# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Levonorgestrel Teva 1.5 mg Tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg levonorgestrel.

Excipient with known effect: each tablet contains 154.00 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet

Round, white to off-white, uncoated flat tablets of 8 mm debossed with ‘145’ on one side and the other side plain.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Emergency contraception within 72 hours after 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 **one tablet**. The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. Therefore, the tablet 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.

Levonorgestrel Teva can be taken at any moment during the menstrual cycle unless menstrual bleeding is overdue.

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

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

*Paediatric population:*
There is no relevant use of Levonorgestrel Teva 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 Levonorgestrel Teva following the second act of intercourse may therefore be ineffective in preventing pregnancy. 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.

Limited and inconclusive data suggest that there may be reduced efficacy of <invented name> 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.

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

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

Cases of thromboembolic events have been reported after Levonorgestrel Teva 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 Levonorgestrel Teva 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 Levonorgestrel Teva 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. Levonorgestrel Teva 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.

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

Concomitant use of Levonorgestrel Teva 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, 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.

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.

Medicines containing levonorgestrel may increase the risk of cyclosporin toxicity due to possible inhibition of cyclosporin metabolism.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
Levonorgestrel Teva should not be given to pregnant women. This medicinal product cannot interrupt an ongoing pregnancy.

In case of failure of this contraceptive meaning continued 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.

*Breast-feeding*
Levonorgestrel is excreted into breast milk. Therefore, it is suggested to breastfeed immediately before taking the Levonorgestrel Teva tablet and to skip nursing at least 8 hours following Levonorgestrel Teva administration.

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

Clinical experience reveal 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 performed**.**
Nevertheless, if women experience fatigue and dizziness after taking Levonorgestrel Teva, 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 (≧ 1/10)** | **Common (≧ 1/100 to 1/10)** |
| Nervous system disorders | Dizziness<br>Headache | |
| Gastrointestinal disorders | Nausea<br>Abdominal pain | Diarrhoea[1]<br>Vomiting |
| Reproductive system and Breast disorders | Uterine pain<br>Breast tenderness<br>Delay of menses[4] | Dysmenorrhoea[3] |

| | | |
|---|---|---|
| | Heavy menses[2]<br>Bleeding[1] | |
| 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 Levonorgestrel Teva. 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 Levonorgestrel Teva.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via IMB Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.imb.ie; e-mail: imbpharmacovigilance@imb.ie

## 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/m2) | 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/m2) | 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.

*Adolescent populations:*
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

Absorption
Orally administered levonorgestrel is rapidly and almost completely absorbed.
Bioavailability of oral levonorgestrel is approximately 100 percent.

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.

Distribution
In the plasma, it is strongly bound to 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.

About 0.1% of the maternal dose can be transferred via milk to the nursed infant.

Biotransformation
Levonorgestrel is not excreted in unchanged form but as metabolites. No pharmacologically active metabolites are known.

The biotransformation follows the known pathways of steroid metabolism, the levonorgestrel is hydroxylated in the liver.

Elimination
Levonorgestrel metabolites, as glucuronide conjugates, are excreted in about equal proportions with urine and faeces. Levonorgestrel is eliminated via kidney (60-80%) and liver (40-50%).

## 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
Silica, colloidal anhydrous
Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

PVC/PVdC/Aluminum-blister containing one tablet. The blister is packed in a carton

### 6.6 Special precautions for disposal and other handling

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

## 7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swensweg 5,
2031 GA Haarlem,
Netherlands

## 8 MARKETING AUTHORISATION NUMBER

PA0749/184/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th April 2014

## 10 DATE OF REVISION OF THE TEXT

March 2017