1. NAME OF THE MEDICINAL PRODUCT

Escapelle 1.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg of levonorgestrel.
Excipient with known effect: Each tablet contains 142.5 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
Almost white, flat tablet, with an oblique edge 8 mm in diameter and an indent "G00" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

4.2 Posology and method of administration

For oral administration.

Posology

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, pharmacist, nurse, or family planning clinic.

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).

Escapelle 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 Escapelle does not contraindicate the continuation of regular hormonal contraception.

Paediatric population
There is no relevant use of Escapelle 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 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 levonorgestrel, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as levonorgestrel prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

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

Levonorgestrel is not recommended in patients with severe hepatic dysfunction.

Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of levonorgestrel.

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

After Escapelle 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 levonorgestrel 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 Escapelle with increasing body weight or body mass index (BMI) (see sections 5.1 and 5.2). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.

Levonorgestrel 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 the 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. 3 mg 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
Levonorgestrel 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 1.5mg 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 breast-feeding at least 8 hours following levonorgestrel administration.

Fertility
Levonorgestrel increases the possibility of cycle disturbances, which can sometimes lead to earlier or later ovulation date resulting in modified fertility date. Although there are no fertility data in the long term, after treatment with levonorgestrel a rapid return to fertility is

expected.

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 19.0	Frequency of adverse reactions	
	Very common (≥1/10)	**Common** (≥1/100 to <1/10)
Nervous system disorders	Headache	Dizziness
Gastrointestinal disorders	Nausea Abdominal pain lower	Diarrhoea Vomiting
Reproductive system and breast disorders	Bleeding not related to menses*	Delay of menses more than 7 days** Menstruation irregular 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 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 the national reporting system ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

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

Mechanism of action
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.

Clinical efficacy and safety
The pregnancy rate was 1.1% (11/976) in an earlier clinical study (Lancet 1998; 352: 428-433) where 750 micrograms of levonorgestrel was taken as two 750 microgram doses with a 12-hour interval. Pregnancy rates appeared to increase with time of start of treatment after intercourse (0.4% [2/450] within 24 hours, 1.2% [4/338] 25-48 hours, 2.7% [5/187] if started between 49 and 72 hours).

Results from a randomised, double-blind clinical study conducted in 2001 (Lancet 2002; 360: 1803-1810) showed 1.34% (16/1 198) pregnancy rate with 1.5mg single dose of levonorgestrel / two 750 microgram tablets of levonorgestrel taken at the same time (taken within 72 hours of unprotected sex) (compared with 1.69% [20/11 832] when two 750 microgram tablets were taken 12 hours apart). 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 ($p>0.2$).

Meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010) showed that the pregnancy rate of levonorgestrel is 1.01% (59/5 863) which means it prevents pregnancy in 99% of situations (compared to an expected pregnancy rate of about 8% in the absence of emergency contraception).

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. (For pharmacokinetic studies in obese women see section 5.2).

Table 1: Meta-analysis on three WHO studies (Von Hertzen et al., 1998 and 2002; Dada et al., 2010)

BMI (kg/m^2)	**Underweight**	**Normal**	**Overweight**	**Obese**

	0-18.5	**18.5-25**	**25-30**	**≥ 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

Absorption
Orally administered levonorgestrel is rapidly and almost completely absorbed.

Distribution
The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of single dose of 1.5mg levonorgestrel 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.

Biotransformation
Levonorgestrel is not excreted in unchanged form but as metabolites.

Elimination
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.

Pharmacokinetics in obese women
A pharmacokinetic study showed that levonorgestrel concentrations are decreased in obese women (BMI > 30 kg/m2) (approximately 50% decrease in Cmax and AUC_{0-24}), compared to women with normal BMI (< 25 kg/m^2) (Praditpan et al., 2017). Another study also reported a decrease of levonorgestrel C_{max} by approximately 50% between obese and normal BMI women, while doubling the dose (3 mg) in obese women appeared to provide plasma concentration levels similar to those observed in normal women who received 1.5 mg of levonorgestrel (Edelman et al., 2016). The clinical relevance of these data is unclear.

5.3 Preclinical safety data

Animal experiments with levonorgestrel have shown virilisation of female fetuses at high doses.
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential beyond the information included in other section of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potato starch,
Corn starch,
Colloidal anhydrous silica,
Magnesium stearate,
Talc,
Lactose monohydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store in the original packaging in order to protect from light.

6.5 Nature and contents of container

One tablet is packed in a PVC/aluminium foil blister. The carton contains one blister with one tablet.

6.6 Special precautions for disposal

Unused medicinal products or used materials should be disposed of in accordance with local requirements.

7. PARALLEL IMPORT LICENCE HOLDER

Neofarma Pharmaceuticals Ltd
42-46, Mill Street, Qormi QRM3105,
Malta

8. PARALLEL IMPORT NUMBER

PI908/34101A

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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