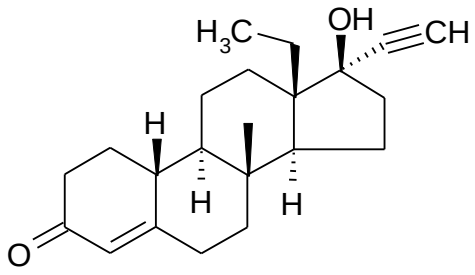
PRODUCT INFORMATION
NORLEVO®-1 1.5MG TABLET

NAME OF THE MEDICINE
Levonorgestrel

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



CAS: 797-63-7

Empirical formula: $C_{21}H_{28}O_2$ MW: 312. 5

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

NorLevo-1 contains levonorgestrel 1.5mg as active ingredient.

NorLevo-1 also contains inactive ingredients:
Lactose monohydrate, starch - maize, povidone, silica – colloidal anhydrous, magnesium stearate.

PHARMACOLOGY
Levonorgestrel is a progestogen.

Pharmacodynamics
The precise mode of action of Norlevo-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. It may also cause endometrial changes that discourage implantation.

Efficacy. From earlier studies where two levonorgestrel tablets (each 750micrograms) have been taken 12 hours apart, it has been estimated that levonorgestrel prevents 85% of expected pregnancies. Efficacy appears to decline with time after intercourse (95% within 24 hours, 85% 24 to 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 1.5mg 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 a single 1.5mg tablet to two 750 microgram tablets, it has been determined that the efficacy would be similar.

Pharmacokinetics
Absorption: After oral administration of 1.5mg levonorgestrel (two 750microgram tablets as a single dose), the plasma terminal half-life of the product is estimated to 43 hours. The maximal plasma concentration of levonorgestrel (approximately 40nmol/L) is reached within 3 hours.

Another study on pharmacokinetics following administration of a 1.5mg levonorgestrel tablet found maximum plasma drug levels of 15.4 nanogram/mL at two hours. Thereafter, levonorgestrel plasma levels decreased with a half-life of approximately 29 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 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.

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 breastfed infant.

CLINICAL TRIALS

Two recent studies compare the efficacy of two 0.75mg doses of levonorgestrel when given 12 hours apart with a single dose of 1.5mg levonorgestrel.

The pivotal study was a randomised, double-blind multi-centre trial conducted in ten countries by the WHO (Lancet 2002, 360:1803-10). Of 4,071 women with known outcome, groups of 1,356 women each took either two doses of 0.75mg levonorgestrel 12 hours apart or 2x0.75mg levonorgestrel at once. There was no significant difference in efficacy between the two levonorgestrel treatment groups. When levonorgestrel was administered within 72 hours after unprotected intercourse 84% (95% CI:.73.0-90.5) of expected pregnancies were prevented with the single dose regimen compared to 79% (95% CI: 66.2-86.8) in the two dose group.

In a second double blind, randomised study (Contraception 2002, 66, 269-273), the efficacy and safety of levonorgestrel given in two doses of 0.75mg 12 hours apart (group A) or 1.5mg given at once (group B) was studied in 1,160 Nigerian women seeking emergency contraception up to 72 hours after unprotected intercourse. Of the 1,118 women analysed for efficacy, 545 were in group A and 573 in group B. Eleven intrauterine pregnancies (7 in group A and 4 in group B) were recorded. Results for the two regimens using the conception probabilities for all conceptions and recognized conceptions calculated from pooled British and North Carolina data indicate that both regimens were effective with the single 1.5mg dose treatment being significantly more effective ($p<0.05$).

For interval between intercourse and initiation of treatment, shorter intervals were associated with lower pregnancy rates in both levonorgestrel treatment groups of both studies.

INDICATIONS

NorLevo-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.

CONTRAINDICATIONS

NorLevo-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 NorLevo-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 NorLevo-1 regimen consisting of the emergency use of one 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 Organization 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.

PRECAUTIONS

Conditions which are regarded as 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.

Isolated cases of thromboembolic events have been reported after levonorgestrel intake. No causal relationship with levonorgestrel has been formally demonstrated, but the possibility of occurrence of a thromboembolic event should be considered in women with other pre-existing thromboembolic risk factor(s), especially personal or family history suggesting thrombophilia.

Since exposure to levonorgestrel with NorLevo-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 NorLevo-1. In individual cases the risk benefit ratio should be assessed by the practitioner in discussion with the patient. Only limited data are available about use in young women of childbearing 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").

NorLevo-1 is not as effective as conventional regular methods of contraception and is suitable only as an emergency measure. Women who present for repeated courses of emergency contraception should be advised to consider a long-term method of contraception.

Emergency contraception does not protect against sexually transmitted infections.

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

<u>Precautions before use</u>

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 recommending NorLevo-1. An elevated blood pressure is not a contraindication to treatment but indicates the need for further investigation.

