

Data Sheet

LEVONELLE[®]-1

Levonorgestrel 1.5 mg tablets

Presentation

Each round white tablet contains 1.5 mg of levonorgestrel.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

Uses

Actions

The precise mode of action of LEVONELLE-1 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 preovulatory phase, when the likelihood of fertilisation is the highest. It may also cause endometrial changes that discourage implantation. LEVONELLE-1 is not effective once the process of implantation has begun.

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

Efficacy

It was estimated from the results of an earlier clinical study (Lancet, 1998; 352: 428-433), that 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). Efficacy after 72 hours is not known.

Results from a recent clinical study (Lancet 2002; 360: 1803-1810) showed that a 1500 microgram single dose of LEVONELLE-1, when taken within 72 hours of unprotected sex, prevented 84% of expected pregnancies. This was in comparison with 79% of expected pregnancies when two 750 microgram tablets were taken 12 hours apart).

It is therefore, recommended that the complete course of one tablet of LEVONELLE-1 is taken as soon as possible (and no later than 72 hours) after unprotected intercourse.

Pharmacokinetics

Orally administered levonorgestrel is rapidly and almost completely absorbed.

The results of a pharmacokinetic study carried out with 15 healthy women showed that following ingestion of one tablet of LEVONELLE-1 maximum drug serum levels of levonorgestrel of 18.5 ng/mL were found at 2 hours. After reaching maximum serum levels, the concentration of levonorgestrel decreased with a mean elimination half-life of about 26 hours.

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.

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.

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.

Indications

LEVONELLE-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.

Dosage and Administration

For oral administration: One tablet should be taken as soon as possible, preferably within 12 hours and no later than 72 hours after unprotected intercourse.

Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

If the patient vomits within three hours of taking the tablet, another tablet should be taken immediately. The patient should be advised to contact her doctor, family planning clinic or pharmacist for advice and another tablet.

LEVONELLE-1 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 or cervical cap) until the next menstrual period starts. The use of LEVONELLE-1 does not contraindicate the continuation of regular hormonal contraception.

Children

LEVONELLE-1 is not recommended in children. Very limited data are available in women under 16 years of age.

Contraindications

LEVONELLE-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.

Hypersensitivity to the active substance levonorgestrel or any of the excipients.

Warnings and Precautions

Emergency contraception is an occasional method. LEVONELLE-1 is not as effective as a conventional regular method of contraception and is suitable only as an emergency measure. It should not 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 LEVONELLE-1 following a 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 LEVONELLE-1, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as LEVONELLE-1 prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

LEVONELLE-1 contains 142.5 mg lactose. This should be taken into account in women with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

After taking LEVONELLE-1, menstrual periods are usually normal and occur at the expected date. They can sometimes occur earlier or later than expected by a few days.

It is recommended to make a medical appointment 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 LEVONELLE-1 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. 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.

LEVONELLE-1 is not recommended in patients with severe hepatic dysfunction. Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of LEVONELLE-1. Women suffering from these conditions should be referred to a doctor for emergency contraception.

Conditions which are considered 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. However, since exposure to levonorgestrel with LEVONELLE-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 LEVONELLE-1.

Effect on ability to drive and use machines

No effect is known.

Preclinical safety data

Levonorgestrel is a well-established progestogen with anti-estrogenic activity. The safety profile following systemic administration is well documented and reveals no special concerns for use beyond that already listed in this text.

In acute toxicity studies performed in mice and rats levonorgestrel induced a decrease of body weight and dermatitis-like (non-irritative or non-allergic) changes on the skin. In repeat dose toxicity studies performed in mice, rats and rabbits, there were no overt signs of toxicity and no target organs or functions were identified other than the reproductive system. Animal experiments with levonorgestrel have shown virilisation of female foetuses at high doses.

Pregnancy and lactation

Use in Pregnancy

LEVONELLE-1 should not be given to pregnant women and it will not interrupt the pregnancy. In the case of failure of emergency contraception, epidemiological studies indicate no adverse effects of progestogens on the foetus. It is generally considered that

known teratogens will not produce malformations before organogenesis starts, which is later than 72 hours after fertilisation.

Use in Lactation

Levonorgestrel is secreted into breast milk. The potential exposure of an infant to levonorgestrel can be reduced if the breastfeeding woman takes the tablet immediately after feeding and avoids nursing following LEVONELLE-1 administration.

Adverse Effects

The most commonly reported undesirable effect was nausea. The following undesirable effects were observed in two different studies^{1,2}.

Body System	Frequency of adverse reactions	
	Very common (>1/10)	Common (>1/100)
Endocrine system	Bleeding not related to menses*	Delay of menses more than 7 days ** Irregular bleeding and spotting
Nervous system		Dizziness Headache
Gastrointestinal system	Nausea Lower abdominal pain	Diarrhoea Vomiting
Reproductive system and breast		Breast tenderness
General	Fatigue	

¹ Task Force on post-ovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet*, 1998; 352:428-433 (*n*=977; data on 0.75 mg levonorgestrel tablet taken as two doses with a 12-hour interval)

² Herten et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet*. 2002; 360:1803-1810 (*n*=1,359; data on LEVONELLE taken as a single dose of 1.5 mg)

* *n*=1,011 out of 1,359 ** *n*=1,334 out of 1,359

Bleeding patterns may be temporarily disturbed, but most women will have their next menstrual period within 7 days of the expected time.

If the next menstrual period is more than 5 days overdue, pregnancy should be excluded.

Interactions

The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers. Medicines suspected of having the capacity to reduce the efficacy of levonorgestrel-containing medication includes: barbiturates, primidone, phenytoin, carbamazepine, herbal medicines containing *Hypericum perforatum* (St Johns' Wort), rifampicin, ritonavir, rifabutin and griseofulvin. Women taking such medicines should be referred to their doctor for advice.

Medicines containing levonorgestrel may increase the risk of cyclosporin toxicity due to possible inhibition of cyclosporin metabolism. Women taking cyclosporin-containing medication should be referred to their doctor for advice.

Overdosage

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.

Pharmaceutical Precautions

Shelf-life: 3 years

Special precautions for storage: Store at or below 25°C in the original container.

Medicine Classification

Pharmacist Only Medicine

Package Quantities

LEVONELLE-1 contains one blister aluminium/PVC blister sheet containing one tablet.

Further Information

List of excipients

Potato starch, maize starch, silicon dioxide (anhydrous), magnesium stearate, purified talc, lactose monohydrate.

Instructions for use/handling

Keep out of reach of children.

Name and Address

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