorgestrel intake, menstrual periods are usually normal and occur at the expected date. They can sometimes occur earlier or later than expected by a few days.

After using emergency contraception, it is recommended to use a local barrier method (e.g. condom, diaphragm, spermicide, cervical cap) until the next menstrual period starts.

Follow up should be offered 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 on future contraception.

The use of levonorgestrel does not contraindicate the continuation of regular hormonal contraception. If no withdrawal bleed occurs in the next pill-free period following the use of levonorgestrel after regular hormonal contraception, pregnancy should be ruled out.

Regular methods of contraception
Emergency contraception is an occasional method. It should in no instance replace a regular contraceptive method.

Levonorgestrel is not effective as a conventional regular method of contraception and is suitable only as an emergency measure.

Repeated administration within a menstrual cycle is not advisable because of the possibility of disturbance of the cycle.

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

Sexually transmitted diseases
Levonorgestrel does not replace the necessary precautions, nor does it protect against sexually transmitted diseases (STDs), including HIV/AIDS

Use in Hepatic Impairment
Levonorgestrel is not recommended in patients with severe hepatic dysfunction.

Paediatric Use
Levonorgestrel is not indicated for use in children.

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.

Excipients
Levonorgestrel-1 contains 140.1 mg lactose. This should be taken into account in women with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption.

4.5 Interactions with Other Medicines and Other Forms of Interactions

The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%.

Medicines suspected of having the similar capacity to reduce plasma levels of levonorgestrel include barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St John's Wort), rifampicin, ritonavir, rifabutin and griseofulvin.

For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a CuIUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3000 microgram within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied.

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

Use in Children
There is no relevant use of levonorgestrel for children of pre-pubertal age in the indication emergency contraception.

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

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

Use in Pregnancy

Category D

Levonorgestrel should not be used during an existing or suspected pregnancy. Research has found no significant effects on foetal development associated with the long-term use of contraceptive doses of combined oral steroids before pregnancy or taken inadvertently during early pregnancy. There have been an insufficient number of pregnancies in patients using levonorgestrel-only oral contraceptives to rigorously evaluate the potential for developmental toxicity; however, based on the combined oral contraceptive experience, an increase in abnormalities is not expected. If taken by the mother at or after 8 weeks post conception, progestogens such as levonorgestrel can cause virilisation of the female foetus. This is a dose dependent effect. Prior to 8 weeks post conception, they have no virilising effects. There are no studies of the effect of the high levonorgestrel doses used in Levonorgestrel-1 on pregnancy and embryo/foetal development.

Use in Lactation

Levonorgestrel is secreted into breast milk. Potential exposure of an infant to levonorgestrel can be reduced if the breast-feeding woman takes the tablets immediately after feeding and avoids nursing at least 8 hours following levonorgestrel administration.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable Effects

The most commonly reported undesirable effect was nausea.

	Frequency of adverse reactions	
System Organ Class MedDRA 19.0	**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

Gastrointestinal disorders
Very rare (<1/10,000): abdominal pain

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

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

The precise mode of action of levonorgestrel is not known.

At the recommended regimen, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if intercourse has taken place in the pre-ovulatory phase, when the likelihood of fertilisation is the highest. Levonorgestrel is not effective once the process of implantation has begun.

There is limited and inconclusive data on the effect of high body weight/high body mass index (BMI) on the contraceptive efficacy. In three WHO studies no trend for a reduced efficacy with increasing body weight/BMI was observed (Table 1), whereas in the two other studies (Creinin et al., 2006 and Glasier et al., 2010) a reduced contraceptive efficacy was observed with increasing body weight or BMI (Table 2). Both meta-analyses excluded intake later than 72 hours after unprotected intercourse (i.e. off-label use of levonorgestrel) and women who had further acts of unprotected intercourse.

Table 1: Meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010)

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

Table 2: Meta-analysis on studies of Creinin et al., 2006 and Glasier et al., 2010

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

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

Paediatric population

A prospective observational study showed that out of 305 treatments with levonorgestrel emergency contraceptive tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

Efficacy

It was estimated from the results of an earlier clinical study, that 750 micrograms of levonorgestrel (taken as two 750 microgram doses with a 12 hour interval) prevents 85% of expected pregnancies. Efficacy appears to decline with time of start of treatment after intercourse (95% within 24 hours, 85% 24-48 hours, 58% if started between 48 and 72 hours).

Results from a recent clinical study showed that two 750 microgram tablets of levonorgestrel taken at the same time (and within 72 hours of unprotected sex) prevented 84% of expected pregnancies. There was no difference between pregnancy rates in case of women who were treated on the third or the fourth day after the unprotected act of intercourse ($p>0.2$).

5.2 Pharmacokinetic Properties

Absorption

A study compared the pharmacokinetics of 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 levonorgestrel 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 quite variable.

Distribution

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.

Metabolism and Excretion

Levonorgestrel is not excreted in unchanged form but as metabolites. Levonorgestrel metabolites are excreted in about equal proportions with 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.

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

About 0.1% of the maternal dose can be transferred via milk to the nursed infant.

5.3 Preclinical Safety Data

Genotoxicity

No studies of the mutagenic potential of levonorgestrel have been performed.

Carcinogenicity

No studies of the carcinogenic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Each white tablet contains the following excipients:
Lactose monohydrate
Maize starch
Povidone
Colloidal anhydrous silica
Magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf Life

2 years

6.4 Special Precautions for Storage

Store below 25°C in original container. Do not remove from primary pack except for immediate use. Protect from light.

6.5 Nature and Contents of Container

Levonorgestrel-1 contains one blister sheet (PVC/PVDC/Aluminium) containing one tablet.

6.6 Special Precautions for Disposal

No special requirements.

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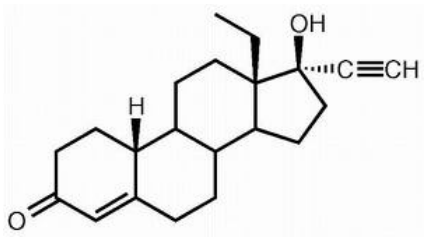
6.7 Physicochemical Properties

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, acetone, and ether; soluble in chloroform; sparingly soluble in methylene chloride.

Chemical Structure

Levonorgestrel-1 is an emergency oral contraceptive tablet containing the synthetic progestogen, levonorgestrel. Levonorgestrel is a progestogen.



Chemical Name: 13- Ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
Molecular Formula: $C_{21}H_{28}O_2$
Molecular Weight: 312.45
Melting Point: 232-239°C

CAS Number
797-63-7

7 MEDICINE SCHEDULE

Pharmacist Only Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

7 March 2024

10 DATE OF REVISION

7 March 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information