1.1 Summary Product Characteristics (SPC)

1.17.1 Product information for health professionals (For All products subject to Medical prescription)

1.17.1.1 Proprietary name of the Medicine

PLS SAFE 72 (Levonorgestrel Tablets BP 0.75mg)

1.17.1.2 Strength

0.75mg (Levonorgestrel BP)

1.17.1.3 Pharmaceutical Form:

Uncoated Tablet

1.17.2 Quantitative and Qualitative Composition:

Each uncoated tablet contains:

Levonorgestrel BP 0.75 mg

S.No	Ingredients	Specification [1]	Label Claim	Qty/tablet (mg)	Function of the Ingredients
	Active				
1.	Levonorgestrel (Micronized)*	BP/Ph.Eur	0.75 mg	0.750	Emergency Contraceptive
	Excipients				
2.	Lactose monohydrate** (Lactose hydrate Mod. Spray Dry Fast Flo)	BP	-----	42.250	Diluent
3.	Lactose monohydrate (Sheffield lactose monohydrate)	BP	-----	25.000	Diluent
4.	Maize Starch	BP	-----	28.000	Disintegrant
5.	Colloidal Anhydrous Silica	BP	-----	2.000	Glidant
6.	Purified Talc	BP	-----	1.500	Lubricant
7.	Magnesium Stearate	BP	-----	0.500	Lubricant

Legends:
Ph.Eur: European Pharmacopeia
BP: British Pharmacopeia
mg: Milligrams

*Actual quantity of Levonorgestrel shall be dispensed based on Assay (on dried basis) and LOD.

**Actual quantity of Lactose monohydrate (Lactose hydrate mod. Spry Dry Fast Flo) shall be adjusted according to the actual quantity of Levonorgestrel.

[1] Current Pharmacopoeial monographs are implied

Note: Actual quantity of Levonorgestrel and Lactose monohydrate (Lactose hydrate Mod. Spry Dry Fast Flo) shall be calculated as per the below calculation.

The actual quantity of **Levonorgestrel** to be taken is calculated using the below given formula,

$$= \text{Standard Quantity} \times \frac{100}{\text{Assay (\%) On dried basis}} \times \frac{100}{(100 - \text{LOD})}$$

The actual quantity of **Lactose monohydrate (Lactose Hydrate Mod. Spry Dry Fast Flo)** to be taken is calculated using the below given formula,

$$= \text{Standard Quantity of Levonorgestrel} + \text{Std qty of Lactose monohydrate (Mod. Spry Dry Fast Flo)} - \text{Actual quantity of Levonorgestrel}$$

Overages: No overages of active pharmaceutical ingredient has been used in the formulation

Container Closure System: (Blister pack of 1 x 2's Tablet)

- A white to off-white, round, flat face bevelled edge tablet debossed as "2" on one side and plain on other side, such 2 tablets are packed in blister of printed Aluminum foil with clear PVC film
- One such blister is packed in a printed carton along with the leaflet.

Reconstitution of Diluents: Not Applicable

1.17.3 Pharmaceutical Form:

Uncoated Tablet

1.17.4 Clinical Particulars:

4.1 Therapeutic Indications

Levonorgestrel tablets are a prescription-only emergency contraceptive, for women age 17 and younger that can be used to prevent pregnancy following unprotected intercourse or a

known or suspected contraceptive failure. This product is not approved for nonprescription use.

To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.

4.2 Posology and Method of Administration

One levonorgestrel tablet should be taken orally as soon as possible within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Efficacy is better if levonorgestrel tablets are taken as directed as soon as possible after unprotected intercourse. Levonorgestrel tablets can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within one hour of taking either dose of medication she should contact her health care professional to discuss whether to repeat that dose

Method of administration: For oral use.

4.3 Contraindications

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Levonorgestrel tablets regimen consisting of the emergency use of two progestin pills. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product

4.4 Special warnings and precautions for use

WARNINGS:

Levonorgestrel tablets are not recommended for routine use as a contraceptive.

Levonorgestrel tablets are not effective in terminating an existing pregnancy.

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking levonorgestrel tablets. At the time of expected menses, approximately 75% of women using levonorgestrel tablets had vaginal bleeding similar to their normal menses, 12% to 13% 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. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1,000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of ower abdominal pain after taking levonorgestrel tablets.

PRECAUTIONS

Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV

Levonorgestrel tablets, like progestin-only contraceptives, do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up

A physical examination is not required prior to prescribing levonorgestrel tablets. A follow-up physical or pelvic examination, however, is recommended if there is any doubt

concerning the general health or pregnancy status of any woman after taking levonorgestrel tablets.

Carbohydrate Metabolism

The effects of levonorgestrel tablets on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking levonorgestrel tablets.

Drug Interactions

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of levonorgestrel tablets would be affected by these or any other medications.

Nursing Mothers

Small amounts of progestin pass into the breast milk in women taking progestinonly pills for long-term contraception resulting in steroid levels in infant plasma of 1% to 6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use

Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of levonorgestrel tablets emergency contraception before menarche is not indicated.

Fertility Following Discontinuation

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

4.5 Interaction with other medicinal products and other forms of interaction

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of levonorgestrel tablets would be affected by these or any other medications.

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1,000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of ower abdominal pain after taking levonorgestrel tablets.

Breast-feeding

Small amounts of progestin pass into the breast milk in women taking progestin only pills for long-term contraception resulting in steroid levels in infant plasma of 1% to 6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Fertility

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

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 common adverse events in the clinical trial for women receiving levonorgestrel tablets included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ≥5% of levonorgestrel tablets users.

