PROFESSIONAL INFORMATION FOR ESTELO

SCHEDULING STATUS

S2

1. NAME OF THE MEDICINE

ESTELO 1,50 mg tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablet contains 1,50 mg levonorgestrel.

Excipients with known effect:

Contains sugar:

The tablet contains 43,30 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

ESTELO is a round, biconvex, white tablet, engraved with “C” on one side and “1” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ESTELO is intended for emergencies only and is completely unsuitable for regular contraception. Its reliability is not as high as that of the familiar “pill”, which is taken for at least 21 days of the menstrual cycle.

4.2 Posology and method of administration

Posology:

Take 1 tablet as soon as possible in a single administration.

The tablet should be taken no later than 72 hours after unprotected intercourse.

If the patient vomits within three to four hours of taking ESTELO, another dose should be taken immediately.

The earlier ESTELO is used, the more effective it is.

Even extremely high doses of hormones can no longer prevent pregnancy once a fertilised ovum has become implanted in the uterine mucosa.

ESTELO 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, foam, pessary) until the next menstrual period starts. The use of ESTELO does not contraindicate the continuation of regular hormonal contraception.

Special populations:

Children:

ESTELO is not recommended in children.

Very limited data are available in women under 16 years of age.

Method of administration:

For oral administration.

4.3 Contraindications

- Hypersensitivity to levonorgestrel or to any of the excipients listed in section 6.1.
- Severe hepatic insufficiency.
- Pregnancy or suspected pregnancy (see section 4.6).
- Patients with undiagnosed vaginal bleeding, or those with a history of or current high risk of arterial disease.
- Depression, which is not well controlled with treatment.

- A history of depression with the use of hormonal contraceptives.

The repeated use of ESTELO within a monthly cycle is to be avoided, since it constitutes undesirable hormonal stress and may result in severe cycle disturbances.

4.4 Special warnings and precautions for use

Emergency contraception is an occasional method. It should in no instance replace a regular contraceptive method. ESTELO 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 ESTELO 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 ESTELO, the possibility of an ectopic pregnancy should be considered, especially in those women who present with abdominal/pelvic pain or collapse and those with a history of ectopic pregnancy, fallopian tube surgery or pelvic inflammatory disease.
The absolute risk of ectopic pregnancy is likely to be low, as ESTELO prevents ovulation and fertilisation.

Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

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

ESTELO is not recommended in patients with severe hepatic dysfunction (see section 4.3).

Severe malabsorption syndromes, such as Crohn’s disease, might impair the efficacy of ESTELO.

After ESTELO 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 ESTELO 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.

A health care provider should be consulted 3 weeks after taking ESTELO regardless of whether bleeding has occurred or not.

Limited and inconclusive data suggest that there may be reduced efficacy of ESTELO with increasing body weight or body mass index (BMI) (see section 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.

ESTELO is not as effective as a conventional regular method of contraception and is suitable only as an emergency measure. ESTELO is intended for emergencies only and is completely unsuitable for regular contraception. Its reliability is not as high as that of the familiar “pill", which is taken for at least 21 days of the menstrual cycle.
Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

ESTELO should not be used diagnostically for pregnancy testing and should not be given in missed or incomplete abortion.

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

ESTELO should be used with caution in patients with a history of mental depression.
Mood changes and depression are side effects reported with the use of hormonal contraceptives including ESTELO. There is some evidence that hormonal contraceptive use may be associated with severe depression and a higher risk of suicidal thoughts/behaviour (e.g., talking about suicide, withdrawing from social contact, having mood swings, being preoccupied with death or violence, feeling hopeless about a situation, increasing use of alcohol/drugs, doing self-destructive things, personality changes) and suicide. Prescribers should inform their patients to contact their doctor for advice if they experience mood changes and depression whilst on treatment with ESTELO.

Certain progesterones may have an adverse effect on serum lipids.

Lactose monohydrate:
ESTELO contains lactose monohydrate. Patients with rare hereditary problems

of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ESTELO.

4.5 Interaction with other medicines 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 %.

Medicines suspected of having the capacity to reduce plasma levels of levonorgestrel include anticonvulsants (phenobarbitone, phenytoin, primidone and carbamazepine), herbal medicines containing *Hypericum perforatum* (St. John's wort), rifampicin, ritonavir, rifabutin, griseofulvin, ampicillin and other antibiotics, including medicines used to treat tuberculosis, ciclosporin.

