PACKAGE INSERT FOR NORLEVO TABLET

Scheduling Status: **S2**

Proprietary Name (and dosage form):

NORLEVO Tablet.

Composition:

Each tablet contains 0,75 mg Levonorgestrel.

Other ingredients: Lactose monohydrate, maize starch, povidone, colloidal anhydrous silica, magnesium stearate.

Pharmacological classification:

A 21.8.2 Progesterones with or without oestrogens.

Pharmacological action:

Pharmacodynamic properties:

The primary mechanism of action of levonorgestrel is blockade and/or delay of ovulation via suppression of the luteinising hormone (LH) peak. Levonorgestrel interferes with the ovulatory process only if it is administered before the onset of the LH surge.

Pharmacokinetic properties:

Oral bioavailability of levonorgestrel is approximately 100 %. In the plasma it is strongly bound to Sex Hormone Binding Globulin (SHBG). Levonorgestrel is eliminated metabolically via the kidney (60 – 80 %) and liver (40 – 50 %). After oral administration of 1,5 mg levonorgestrel the plasma terminal half-life is estimated to be 43 hours.

The maximal plasma concentration (approximately 40 nmol/l) is reached within 3 hours. Levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucoronide conjugates.

Indications:

NORLEVO is indicated for the prevention of pregnancy as soon as possible but within 72 hours of unprotected sexual intercourse or the recognisable failure of mechanical methods.

NORLEVO is intended for emergencies only and is completely unsuitable for regular contraception.

NORLEVO has no emergency contraceptive effect when administered later in the cycle. In clinical trials, the proportion of pregnancies avoided after the use of levonorgestrel varied from 52 % to 85 % of expected pregnancies. Efficacy appears to decline with time after intercourse (95 % within 24 hours, 85 % within 24-48 hours and 58 % if used between 48 and 72 hours).

Efficacy after 72 hours has not been established.

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 Warnings).

Table 1. 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]

Contra-indications:

Pregnancy.

NORLEVO should not be used if there is a possibility that pregnancy already exists, e.g. if unprotected sexual intercourse has already taken place in the same cycle or if the last menstrual period failed to occur.

Hypersensitivity to any of the ingredients.

NORLEVO should not be given to patients with undiagnosed vaginal bleeding, nor to those with a history of, or current high risk of arterial disease.

Severe hepatic impairment.

The repeated use of NORLEVO within a monthly cycle is to be avoided, since it constitutes undesirable hormonal stress and may result in severe cycle disturbances.

Warnings and Special Precautions:

Pregnancy, puerperium and perinatal conditions:

Patients who become pregnant despite emergency contraception should be carefully evaluated for ectopic pregnancy. Therefore, NORLEVO is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).

The effect of NORLEVO on the conceptus in the event of a failure to prevent conception is not known. Therefore, a pregnancy test must be performed if there is any doubt.

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

Cases of thromboembolic events have been reported after NORLEVO intake. 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.

NORLEVO should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

NORLEVO use for emergency contraception does not prevent a pregnancy from occurring in every instance, especially if uncertainty about the timing of the unprotected intercourse. In case of doubt (menstrual period delayed by more than five days or abnormal bleeding at the expected date of menstrual periods, symptoms of pregnancy), it is mandatory to check the absence of pregnancy by performing a pregnancy test.

If the woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, conception may have occurred. Treatment with NORLEVO following the second act of intercourse may therefore be ineffective in preventing pregnancy.

NORLEVO is intended for emergencies only and is completely unsuitable for regular contraception. The use of emergency contraception does not replace the necessary precautions against sexual transmitted diseases.

Endocrine disorders:

The next menstrual period may occur earlier or later than usual. A health professional should be consulted 3 weeks after taking NORLEVO regardless of whether bleeding has occurred or not.

Psychiatric disorders:

NORLEVO should be used with caution in patients with a history of mental depression.

Others

Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of NORLEVO

Concomitant use of NORLEVO and medicines containing ulipristal acetate is not recommended (see Interactions).