Adverse Events in ≥5% of Women, by % Frequency

Most Common Adverse Events	Levonorgestrel 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
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Levonorgestrel tablets demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

Nausea: Occurred in 23% of women taking levonorgestrel tablets (compared to 50% with Yuzpe)

Vomiting: Occurred in 6% of women taking levonorgestrel tablets (compared to 19% with Yuzpe)

4.9 Overdose

There are no data on overdosage of levonorgestrel tablets, although the common adverse event of nausea and its associated vomiting may be anticipated.

1.17.5 Pharmacological Properties:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Sex hormones and modulators of the genital system, emergency contraceptives

ATC code: G03AD01

Emergency contraceptives are not effective if the woman is already pregnant. Levonorgestrel tablets are believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, they may inhibit implantation (by altering the endometrium). They are not effective once the process of implantation has begun.

5.2 Pharmacokinetic properties

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel tablets 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 tablets (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/mL (mean ± SD) at an average of 1.6 ± 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.

Table 1 Pharmacokinetic Parameter Values Following Single Dose Administration of Levonorgestrel Tablets, 0.75 mg to Healthy Female Volunteers
Mean (± S.D.)

N	Cmax (ng/mL)	Tmax (h)	CL (L/h)	Vd (L)	T1/2 (h)	AUC0-∞ (ng/mL/h)
16	14.1 ± 7.7	1.6 ± 0.7	7.7 ± 2.7	260.0	24.4 ± 5.3	123.1 ± 50.1

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism

Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3α,5β- and 3α,5α-tetrahydrolevonorgestrel with 16β-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2α and 16β positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion

The elimination half-life of levonorgestrel following single dose administration as levonorgestrel tablets (0.75 mg) is 24.4 ± 5.3 hours. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

1.1

1.2 SPECIAL POPULATIONS

Geriatric

This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

Pediatric

This product is not intended for use in pediatric (premenarcheal) populations, and pharmacokinetic data are not available for this population.

Race

No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both levonorgestrel tablets and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency

No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions

No formal studies of drug-drug interactions were conducted.

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 Summary of Product Characteristics.

Clinical Studies

A double-blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of levonorgestrel tablets, (one 0.75 mg tablet of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Levonorgestrel tablets, were at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with levonorgestrel tablets.

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

Table 2 Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception, and the percentage continuing use at the end of the first year, United States.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year3
Method (1)	Tpical Use1 (2)	Perfect Use2 (3)	**(4)**
Chance4	85	85	
Spermicide5	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-thermal6		2	
Post-ovulation		1	

Withdrawal	19	4	
Cap7			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm7	20	6	56
Condom8			
Female (Reality®*)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined 0.1		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera®*	0.3	0.3	70
Norplant®* and Norplant-2®*	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.9

Lactational Amenorrhea Method: LAM is a highly effective, *temporary*, method of contraception.10

Source: Trussell J, Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers, 1998.

1 *Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an unintended pregnancy during the first year if they do not stop use for any other reason.*

2 *Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an unintended pregnancy during the first year if they do not stop use for any other reason.*

3 *Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.*

4 *The percentages of women becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within one year among women*

now relying on reversible methods of contraception if they abandoned contraception altogether.

5 *Foams, creams, gels, vaginal suppositories and vaginal film.*
6 *Cervical mucus (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the post-ovulatory phases.*
7 *With spermicidal cream or jelly.*
8 *Without spermicides.*
9 *The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral®* (1 dose is 2 white pills), Alesse®* (1 dose is 5 pink pills), Nordette®* or Levlen®* (1 dose is 2 light-orange pills), Lo/Ovral®* (1 dose is 4 white pills), Triphasil®* or Tri-Levlen®* (1 dose is 4 yellow pills).*
10 *However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced or the baby reaches six months of age.*

1.17.6 Pharmaceutical particulars

6.1 List of Excipients

Lactose monohydrate (Lactose hydrate mod. Spray dry fast flo & Sheffield lactose monohydrate), Maize Starch, Colloidal Anhydrous Silica, Purified Talc, Magnesium Stearate.

6.2 Incompatibilities:

Not applicable

6.3 Shelf Life:

36 months.

6.4 Special Precaution for Storage:

Store below 30°C. Protect from light. Keep out of reach of children.

6.5 Nature and composition of container:

Clear PVC-Aluminium Blister. (1x2’s)

6.6 Instructions for use/handling

No special requirements

6.7 Special precautions for disposal and other handling

Not applicable

6.8 Restriction on sale/distribution

Nil

1.17.7 Administrative data:

7.1 Holder of a Product License:

M/s. Steril-Gene Life Sciences (P) Ltd,

Registered Office:

M/s. Steril-Gene Life Sciences (P) Ltd,
No, 15 Gopalakrishna Road, T. Nagar,
Chennai 600 017,
Tamil Nadu, India

Facility:

M/s. Steril-Gene Life Sciences (P) Ltd,
No: 45, Mangalam Main Road,
Mangalam Village, Villianur Commune,
Puducherry – 605 110,
India

7.2 Registration number

Manufacturing License No: 08 22 2288 in Form 28 dated 19.02.2009.

7.3 Date of first registration/renewal of a Product license

19.02.2009

7.4 Date of revision of the text

20.04.2021

1.17.8 Registration in a SADC member state

Not Applicable