Mylan

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of The Medicinal Product

Revoke-72 (Levonorgestrel Tablets 750 mcg)

2. Qualitative and Quantitative Composition

Each Uncoated tablet contains:

Levonorgestrel 750 mcg

Excipients Q.S.

Excipient with known effect:

Each uncoated tablet contains

Lactose Monohydrate 77.00 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Round, white to off-white, uncoated flat tablets debossed '207' on one side and other side plain.

4. Clinical Particulars

4.1 Therapeutic indications

Levonorgestrel Tablets 0.75 mg are progestin only emergency contraceptive indicated for prevention of pregnancy following unprotected intercourse or a known or suspected contraceptive failure

4.2 Posology and method of administration

For oral administration.

The treatment course comprises two tablets.

The first tablet should be taken as soon as possible within 72 hours of after unprotected intercourse or a known or suspected contraceptive failure.

The second tablet should be taken 12 hours (and no later than 16 hours) after the first tablet (for efficacy data, see section 5.1).

The highest efficacy is achieved if the first tablet is taken as soon as possible (and no later than 72 hours) after unprotected intercourse.

If vomiting occurs within two hours of taking the tablet, consideration should be given to repeating the dose.

Levonorgestrel Tablets 0.75 mg can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

Levonorgestrel Tablets 0.75 mg are not recommended for use by young women aged under 16 years without medical supervision.

Levonorgestrel Tablets 0.75 mg are not indicated for routine use as a contraceptive.

Pediatric population

Levonorgestrel Tablets 0.75 mg is not recommended in children.

Data for women under 16 is very limited. Use of Levonorgestrel Tablets 0.75 mg emergency contraception before menarche is not indicated.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known or suspected pregnancy.

4.4 Special warnings and precautions for use

- Emergency contraception is not effective in terminating an existing pregnancy. Levonorgestrel Tablets 0.75 mg are not effective in terminating an existing pregnancy.
- Emergency contraception is an occasional method. It should **not** replace a regular contraceptive method.
- Emergency contraception does not prevent a pregnancy in every instance.
- Efficacy appears to decline with time (see section 5.1).
- 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 Tablets 0.75 mg 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 ruled out.

- If pregnancy occurs after treatment with Levonorgestrel Tablets 0.75 mg, the possibility of an ectopic pregnancy should be considered, especially in women in whom severe abdominal pain or fainting occurs, or if there is a history of ectopic pregnancy, Fallopian tube surgery or pelvic inflammatory disease. Ectopic pregnancy may continue despite uterine bleeding. Therefore, Levonorgestrel Tablets 0.75 mg is not recommended for women at risk of ectopic pregnancy (history of salpingitis or of ectopic pregnancy).
- After taking Levonorgestrel Tablets 0.75 mg, 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 see a health care provider 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 Tablets 0.75 mg after regular hormonal contraception, pregnancy should be ruled out.

  Repeated administration within a menstrual cycle is not advisable because of the possibility of disturbing the cycle.
- Levonorgestrel Tablets 0.75 mg is not recommended in patients with severe hepatic dysfunction.
- Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of Levonorgestrel Tablets 0.75 mg.
- Any regular contraceptive method can be started immediately after the use of Levonorgestrel Tablets 0.75 mg emergency contraceptive pills.

If the woman starts a hormonal contraceptive:

- she needs to abstain from sexual intercourse or use barrier contraception for 7 days.
- she should be advised to have a pregnancy test if she does not have a withdrawal bleed within 3 weeks.

- A rapid return of fertility is likely following treatment with Levonorgestrel Tablets 0.75 mg for emergency contracept on; therefore, routine contraception should be continued or initiated as soon as possible following use of levonorgestrel tablets, 0 75 mg to ensure ongoing prevention of pregnancy.
- Levonorgestrel Tablets 0.75 mg 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.
- The tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

Use in Specific Populations

Pediatric population

Levonorgestrel Tablets 0.75 mg is not recommended in children.

Data for women under 16 is very limited. Use of Levonorgestrel Tablets 0.75 mg emergency contraception before menarche is not indicated.

Geriatric Use

This product is not intended for use in postmenopausal women.

Race

No formal studies have evaluated the effect of race However, clinical trials demonstrated a higher pregnancy rate in Chinese women with both levonorgestrel tablets, 0 75 mg and the Yuzpe regimen (another form of emergency contraception) The reason for this apparent increase in the pregnancy rate with emergency contraceptives in Chinese women is unknown.

Hepatic Impairment

Levonorgestrel Tablets 0.75 mg is not recommended in patients with severe hepatic dysfunction.

***Renal Impairmen*t**

No formal studies were conducted to evaluate the effect of renal disease on the disposition of levonorgestrel tablets 0.75 mg.

