Emergency Contraceptive: Read carefully before use

1. NAME OF THE MEDICINAL PRODUCT

GINNY 750 microgram tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 microgram levonorgestrel.
Excipient with known effect: each tablet contains 50.00 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
White round flat tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Use this drug to prevent pregnancy in the following cases.
1. Rape.
2. Failure of a usual contraceptive method, incorrect contraceptive method or in emergency cases, eg. Condom rupture, miscalculation of periodic abstinence method, diaphragm or cap dislodgement, breakage or early removed, IUD ex-pulsion, missed parenteral contraceptive or missed regular oral contraceptive pills for three or more days in a cycle.

4.2 Posology and method of administration

Posology
The treatment necessitates the intake of **one tablet and followed by one additional tablet 12 hours after taking the first tablet.** The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. Therefore, the first tablets must be taken **as soon as possible, preferably within 12 hours after the unprotected intercourse,** and no longer than 72 hours (3 days) after the intercourse.

Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to use a non-hormonal EC, 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).

Ginny can be taken at any moment during the menstrual cycle.

If vomiting occurs within three hours of taking the tablet, the woman should return to pharmacist, doctor or clinic where an additional tablet may be given.

After using an emergency contraception, it is recommended to use a local contraceptive mean (condom, spermicide, cervical cap) until the next menstrual periods resume. The use of Ginny does not contraindicate the continuation of regular hormonal contraception.

Paediatric population
There is no relevant use of Ginny for children of prepubertal age in the indication emergency contraception.

Method of administration
Oral use.

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 in no instance replace a regular contraceptive method.
Emergency contraception does not prevent a pregnancy to occur in every instance, especially if uncertainty about the timing of the unprotected intercourse. In case of doubt (menstrual periods delayed by more than five days or abnormal bleeding at the expected date of menstrual periods, symptoms of pregnancy), it is mandatory to check the absence of pregnancy by performing a pregnancy test.

If the woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, conception may have occurred. Treatment with Ginny following the second act of intercourse may therefore be ineffective in preventing pregnancy.

Limited and inconclusive data suggest that there may be reduced efficacy of Ginny with increasing body weight or body mass index (BMI) (see section 5.1). In all women, emergency contraception should be taken as soon as possible after unprotected intercourse, regardless of the woman's body weight or BMI.

If pregnancy occurs after treatment with Ginny, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low as Ginny prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding. Therefore, Ginny is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).

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

Cases of thromboembolic events have been reported after Ginny intake. The possibility of occurrence of a thromboembolic event should be considered in women with other pre-existing thromboembolic risk factor(s), especially personal or family history suggesting thrombophilia.

After Ginny intake, menstrual periods are usually of normal abundance and occur at the expected date. They can sometimes occur earlier or later than expected by a few days. It is recommended to have a medical visit to initiate or adapt a method of regular contraception. In case no menstrual period occurs in the next pill-free period following the use of Ginny after regular hormonal contraception, pregnancy should be ruled out.

Repeated administration within a menstrual cycle is not advisable, because of an undesirable high load of hormones for the patient and the possibility of severe disturbances of the cycle. Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

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

Concomitant use of Ginny and drugs containing ulipristal acetate is not recommended (see section 4.5).

This medicinal product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Associations to be taken into consideration:

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

Ulipristal acetate is a progesterone receptor modulator that may interact with the progestational activity of levonorgestrel. Therefore the concomitant use of levonorgestrel and drugs containing ulipristal acetate is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

This medicinal product cannot interrupt an ongoing pregnancy.
In case of failure of this contraceptive mean with persisting pregnancy, epidemiological studies indicate no malformative effects of progestins on foetus.
Nothing is known on the consequences for the child if doses higher than 1.5 mg levonorgestrel are taken.

Breast-feeding

Levonorgestrel is excreted into breast milk. Therefore, it is suggested to breastfeed immediately before taking Ginny and to skip nursing at least 8 hours following Ginny administration.

Fertility

A rapid return to fertility is likely following treatment with Ginny for emergency contraception; therefore, regular contraception should be continued or initiated as soon as possible following the use of Ginny to ensure ongoing prevention of pregnancy.
Clinical experience reveal no effect on fertility in humans after use of levonorgestrel. Similarly nonclinical studies show no evidence of adverse effects in animals (see section 5.3).

