SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tomonil 1.5 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.5 mg of levonorgestrel

Excipient with known effect: 120 mg of lactose monohydrate.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

White to off-white round, flat tablets with bevelled edges, debossed with “J06” on one side and plain on the other side with a diameter of about 8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of 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 the woman vomits within three hours of taking the tablet, another tablet 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; women who are unable or unwilling to use Cu-IUD should take a double dose of levonorgestrel (i.e. 2 tablets taken together) for those women Cu-IUD (see section 4.5).

Tomonil 1.5 mg tablets can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

After using postcoital 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 levonorgestrel does not contraindicate the continuation of regular hormonal contraception.

Paediatric population
There is no relevant use of Tomonil children of prepubertal age in the indication postcoital 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

Postcoital contraception is an occasional method. The method must never replace a regular contraceptive method. Postcoital 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, a pregnancy test should be taken to exclude pregnancy.

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 women 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.

After Tomonil 1.5 mg tablet 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 consult a doctor/midwife to adopt or initiate a method of regular contraception. Pregnancy should be ruled out, if no bleed occurs in the next pill-free period following the use of levonorgestrel after regular hormonal contraception.

Repeated use of Tomonil 1.5 mg tablet within the same menstrual cycle is not recommended because of the risk of disturbance of the menstrual cycle.

Limited and inconclusive data suggest that there may be reduced efficacy of Tomonil 1.5 mg tablets with increasing body weight or body mass index (BMI) (see section 5.1). Emergency contraception should be taken as soon as possible after unprotected intercourse. This applies to all women, regardless body weight and BMI.

Levonorgestrel is not as safe 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 postcoital contraceptive method does not replace the necessary precautions against sexually transmitted diseases.

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

this medicine.

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., 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 cyclosporine toxicity due to possible inhibition of cyclosporin metabolism.

4.6 Fertility, pregnancy and lactation

Pregnancy
Levonorgestrel should not be given to pregnant women. Tomonil 1.5 mg tablet 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 (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 nursing 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. These changes may result in modified fertility days, although there are no fertility data in the long-term data.

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. **Organ system (MedDRA 17.0)**	**Frequency of adverse reactions**	
	Very common (≥10%)	**Common** (□1% till <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 5 to 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 to:
Läkemedels
verket Box
26
751 03 Uppsala
www.lakemedelsverket.se

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 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 1.5 mg single dose of levonorgestrel (taken within 72 hours of unprotected sex) prevented 84% of expected pregnancies (compared with 79% when the two 0.75 mg 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 (see 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 (see 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 of women with severe overweight (obesity) 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 weight 18.5–25**	**Overweight 25–30**	**Obesity ≥ 30**
N total	600	3,952	1,051	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 studies on studies of Creinin et al., 2006 and Glasier et al., 2010

BMI (kg/m2)	Underweight 0–18.5	Normal weight 18.5–25	Overweight 25–30	Obesity ≥ 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 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.
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 1.5mg maximum drug 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, levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucuronide conjugates.

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 AUC0-24), 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. A doubling of the dose (3 mg) in obese women appeared to provide plasma concentration levels similar to those observed in normal BMI 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 foetuses 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 sections of the SmPC

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Potato starch,
Talc
Silica, colloidal anhydrous
Magnesium stearate E 470 b
Lactose monohydrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear and transparent PVC/aluminium blister containing one tablet. The blister is further packed in to a folded carton.

6.6 Special precautions for disposal and other handling

No specific requirements.

Any unused medicinal product or waste material should be disposed of in accordance with

local requirements

7. MARKETING AUTHORISATION HOLDER

NAARI B.V
Rietveldenweg 102,
5222AS's Hertogenbosch
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

56750

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 July 2019

10. DATE OF REVISION OF THE TEXT

19/07/2019