

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NORLEVO 750 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 microgram levonorgestrel
Excipients: each tablet contains 45.45 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
White, round and biconvex tablet with no marking.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Emergency contraception within 72 hours after an unprotected sexual intercourse or in case of failure of a contraceptive method.

4.2 Posology and method of administration

Oral use.

The treatment necessitates the intake of two tablets in a single administration. The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. Therefore, the two tablets 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.

Norlevo can be taken at any moment during the menstrual cycle.

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

After using an emergency contraception, it is recommended to use a local contraceptive mean (condom, spermicide, cervical cap) until the next menstrual periods resume. The use of Norlevo does not contraindicate the continuation of regular hormonal contraception.

4.3 Contraindications

Hypersensitivity to levonorgestrel or 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 to occur in every instance, especially if uncertainty about the timing of the unprotected intercourse. Limited and inconclusive data suggest that there may be reduced efficacy of Norlevo with increasing body weight or body mass index (BMI) (see section 5.1). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI. In case of doubt (menstrual periods 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.

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

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

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.

After Norlevo intake, menstrual periods are usually of normal abundance and occur at the expected date. They can sometimes occur earlier or later than expected by a few days. It is recommended to have a medical visit to initiate or adapt a method of regular contraception. In case no menstrual period occurs in the next pill-free period following the use of Norlevo after regular hormonal contraception, pregnancy should be ruled out.

Repeated administration within a menstrual cycle is not advisable, because of an undesirable high load of hormones for the patient and the possibility of severe disturbances of the cycle. Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

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

Concomitant use of Norlevo and drugs containing ulipristal acetate is not recommended (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Associations to be taken into consideration:

The metabolism of levonorgestrel is enhanced by the concomitant use of liver enzyme inducers: anticonvulsant (phenobarbital, phenytoin, primidone, carbamazepine); rifabutin; rifampicin; griseofulvin; ritonavir; *Hypericum perforatum* (St. John's wort). The efficacy of Norlevo may be decreased in case of concomitant intake of these active substances.

Ulipristal acetate is a progesterone receptor modulator that may interact with the progestational activity of levonorgestrel. Therefore the concomitant use of levonorgestrel and drugs containing ulipristal acetate is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

This medicinal product cannot interrupt an ongoing pregnancy.

In case of failure of this contraceptive mean with persisting pregnancy, epidemiological studies indicate no malformative effects of progestins on foetus.

Nothing is known on the consequences for the child if doses higher than 1.5 mg levonorgestrel are taken.

Breastfeeding

Levonorgestrel is excreted into breast milk. Therefore, it is suggested to breastfeed immediately before taking Norlevo 750 microgram tablets and to skip nursing at least 8 hours following Norlevo administration.

Fertility

A rapid return to fertility is likely following treatment with Norlevo for emergency contraception; therefore, regular contraception should be continued or initiated as soon as possible following the use of Norlevo to ensure ongoing prevention of pregnancy.

Clinical experience reveals no effect on fertility in humans after use of levonorgestrel. Similarly nonclinical studies show no evidence of adverse effects in animals (see section 5.3)

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 reported. Nevertheless, if women experience fatigue and dizziness after taking Norlevo, they should not drive or use machines.

4.8 Undesirable effects

The following table gives the frequency of undesirable effects after intake of 1.5 mg levonorgestrel reported in clinical trials*.

Body System	Frequency of adverse reactions	
	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $1/10$)
Nervous system disorders	Dizziness Headache	
Gastrointestinal disorders	Nausea Abdominal pain	Diarrhoea ¹ Vomiting
Reproductive system and Breast disorders	Uterine pain Breast tenderness Delay of menses ³ Heavy menses ² Bleeding ¹	Dysmenorrhoea ³
General disorders and administration site conditions	Fatigue ¹	

* Trial 1 (n=544): Contraception, 2002, 66, 269-273

* Trial 2 (n=1359): Lancet, 2002, 360:1803-10

* Trial 3 (n=1117): Lancet 2010; 375:555-62

* Trial 4 (n=840): Obstetrics and Gynecology 2006; 108:1089-1097

¹ Not recorded in Trial 1

² Not recorded in Trial 2

³ Not reported in Trial 1 or 2

⁴ Delay defined as more than 7 days.

These undesirable effects usually disappear within 48 hours after the intake of Norlevo. 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.

Hypersensitivity reactions such as pharyngeal/face oedema and cutaneous reactions have been reported after the intake of Norlevo.

Cases of thromboembolic events have been reported during the postmarketing period (see section 4.4).

4.9 Overdose

Serious 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: EMERGENCY CONTRACEPTIVES – G03AD01

The primary mechanism of action is blockade and/or delay of ovulation via suppression of the luteinizing hormone (LH) peak. Levonorgestrel interferes with the ovulatory process only if it is administered before the onset of the LH surge. Levonorgestrel 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% (Glasier, 2010) to 85% (Von Hertzen, 2002) of expected pregnancies. Efficacy appears to decline with time after intercourse.

There is limited and inconclusive data on the effect of high body weight/high 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 used regimen, levonorgestrel is not expected to induce significant modifications of blood clotting factors, and lipid and carbohydrate metabolism.

5.2 Pharmacokinetic properties

Bioavailability of oral levonorgestrel is approximately 100 percent. In the plasma, it is strongly bound to SHBG. Levonorgestrel is eliminated via kidney (60-80%) and liver (40-50%).

After oral administration of 1.5 mg levonorgestrel, the plasma terminal half-life of the product is estimated to 43 hours.

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

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans, beyond the information included in other sections of the SPC. Animal experiments with levonorgestrel have shown virilization of female fetuses at high doses.

A preclinical study conducted in mice showed no effect on fertility in the progeny of treated dams. Two studies investigating the consequence of exposure to levonorgestrel on the development of pre-embryos before implantation, showed that levonorgestrel had no adverse effects on fertilisation and the *in vitro* growth of mouse pre-embryos.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Povidone,
Colloidal anhydrous silica,
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/PE/PVDC/Aluminium blister of 2 tablets.
Pack sizes with 2 tablets and 10, 20, 50 and 100 tablets as hospital packs only.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire HRA Pharma
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8 MARKETING AUTHORISATION NUMBER

PA 1166/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

January 2015