NORLEVO contains Lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose-galactose malabsorption should not take NORLEVO.

Effects on ability to drive and use machines:

Women should be advised to exercise caution after taking NORLEVO as fatigue and dizziness may occur.

Interactions:

The metabolism of NORLEVO is enhanced by the concomitant use of liver enzyme inducers: anticonvulsants (phenobarbitone, phenytoin, primidone, carbamazepine); rifabutin, rifampicin, griseofulvin, ritonavir, Hypericum perforatum (St John's wart). The efficacy of NORLEVO may be decreased in cases of concomitant intake of the above-mentioned medicines.

Ulipristal acetate is a progesterone receptor modulator that may interact with the progestational activity of levonorgestrel. Therefore the concomitant use of NORLEVO and medicines containing ulipristal acetate is not recommended (see Warnings and Special Precautions).

Pregnancy and lactation:

Pregnancy:

NORLEVO is not indicated in pregnancy and cannot be used to abort an existing pregnancy.

(See contra – indications)

Lactation:

NORLEVO is secreted into breast milk. Therefore it is recommended to breastfeed immediately before taking NORLEVO and to skip nursing for at least 8 hours following the administration of NORLEVO .

Dosage and directions for use:

NORLEVO can be taken at any time during the menstrual cycle.

Two tablets should be taken in a single administration as soon as possible, preferably within 12 hours, but not later than 72 hours after unprotected sexual intercourse.

The earlier NORLEVO is used, the more effective it is. Even extremely high doses of hormone can no longer prevent pregnancy once a fertilised ovum has become implanted in the uterine mucosa.

All further unprotected sexual intercourse must be avoided until the next menstrual period; till then, only mechanical and/or chemical methods (condom, foam, pessary) of contraception may be used.

If vomiting occurs within three hours of taking the tablets, another two tablets should be taken immediately.

Side-effects:

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

Body System	**Frequency of Adverse Reaction**	
	Very common (>1/10)	**Common (>1/100 to 1/10)**
Nervous System Disorders	Dizziness Headache	
Gastrointestinal Disorders	Nausea Abdominal pain	Diarrhoea Vomiting
Reproductive System and Breast Disorders	Uterine pain Breast tenderness Delay of menses Heavy menses Bleeding	
General Disorders and Administrative Site conditions	Fatigue	

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

Post-marketing side-effects:

The following side-effects have been reported during post-marketing period and the frequencies are unknown.

Blood and the lymphatic system disorders:

Thromboembolic events (see Warnings and Special Precautions).

Endocrine disorders:

Premenstrual syndrome-like symptoms and altered menstrual cycles or irregular menstrual bleeding.

Certain progestogens may have an adverse effect on serum lipids.

Metabolism and nutrition disorders:

Changes in appetite or weight and fluid retention as well as oedema.

Skin and subcutaneous tissue disorders:

Acne, melasma or chloasma, allergic skin reactions, urticaria, hair loss or hirsutism and fever.

Psychiatric disorders:

Mental depression.

Reproductive system and breast disorders:

Breast changes, including discomfort or less frequently pain and changes in libido.

Nervous system disorders:

Drowsiness or insomnia.

Immune system disorders:

Anaphylaxis or anaphylactoid reactions.

Hypersensitivity reactions such as angioedema and cutaneous reactions.

Hepato-biliary disorders:

Alterations in liver function tests. Jaundice has been reported less frequently during prolonged Levonorgestrel administration.

Known symptoms of overdosage and particulars of its treatment:

See side-effects and warnings and special precautions.

Treatment is symptomatic and supportive.

Identification:

White, round, biconvex tablet engraved with “NL” on both faces.

Presentation:

2 Tablets in orange PVC/PE/PVDC plastic foil sealed on aluminium foil blisters strips.

1 blister strip packed in a printed cardboard box.

Storage instructions:

Store in a cool place below 25 ˚C. Protect from moisture and light.

KEEP OUT OF REACH OF CHILDREN.

Registration number:

NORLEVO - 33/21.8.2/0471

Name and business address of the applicant:

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