SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tansy 750 microgram tabletten.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 micrograms of levonorgestrel.

Excipient with known effect: 44 mg of lactose monohydrate
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

Tansy 750 microgram tabletten tablet is round and white, with approximate 6 mm of diameter and marked "C" on one side and "2" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Two tablets should be taken together 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 tablets, another two tablets should be taken immediately.

Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal EC(emergency contraception), i.e. Cu-IUD or take a double dose of levonorgestrel (i.e. 4 tablets taken together) for those women unable or unwilling to use Cu-IUD (see section 4.5).

Tansy 750 microgram tabletten 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 Tansy 750 microgram tabletten does not contraindicate the continuation of regular hormonal contraception.

Paediatric population

There is no relevant use of Tansy 750 microgram tabletten for children of prepubertal age in the indication emergency contraception.

Method of administration
For oral administration.

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 no instance replace a regular contraceptive method.
Emergency contraception does not prevent 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 Tansy 750 microgram tabletten 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 Tansy 750 microgram tabletten, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as Tansy 750 microgram tabletten prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.
Therefore, Tansy 750 microgram tabletten is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or ectopic pregnancy).

Tansy 750 microgram tabletten is not recommended in patients with severe hepatic dysfunction.
Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of Tansy 750 microgram tabletten

After taking Tansy 750 microgram tabletten, menstrual periods are usually normal and occur on the expected date. They can sometimes occur earlier or later than expected by a few days. Women should be advised to make an appointment with their doctor to start or adopt a method of regular contraception. If no withdrawal bleeding occurs during the next tablet-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 Tansy 750 microgram tabletten with increasing body weight or body mass index (BMI) (see section 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.

Tansy 750 microgram tabletten is not as effective as conventional methods of contraception and is only indicated as an emergency measure. Women who request emergency contraception on repeated occasions should be advised to consider long-term methods of contraception.

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

Tansy 750 microgram tabletten contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Tansy 750 microgram tabletten should not be administered to pregnant women. It will not interrupt a pregnancy. If pregnancy continues, the limited epidemiological data available indicate no adverse effects on the foetus but there are not clinical data on the potential consequences if doses greater than 1.5 mg of levonorgestrel are taken (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been performed on the effect on the ability to drive or use machines.

4.8 Undesirable effects

The most commonly reported undesirable effect was nausea.

System Organ Class	Frequency of adverse effects	
	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 mense*	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 5-7 days of the expected date.

** If the next menstrual period is more than 5 days late, pregnancy should be excluded.

From Post-marketing surveillance additionally, the following adverse events have been reported:
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 listed in Appendix V*.

4.9 Overdose

Serious undesirable effects have not been reported following acute ingestion of large doses of oral contraceptives. Overdose may cause nausea and possible 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 mechanism of action of Tansy 750 microgram tabletten is not known. At the recommended dose, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if intercourse has taken place in the pre-ovulatory phase, when the likelyhood of fertilisation is highest. It may also cause endometrial changes that discourage implantation. Tansy 750 microgram tabletten 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 Tansy 750 microgram tabletten (taken within 72 hours of unprotected sex) prevented 84% of expected pregnancies (compared with 79% when two 750 microgram tablets were taken 12 hours apart).

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 reduce 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/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

Paedriatic 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 administration of 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 Tansy 750 microgram tabletten, maximum . serum levels of levonorgestrel of 18.5 ng/ml were found after 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, i.e. levonorgestrel is hydroxylated by liver enzymes, namely by CYP3A4, and its metabolites are excreted after glucuronidation by 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 approximately equal proportions in 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) (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

Experimental studies in animals have shown virilisation of female foetuses at high doses.
Preclinical data from conventional chronic toxicity, mutagenicity and carcinogenicity studies have not revealed any special hazard for humans beyond the information included in other sections of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Lactose monohydrate
Poloxamer 188
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of the container

Blisters of PVC/PVDC/Aluminium.

Each box contains one blister with two tablets

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Laboratorios León Farma, S.A
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24193, Villaquilambre, León.
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8. MARKETING AUTHORISATION NUMBERS

RVG111881

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vargunning: 30 april 2014
Datum van laatse verlenging: 25 oktober 2018

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 7: 8 november 2024