Drug Drug Interactions

No formal drug-drug interaction studies were conducted with levonorgestrel tablets 0.75 mg.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of levonorgestrel is enhanced by concomitant use of liver enzyme inducers.

Drugs suspected of having the capacity to reduce the efficacy of levonorgestrel include barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing St. John's wort

(*Hypericum perforatum*), rifampicin, ritonavir, rifabutin, bosentan, felbamate, topiramate, oxcarbazepine and griseofulvin. Women taking such drugs should be referred to the doctor for advice.
Significant changes (increase or decrease) in the plasma levels of the progestogen have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. The potential interaction may require close monitoring, alteration of drug dosage or timing of administration.
Medicines containing levonorgestrel may increase the risk of ciclosporin toxicity due to possible inhibition of ciclosporin metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy

Levonorgestrel Tablets 0.75 mg should not be given to pregnant women. It will not interrupt the pregnancy.
In case of failure of this emergency contraception and developing pregnancy, epidemiological studies indicate no adverse effects of progestogens on the fetus.
There are no clinical data on the potential consequences if doses greater than 1.5 mg levonorgestrel are taken (see section 5.3.).
The few studies of infant growth and development that have been conducted with progestin only pills have not demonstrated significant adverse effects.

Lactation

Levonorgestrel is secreted into breast milk. Isolated post marketing cases of decreased milk production have been reported Small amounts of progestins pass into the breast milk of nursing mothers taking progestin only pills for long term contraception, resulting in detectable steroid levels in infant plasma.
In general, no adverse effects of progestin only pills have been found on breastfeeding performance or on the health, growth, or development of the infant
Potential exposure of an infant to levonorgestrel can be reduced if the breast-feeding woman takes the tablets immediately after feeding and avoids nursing following each Levonorgestrel Tablets 0.75 mg administration.

Fertility

Clinical experience reveals no effect on fertility after use of levonorgestrel. Non-clinical 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 effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

A double blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of levonorgestrel tablet 0.75 mg (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to Yuzpe regimen (two tablets each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later).

The most common adverse events (>10%) in the clinical trial for women receiving levonorgestrel 0.75 mg included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), dizziness (11%), breast tenderness (11%) and menstrual changes (26%).

Table 1 below shows those adverse events that occurred in ≥ 5% of levonorgestrel 0.75 mg users.

Table 1: Adverse events in ≥ 5% of women, by frequency	
Adverse events	**Levonorgestrel 0.75 mg (n = 977)**
Nausea	23.1%
Abdominal pain	17.6%
Fatigue	16.9%
Headache	16.8%
Heavier menstrual bleeding	13.8%
Lighter menstrual bleeding	12.5%
Dizziness	11.2%
Breast tenderness	10.7%
Vomiting	5.6%
Diarrhea	5.0%

Post-marketing Experience

The following adverse reactions have been identified during post approval use of Levonorgestrel tablets 0.75 mg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders

Abdominal Pain, Nausea, Vomiting

General Disorders and Administration Site Conditions

Fatigue

Nervous System Disorders

Dizziness, Headache

Reproductive System and Breast Disorders

Dysmenorrhea, Irregular Menstruation, Oligomenorrhea, Pelvic Pain

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 ruled out.

4.9 Overdose

Serious undesirable effects have not been reported following acute ingestion of large doses of oral contraceptives. Overdose may cause nausea and vomiting; withdrawal bleeding may occur. There are no specific antidotes and treatment should be symptomatic.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens, ATC code: G03AD01

The precise mode of action of Levonorgestrel tablets 0.75 mg is not known.

At the recommended regimen, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if the 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. It is not effective once implantation has begun.

Efficacy: It has been estimated that levonorgestrel emergency contraceptive pills prevent 85% of expected pregnancies. Efficacy appears to decline with time after intercourse (95% within 24 hours, 85% if used between 24 and 48 hours, 58% if used between 48 and 72 hours).

It is therefore, recommended that the course of PILL 72 tablets is started as soon as possible (and no later than 72 hours) after unprotected intercourse.

At the recommended regimen, levonorgestrel is not expected to significantly modify blood clotting factors, or lipid and carbohydrate metabolism.

Safety: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A double-blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of Levonorgestrel (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later).

The most common adverse events (>10%) in the clinical trial for women receiving levonorgestrel 0.75 mg included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), dizziness (11%), breast tenderness (11%) and menstrual changes (26%).

Clinical Studies

A double blind, randomized, multinational controlled clinical trial in 1,955 evaluable women (mean age 27) compared the efficacy and safety of levonorgestrel tablets, 0.75 mg (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets each containing 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two additional tablets taken 12 hours later). After a single act of intercourse occurring anytime during the menstrual cycle, the expected pregnancy rate of 8% (with no contraceptive use) was reduced to approximately 1% with levonorgestrel tablets, 0.75 mg.