For women who have used enzyme-inducing medicines 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 ESTELO (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 ESTELO during concomitant use of an enzyme inducer) has not been studied.

The requirement for oral antidiabetics and insulin can change as a result of an effect on glucose tolerance.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

ESTELO 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 foetus but there are no clinical data on the potential consequences if doses greater than 1,5 mg of levonorgestrel are taken.

In case of unprotected sexual intercourse more than 72 hours earlier, the patient may be pregnant. In these cases, pregnancy should be investigated.

Lactation:

About 0,1 % of the maternal ESTELO dose can be transferred via breast milk to the nursed infant. Potential exposure of an infant to ESTELO can be reduced if the breastfeeding woman takes the tablet immediately after feeding and avoids nursing at least 6 hours following ESTELO 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 ESTELO a rapid return to fertility is expected and therefore, regular contraception should be continued or initiated as soon as possible after ESTELO use.

4.7 Effects on ability to drive and use machines

ESTELO can cause side effects, such as dizziness and can affect the ability to drive a vehicle and use machines. Caution is advised when driving a vehicle or operating machinery until the effects of ESTELO are known.

4.8 Undesirable effects

System Organ	Frequency	Side effects

Class		
Immune system disorders	Less frequent	Anaphylaxis, anaphylactoid reactions
Metabolism and nutrition disorders	Frequency unknown	Changes in appetite or weight, fluid retention, oedema
Psychiatric disorders	Frequency unknown	Mental depression
Nervous system disorders	Frequent Frequency unknown	Headache, dizziness Drowsiness, insomnia
Gastrointestinal disorders	Frequent Frequency unknown	Nausea, lower abdominal pain, diarrhoea, vomiting Gastrointestinal disturbances
Skin and subcutaneous tissue disorders	Frequency unknown	Acne, melasma or chloasma, allergic skin reactions, hair loss or hirsutism
Reproductive system and breast disorders	Frequent Less frequent Frequency unknown	Bleeding not related to menses*, delay of menses more than 7 days**, irregular menstruation or spotting, breast tenderness Gynaecomastia, changes in libido Breast changes, premenstrual syndrome-like

		symptoms
Hepato-biliary disorders	Less frequent	Alterations in liver function tests, jaundice
General disorders and administration site conditions	Frequent	Fatigue, fever
*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.		
Post-marketing experience		
System Organ Class	**Frequency**	**Side effects**
Psychiatric disorders	Less frequent	Severe depression with a higher risk of suicidal thoughts/behaviour and suicide
Gastrointestinal disorders	Less frequent	Abdominal pain
Skin and subcutaneous tissue disorders	Less frequent	Rash, urticaria, pruritus
Reproductive system and breast disorders	Less frequent	Pelvic pain, dysmenorrhoea
General disorders and	Less frequent	Face oedema

administration site conditions		

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of ESTELO is important. It allows continued monitoring of the benefit/risk balance of ESTELO. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Category and class: A. 21.8.2 Progesterones with or without oestrogens.

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, emergency contraceptives.

ATC code: G03AD01

Mechanism of action:

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.

5.2 Pharmacokinetic Properties

Absorption:

Orally administered levonorgestrel is rapidly and almost completely absorbed.

The absolute bioavailability of levonorgestrel was determined to be almost 100 % of the dose administered.

The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of one tablet of levonorgestrel 1,5 mg, maximum medicine serum levels of levonorgestrel of 18,5 ng/mL were found at 2 hours.

Distribution:

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.

About 0,1 % of the maternal dose can be transferred via milk to the nursed infant.

Biotransformation:

The biotransformation follows the known pathways of steroid metabolism, the levonorgestrel is hydroxylated by liver enzymes mainly by CYP3A4 and its metabolites are excreted after glucuronidation by liver glucuronidase enzymes (see section 4.5).

No pharmacologically active metabolites are known.

Elimination:

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.

Pharmacokinetics in obese women:
A pharmacokinetic study showed that levonorgestrel concentrations are decreased in obese women (BMI ≥ 30 kg/m²) (approximately 50 % decrease in C_{max} and AUC_{0-24}), compared to women with normal BMI (< 25 kg/m²).

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. The clinical relevance of these data is unclear.

5.3 Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Poloxamer 188

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear to slightly opaque PVC-PVDC/Aluminium foil blister strip packed in an outer carton.

Pack size: 1 tablet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

Block B, Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBER

52/21.8.2/1021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 12 October 2021