# SUMMARY OF PRODUCT CHARACTERISTICS

**Patient safety information Card**
The marketing of Postinor is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

## 1 NAME OF THE MEDICINAL PRODUCT

Postinor

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablet contains 1500 microgram of levonorgestrel.
Each tablet contains 142.5 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

The tablet is round and white.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Emergency contraception

### 4.2 Posology and method of 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 (see section 5.1).

If vomiting occurs within three hours of taking the tablet another tablet should be taken immediately. The patient should seek advice from her doctor, nurse, family planning clinic or pharmacist.
Postinor 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, spermicide, cervical cap) until the next menstrual period starts. The use of Postinor does not contraindicate the continuation of regular hormonal contraception.

Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal EC, i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. 2 tablets taken together) for those women unable or unwilling to use Cu-IUD (see section 4.5).

*Paediatric population*:
There is no relevant use of Postinor for children of prepubertal age in the indication emergency contraception.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 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 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 Postinor 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 excluded. *If pregnancy occurs after treatment* with Postinor, *the possibility of an ectopic pregnancy should be considered*. The absolute risk of ectopic pregnancy is likely to be low, as Postinor prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

Therefore, Postinor is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).

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

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.

After Postinor intake, 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 make a medical appointment to initiate or adopt a method of regular contraception. If no withdrawal bleed occurs in the next pill-free period following the use of Postinor 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.

Limited and inconclusive data suggest that there may be reduced efficacy of Postinor 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.

Postinor 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.

## 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, mainly CYP3A4 enzyme inducers. Concomitant administration of efavirenz has been found to reduce plasma levels of levonorgestrel (AUC) by around 50%.

Drugs suspected of having similar capacity to reduce plasma levels of levonorgestrel include barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing Hypericum perforatum (St. John's Wort), rifampicin, ritonavir, rifabutin, and griseofulvin.

For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, the use of non-hormonal emergency contraception (i.e. a Cu-IUD) should be considered. Taking a double dose of levonorgestrel (i.e. 3000 mcg within 72 hours after the unprotected intercourse) is an option for women who are unable or unwilling to use a Cu-IUD, although this specific combination (a double dose of levonorgestrel during concomitant use of an enzyme inducer) has not been studied
Medicines containing levonorgestrel may increase the risk of cyclosporin toxicity due to possible inhibition of cyclosporin metabolism.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Postinor should not be given to pregnant women. It will not interrupt a pregnancy. In the case of continued pregnancy, limited epidemiological data indicate no adverse effects on the fetus but there are no clinical data on the potential consequences if doses greater than 1.5 mg of levonorgestrel are taken (see section 5.3.).

*Breast-feeding*
Levonorgestrel is secreted into breast milk. Potential exposure of an infant to levonorgestrel can be reduced if the breast-feeding woman takes the tablet immediately after feeding and avoids nursing at least 8 hours following Postinor administration.

*Fertility*
Levonorgestrel 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 fertility data in the long term.

## 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 performed.

## 4.8 Undesirable effects

The most commonly reported undesirable effect was nausea

| System Organ Class MedDRA 16.0 | Frequency of adverse reactions | |
|---|---|---|
| | **Very common** (≥10%) | **Common** (≥ 1% to <10%) |
| **Nervous system disorders** | Headache | Dizziness |
| **Gastrointestinal disorders** | Nausea<br>Abdominal pain lower | Diarrhoea<br>Vomiting |
| **Reproductive system and breast disorders** | Bleeding not related to menses* | Delay of menses more than 7 days **<br>Menstruation irregular<br>Breast tenderness |
| **General disorders and administration site conditions** | Fatigue | |

*Bleeding patterns may be temporarily disturbed, but most women will have their next menstrual period within 5-7 days of the expected time.
**If the next menstrual period is more than 5 days overdue, pregnancy should be excluded.

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

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

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

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

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

**Reporting of suspected adverse reactions**
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
**https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il**

Side effects can also be reported to the following email: safety@trima.co.il

## 4.9 Overdose

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.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives, ATC code: ***G03AD01***

The precise mode of action of levonorgestrel as an emergency contraceptive 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. Levonorgestrel is not effective once the process of implantation has begun.

Efficacy:
It was estimated from the results of an earlier clinical study (Lancet 1998: 352: 428-33), that 750 micrograms of 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).

Results from a recent clinical study (Lancet 2002: 360: 1803-1810) showed that two 750 microgram tablets of levonorgestrel taken at the same time (and within 72 hours of unprotected sex) prevented 84% of expected pregnancies. There was no difference between pregnancy rates in case of women who were treated on the third or the fourth day after the unprotected act of intercourse ($p>0.2$).
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 recommended regimen, levonorgestrel is not expected to induce significant modification of blood clotting factors, and lipid and carbohydrate metabolism.

Paediatric population:
A prospective observational study showed that out of 305 treatments with levonorgestrel emergency contraceptive tablets, seven women became pregnant resulting in an overall failure rate of 2.3%. The failure rate in women under 18 years (2.6% or 4/153) was comparable to the failure rate in women 18 years and over (2.0% or 3/152).

## 5.2 Pharmacokinetic properties

Orally administered levonorgestrel is rapidly and almost completely absorbed.
The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of single dose of 1.5 mg levonorgestrel maximum drug serum levels of 18.5ng/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.

## 5.3 Preclinical safety data

Animal experiments with levonorgestrel have shown virilisation of female fetuses at high doses.

Preclinical data from conventional studies on chronic toxicity, mutagenicity and carcinogenicity reveal no special hazard for humans, beyond the information included in other section of the SPC.

## PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**

Potato starch,
Silica colloidal anhydrous
Magnesium stearate,
Talc,
Maize starch,
Lactose monohydrate.

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

4 years.

**6.4 Special precautions for storage**

Store below 25°C
Store in original packaging in order to protect from light

**6.5 Nature and contents of container**

PVC/Aluminium-blister containing one tablet.

**6.6 Special precautions for disposal**

No special requirements

**7 Manufacturer:**

Gedeon Richter Plc.
Gyömrői út 19-21, 1103 Budapest, Hungary.

**License Holder:**

Trima Israel Pharmaceutical Products Maabarot Ltd, Maabarot 4023000, Israel

## 8 MARKETING AUTHORISATION NUMBER

134.46.31286.00

**The Ministry of Health approved the format of this insert and its content was checked and approved by it in August 2017.**