Emergency contraceptives are not as effective as routine hormonal contraception since their failure rate, while low based on a single use, would accumulate over time with repeated use.

At the time of expected menses, approximately 74% of women using levonorgestrel tablets, 0.75 mg had vaginal bleeding similar to the normal menses, 14% bled more than usual, and 12% bled less than usual The majority of women (87%) had their next menstrual period at the expected time or within + 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses.

5.2 Pharmacokinetic properties

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel in humans has been conducted However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism After a single dose of levonorgestrel (0 75 mg) administered to 16 women under fasting conditions, the mean maximum serum concentration of levonorgestrel was 141 ng/mL at an average of 16 hours.

Table 2: Pharmacokinetic Parameter Values Following Single Dose Administration of Levonorgestrel Tablet, 0.75 mg to Healthy Female Volunteers under Fasting Conditions

	Mean (± SD)					
	C_{max} (ng/mL)	**T max (hr)**	**CL (L/h)**	**V_d (L)**	**$t_{1/2}$ (h)**	**AUC_{inf} (ng hr/mL)**
Levonorgestrel	14 1 (7 7)	1 6 (0 7)	77 (2 7)	260 0	24 4 (5 3)	123 1 (50 1)

C_{max} = maximum concentration

T_{max} = time to maximum concentration

CL = clearance

Vd = volume of distribution

$t_{1/2}$ = elimination half life

AUC_{inf} = area under the drug concentration curve from time 0 to infinity

Effect of Food: The effect of food on the rate and the extent of levonorgestrel absorption following single oral administration of levonorgestrel tablets, 0.75 mg have not been evaluated.

Table 3: Pharmacokinetic parameters of levonorgestrel tablets, 0.75 mg (levonorgestrel test formulation) and the reference product are shown in the Table 3 below:

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD	log - transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVA log)
T_{max} (hour)	1.46 ± 0.67	1.76 ± 0.96	–	–
C_{max} (ng/ml)	13.17 ± 5.69 (12.03)	11.53 ± 5.30	114.0	104.1 – 124.9
AUC_{0-t}	149 ± 104 (128)	139 ± 86 (122)	105.0	96.1 – 114.6
AUC_{0-inf}	160 ± 107 (139)	152 ± 87 (135)	103.1	95.1 – 111.8

* geometric mean

Distribution

The apparent volume of distribution of levonorgestrel is reported to be approximately 1 8 L/kg. It is about 97.5 to 99% protein bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. 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.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17β OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α, 5β tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α, 5α tetrahydrolevonorgestrel and 16β hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Levonorgestrel is not excreted as metabolites. Levonorgestrel metabolites are excreted in about equal proportions in 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.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

There is no evidence of increased risk of cancer with short term use of progestins.

There was no increase in tumorgenicity following administration of levonorgestrel to rats for 2 years at approximately 5 mcg/day, to dogs for 7 years at up to 0 125 mg/kg/day, or to rhesus monkeys for 10 years at up to 250 mcg/kg/day. In another 7 year dog study, administration of levonorgestrel at 0.5 mg /kg/day did increase the number of mammary adenomas in treated dogs compared to controls. There were no malignancies.

Genotoxicity

Levonorgestrel was not found to be mutagenic or genotoxic in the Ames Assay, in vitro mammalian culture assays utilizing mouse lymphoma cells and Chinese hamster ovary cells, and in an in vivo micronucleus assay in mice.

Fertility: There are no irreversible effects on fertility following cessation of exposures to levonorgestrel or progestins in general.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Polyvinyl Pyrrolidone K-25 (Kolidon-25)

Lactose Monohydrate

Corn Starch

Colloidal silicon dioxide

Magnesium Stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C.

Keep out of reach of children.

6.5 Nature and contents of container

Blister pack of 2 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7.0 MARKETING AUTHORISATION HOLDER

Mylan Laboratories Limited, India

8.0 MARKETING AUTHORISATION NUMBER(S)

To be decided

9.0 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be decided

Reference:

- Levonorgestrel tablets 0.75 mg, Prescribing Information (Lupin Pharmaceuticals Inc.; December 2011); Accessed from https://www.accessdata.fda.gov/drugsatfda_docs/anda/2013/091328Orig1s000.pdf; Accessed on 26th February, 2019.
- Pill 72 (Levonorgestrel tablets 0.75 mg); Summary of Product Characteristics (Cipla Ltd.; June 2014); Accessed from https://extranet.who.int/prequal/sites/default/files/RH040part4v1.pdf. Accessed on 27th February, 2019.