SUMMARY OF PRODUCT CHARACTERISTIC (SMPC)

1. Name of the Medicinal Product

ACE LEVO 1.5 (Levonorgestrel Tablets BP 1.5 mg)

2. Qualitative and Quantitative Composition

Each Film coated tablet contains:

Levonorgestrel BP ……...……. 1.5 mg
Excipients…… …….q.s.
Colour: Titanium dioxide BP

3. Pharmaceutical Form

White to off white, round, biconvex, uncoated tablets, plain on both sides.

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.
If vomiting occurs within three hours of taking the tablet, another tablet should be taken immediately.
Levonorgestrel Tablets 1.5 mg 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 barrier method (e.g. condom, diaphragm or cap) until the next menstrual period starts. The use of Levonorgestrel Tablets 1.5 mg does not contraindicate the continuation of regular hormonal contraception.

***Paediatric population*:**

Levonorgestrel Tablets 1.5 mg is not recommended in children.
Very limited data are available in women under 16 years of age.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.

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 Tablets 1.5 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 excluded.

If pregnancy occurs after treatment with Levonorgestrel Tablets 1.5 mg, the possibility of an ectopic pregnancy should be considered.

The absolute risk of ectopic pregnancy is likely to be low, as Levonorgestrel Tablets 1.5 mg prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding. Therefore, Levonorgestrel Tablets 1.5 mg is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).
Levonorgestrel Tablets 1.5 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 1.5 mg.
Levonorgestrel Tablets 1.5 mg 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 Levonorgestrel Tablets 1.5 mg 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 Tablets 1.5 mg 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 Levonorgestrel Tablets 1.5 mg with increasing body weight or body mass index (BMI). 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 Tablets 1.5 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.

4.5 interactions 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 containing medication include Barbiturates (including Primidone), Phenytoin,

Carbamazepine, Herbal medicines containing Hypericum perforatum (St. John's Wort), Rifampicin, Ritonavir, Rifabutin, Griseofulvin.
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 Tablets 1.5 mg 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.

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 following Levonorgestrel Tablets 1.5 mg 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 and therefore, regular contraception should be continued or initiated as soon as possible after Levonorgestrel EC use.

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.
All adverse drug reactions are listed by system, organ class and frequency.

System Organ Class Med DRA 16.1	**Frequency of adverse reactions**	
	Very common (≥ 10%)	**Common (≥1/100 to <1/10)**
Nervous system disorders	Headache	Dizziness
Gastrointestinal disorders	Nausea Lower abdominal pain	Diarrhoea Vomiting
Reproductive system and breast disorders	Bleeding not related to menses*	Delay of menses more than 7 days ** Irregular menstruation 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 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

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

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 Tablets 1.5 mg is not effective once the process of implantation has begun.

Clinical efficacy and safety

Results from a randomised, double-blind clinical study conducted in 2001 (Lancet 2002; 360: 1803-1810) showed that a 1500 microgram single dose of Levonorgestrel Tablets 1.5 mg (taken within 72 hours of unprotected sex) prevented 84% of expected pregnancies (compared with 79% when the two 750 microgram tablets were taken 12 hours apart).

Another study conducted in 1997 (Lancet 1998; 352: 428-33) showed that two 750 microgram doses taken 12 hours apart prevents 85% of expected pregnancies.

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)

	Levonorgestrel Dose	**Treatment delay in days**	**Prevented fraction (95%CI)***	**Pregnancy rate**
Von Hertzen, 1998	**0.75 mg (two doses taken 12 h apart)**	Day 1 (≤ 24 h)	95%	0.4 %
		Day 2 (25-48 h)	85%	1.2%
		Day 3 (49-72 h)	58%	2.7%
		All woman	85%	1.1%
Von Hertzen, 2002	**1.5 mg (single dose)**	1-3 days	84%	1.34%
	0.75 mg (two doses taken together)	1-3 days	79%	1.69%
Dada, 2010	**1.5 mg (single dose)**	1-3 days	96.7 %	0.40%
	0.75 mg (two doses taken together)	1-3 days	97.4%	0.32%
Meta-analysis of all three WHO studies		-	-	1.01%

Table 2: 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 3: 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.

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 one tablet of Levonorgestrel Tablets 1.5 mg maximum drug serum levels of Levonorgestrel 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.

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.

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, carcinogenicity potential beyond the information included in other section of the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose

Maize Starch

Povidone (PVPK-30)

Colloidal Anhydrous Silica
Magnesium Stearate
Macrogols 400 (Polyethylene Glycol 400)
Hypromellose (HPMC E-15)
Titanium Dioxide
Purified Talc
Isopropyl Alcohol
Methylene Chloride

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30ºC. Protect from light and moisture.

6.5 Nature and contents of container

Alu-PVC Blister pack of 1 tablet packed in a carton along with package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorisation Holder

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8. Marketing Authorisation Number(s)

07948/08428/REN/2022

9. Date of first Authorisation/Renewal of the Authorisation

12 October 2022

10. Date of Revision of the Text

Not Applicable