No routine laboratory testing is required.

Explain the importance of follow up and the 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 until the onset of the next period. Follow up with a doctor three weeks after administration of therapy should be advised 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. Women should be warned that if pregnancy occurs after treatment with NorLevo-1, there is a possibility of an ectopic pregnancy.

Precautions after use
If pregnancy occurs after treatment with NorLevo-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 NorLevo-1. Women suffering from conditions associated with possible malabsorption should be referred for medical consultation as consideration should be given to the taking of more tablets. Patients should be given another tablet if they vomit within two hours of taking NorLevo-1 (see also "Dosage and Administration").

Impaired hepatic function.
NorLevo-1 is not recommended in patients with severe hepatic dysfunction.

Use in pregnancy [Category D]
NorLevo-1 is not to be used during an existing or suspected pregnancy. Research has found no significant effects on fetal 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 eight weeks postconception, progestogens such as levonorgestrel can cause virilisation of the female fetus. This is a dose dependent effect. Prior to eight weeks postconception, they have no virilising effects. There are no studies of the effect of the high levonorgestrel doses used in levonorgestrel 1.5mg tablets on pregnancy and embryo/fetal development.

Use in lactation
Progestogens do not appear to affect the quantity or quality of breast milk. However, levonorgestrel is secreted into breast milk. Therefore, it is suggested to breastfeed immediately before taking the NorLevo-1 tablet and to skip nursing following NorLevo-1 administration for at least 8 hours. The milk should be expressed and discarded during the first 8 hours after dosing.

Effect on fertility
Levornorgestrel 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
NorLevo-1 is not indicated for the use in children.

Carcinogenesis und mutagenesis
No studies of the carcinogenic or mutagenic potential of levonorgestrel 1.5mg 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.

INTERACTIONS WITH OTHER MEDICINES

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 NorLevo-1 in preventing pregnancy. Drugs suspected of having the capacity to reduce the efficacy of levonorgestrel containing medications include barbiturates (including primodone), 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.

ADVERSE EFFECTS

The following table gives the frequency of undesirable effects reported in clinical trials.

Table 1 – Undesirable effects in women after the intake of 2 tablets (each 750micrograms) as a single dose

Effect	Percent of women with effect in two trials*	
	Trial 1	Trial 2
Nausea	24.3	14
Low abdominal pain	15.6	14
Fatigue	-	14
Headache	21.3	10
Dizziness	12.6	10
Breast tenderness	12.9	8
Vomiting	7.8	1
Heavy menses	15.5	-
Diarrhoea	-	4

Bleeding	-	31
Delay of menses[1]	19.9	5

* Trial 1 (n=544): Contraception, 2002, 66, 269-273
* Trial 2 (n=1359): Lancet, 2002, 360:1803-10
[1] Delay defined as more than 7 days.

One ectopic pregnancy was observed in Trial 2 and none in Trial 1.

There have been rare reports of ectopic pregnancies reported during post-marketing surveillance.

Breast tenderness, spotting and irregular bleeding are reported in up to 30 percent of patients and can last until the next menstrual period which can be delayed.

Cutaneous hypersensitivity reactions have been reported following administration of levonorgestrel.
Isolated cases of thromboembolic events have been reported during the post-marketing period, but no causal relationship with levonorgestrel has been formally demonstrated.

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

Skin and subcutaneous tissue disorders
Very rare (<1/10,000): rash, urticarial, pruritus

Reproductive system and breast disorders
Very rare (<1/10,000): pelvic pain, dysmenorrhoea

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

General disorders and administration site conditions
Very rare (<1/10,000): face oedema

DOSAGE AND ADMINISTRATION

Adults

One tablet should be taken. The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. Therefore, the tablet 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.

If the patient vomits within two hours of taking the tablet, she should return to her pharmacist, doctor or clinic where another tablet may be given.

NorLevo-1 can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

Children
NorLevo-1 is not recommended in children. Only limited data are available in young women of childbearing potential aged 14 to 16 years. No data are available about use in young women aged less than 14 years or in children.

OVERDOSAGE
Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Symptoms
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives. Overdose may cause nausea and withdrawal bleeding may occur.

Treatment
In case of overdose treatment should be supportive and symptomatic. There are no specific antidotes.

PRESENTATION AND STORAGE CONDITIONS
NorLevo-1 1.5mg tablet: white, round, biconvex tablet engraved with code NL 1.5 on one face.
NorLevo-1 tablet is available in blister packs of 1 tablet.

Store below 30°C. Store in the original package to protect from light.

Shelf-life: 36 months.

NAME AND ADDRESS OF THE SPONSOR
Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park
NSW 2113
AUSTRALIA

POISON SCHEDULE OF THE MEDICINE
Schedule 3 – Pharmacist Only Medicine

Date of TGA approval: 30/09/2009

Date of most recent amendment: 13/09/2016