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 reported. Nevertheless, if women experience fatigue and dizziness after taking Ginny, they should not drive or use machines.

4.8 Undesirable effects

The following table gives the frequency of undesirable effects after intake of 1. 5 mg levonorgestrel reported in clinical trials*.

Body System	Frequency of adverse reactions	
	Very common (≤ 1/10)	**Common (≤ 1/100 to 1/10)**
Nervous system disorders	Headache	Dizziness
Gastrointestinal disorders	Nausea Abdominal pain	Diarrhoea[1] Vomiting
Reproductive system and Breast disorders	Uterine pain Breast tenderness Delay of menses[4] Heavy menses[2] Bleeding[1]	Dysmenorrhoea[3]
General disorders and administration site conditions	Fatigue[1]	

* Trial 1 (n=544): Contraception, 2002, 66, 269-273
* Trial 2 (n=1359): Lancet, 2002, 360:1803-10
* Trial 3 (n=1117): Lancet 2010; 375:555-62
* Trial 4 (n=840): Obstetrics and Gynecology 2006; 108:1089-1097

1 Not recorded in Trial 1

2 Not recorded in Trial 2

3 Not reported in Trial 1 or 2

4 Delay defined as more than 7 days.

These undesirable effects usually disappear within 48 hours after the intake of Ginny. Breast tenderness, spotting and irregular bleeding are reported in up to 30 percent of patients and can last until the next menstrual period which can be delayed.

Hypersensitivity reactions such as pharyngeal/face oedema and cutaneous reactions have been reported after the intake of Ginny.

Cases of thromboembolic events have been reported during the postmarketing period (see section 4.4).

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.

4.9 Overdose

Serious 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: EMERGENCY CONTRACEPTIVES, ATC code: G03AD01

Mechanism of action
The primary mechanism of action is blockade and/or delay of ovulation via suppression of the luteinizing hormone (LH) peak. Levonorgestrel interferes with the ovulatory process only if it is administered before the onset of the LH surge. Levonorgestrel has no emergency contraceptive effect when administered later in the cycle.

Clinical efficacy and safety
In clinical trials, the proportion of pregnancies avoided after the use of levonorgestrel varied from 52% (Glasier, 2010) to 85% (Von Hertzen, 2002) of expected pregnancies. Efficacy appears to decline with time after intercourse.

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. 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

At the used regimen, levonorgestrel is not expected to induce significant modifications of blood clotting factors, and lipid and carbohydrate metabolism.

Paediatric 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
After oral administration of 1.5 mg levonorgestrel, the plasma terminal half-life of the product is estimated to 43 hours. The maximal plasma concentration of levonorgestrel (approximately 40 nmol/l) is reached within 3 hours.

Distribution/Biotransformation
Levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucuronide conjugates.

Elimination
Bioavailability of oral levonorgestrel is approximately 100 percent. In the plasma, it is strongly bound to SHBG. Levonorgestrel is eliminated via kidney (60-80%) and liver (40-50%).

Pharmacokinetic in obese women
A pharmacokinetic study showed that total levonorgestrel concentrations are decreased in obese women (BMI ≥ 30 kg/m²) (approximately 50% decrease in Cmax and AUC_{0-24}), compared to women with normal BMI (< 25 kg/m²) (Praditpan et al., 2017). Another study also reported a decrease of total 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, beyond the information included in other sections of the SmPC. Animal experiments with levonorgestrel have shown virilization of female fetuses at high doses.
A preclinical study conducted in mice showed no effect on fertility in the progeny of treated dams. Two studies investigating the consequence of exposure to levonorgestrel on the development of pre-embryos before implantation, showed that levonorgestrel had no adverse effects on fertilisation and the *in vitro* growth of mouse pre-embryos.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone (PVP K90),
95% Alcohol (Ethanol),
Corn Starch,
Lactose monohydrate,
Colloidal silicon dioxide (Aerosil)
Talc (Talcum),
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Clear PVC-Aluminium Blister (2 tablets)/box

6.6 Special precautions for disposal

No special requirements.

6.7 Date of revision of the text

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7. Company Contact Details

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