

New Zealand Data Sheet

1 LEVONORGESTREL BNM

LEVONORGESTREL BNM 1.5 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levonorgestrel 1.5 mg

Excipient(s) with known effect:

Each tablet contains 43.3 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Levonorgestrel tablet is a round, biconvex, white tablet, engraved with “C” on one side and “1” 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

Dose

One tablet should be taken, as soon as possible, preferably within 12 hours, and no later than 72 hours after unprotected intercourse (see section 5.1 Pharmacodynamic properties – Clinical 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 4.5 Interaction with other medicines and other forms of interaction).

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 levonorgestrel or to any of the excipients.

4.4 Special warnings and precautions for use

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

Emergency contraception does not prevent a pregnancy in every instance. If there is uncertainty about the timing of the unprotected intercourse or if the woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, conception may have occurred. Treatment with levonorgestrel following the second act of intercourse may therefore be ineffective in preventing pregnancy. 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).

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

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. Women should be advised to make a medical appointment to initiate or adopt a method of regular 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.

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

Limited and inconclusive data suggest that there may be reduced efficacy of levonorgestrel with increasing body weight or body mass index (BMI) (see section 5.1 Pharmacodynamic properties – Pharmacodynamic effects). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.

Levonorgestrel is not as effective as a conventional regular method of contraception and is suitable only as an emergency measure. Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

Use of emergency contraception does not replace the necessary precautions against sexually transmitted diseases.

4.5 Interaction with other medicines and other forms of interaction

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%.

Drugs 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 Cu-IUD) 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.

Paediatric population

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Levonorgestrel should not be given to pregnant women. It will not interrupt a pregnancy. In the case of continued pregnancy, limited epidemiological data indicate no adverse effects on the foetus but there are no clinical data on the potential consequences if doses greater than 1.5 mg of levonorgestrel are taken.

Breastfeeding

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. See section 5.2 Pharmacokinetic properties – Elimination.

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 fertility data in the long term.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported undesirable effect was nausea.

System Organ Class MedDRA 19.0	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

Gastrointestinal disorders

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

General disorders and administration site reactions

Very rare (< 1/10000): face oedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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.

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

Pharmacotherapeutic group: Emergency contraceptives
 ATC code: G03AD01

Mechanism of action

The precise mode of action of levonorgestrel is not known.

Pharmacodynamic effects

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/m²)	Underweight 0 to 18.5	Normal 18.5 to 25	Overweight 25 to 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 to 3.26	0.70 to 1.35	0.21 to 1.24	0.24 to 3.39

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

BMI (kg/m²)	Underweight 0 to 18.5	Normal 18.5 to 25	Overweight 25 to 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 to 8.40	0.44 to 1.82	1.02 to 4.60	2.62 to 9.09

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

Clinical 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 ($p>0.2$).

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).

5.2 Pharmacokinetic properties

Absorption

Orally administered levonorgestrel is rapidly and almost completely absorbed.

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

Distribution

The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of single dose of 1.5 mg levonorgestrel maximum drug serum levels of 18.5 ng/ml were found at 2 hours.

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.

Biotransformation

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, the levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucuronide conjugates.

No pharmacologically active metabolites are known.

Elimination

After reaching maximum serum levels, the concentration of levonorgestrel decreased with a mean elimination half-life of about 26 hours.

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

5.3 Preclinical safety data

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Lactose monohydrate
Poloxamer 188
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

PVC/PVDC/aluminium blister containing one tablet, which is further packed into a carton

6.6 Special precautions for disposal and other handling

No special requirements

7 MEDICINE SCHEDULE

Pharmacist Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30 April 2020

10 DATE OF REVISION OF TEXT

30 April 2020