WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]
The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[RH068 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Levonorgestrel 0.75 mg

Excipients with known effects:

Each tablet contains about 44.03 mg lactose monohydrate.

3. PHARMACEUTICAL FORM

Tablets

White, round, biconvex tablet engraved with 'C' on one side and '2' 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.

4.2 Posology and method of administration

For oral administration, the treatment course comprises two tablets.

The highest efficacy is achieved if the first tablet is taken as soon as possible (and no later than 72 hours) after unprotected intercourse. The second tablet should be taken 12 hours (and no later than 16 hours) after the first tablet (for efficacy data, see section 5.1.)

[RH068 trade name] can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

If vomiting occurs within three hours of taking the tablet, another tablet should be taken immediately. If repeated vomiting occurs, the tablet may be administered vaginally.

Women who have used enzyme-inducing drugs during the last 4 weeks and need emergency contraception are recommended to take a double dose of levonorgestrel (i.e., 2 tablets taken at once together, followed by 2 tablets taken after 12 hours).

After using emergency contraception, it is recommended to use a local barrier method (condom, diaphragm, spermicide, cervical cap) until the next menstrual period starts. The use of [RH068 trade name] does not contraindicate the continuation of regular hormonal contraception.

[RH068 trade name] is not recommended for use by young women aged under 16 years without medical supervision.

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 not effective in terminating an existing pregnancy.

Emergency contraception is an occasional method. It should **not** replace a regular contraceptive method.

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

Efficacy appears to decline with time (see section 5.1).

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 [RH068 trade name] 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 ruled out.

If pregnancy occurs after treatment with [RH068 trade name], the possibility of an ectopic pregnancy should be considered, especially in women in whom severe abdominal pain or fainting occurs, or if there is a history of ectopic pregnancy, Fallopian tube surgery or pelvic inflammatory disease. The absolute risk of ectopic pregnancy is likely to be low, as levonorgestrel prevents ovulation and fertilisation. Ectopic pregnancy may continue despite uterine bleeding. Therefore, [RH068 trade name] is not recommended for women at risk of ectopic pregnancy (history of salpingitis or of ectopic pregnancy).

[RH068 trade name] is not recommended in patients with severe hepatic dysfunction.

Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of [RH068 trade name].

After taking [RH068 trade name], 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 see a health care provider to initiate or adopt a method of regular contraception. If no withdrawal bleed occurs in the next pill-free period following the use of [RH068 trade name] after regular hormonal contraception, pregnancy should be ruled out.

Repeated administration within a menstrual cycle is not advisable because of the possibility of disturbing the cycle.

Any regular contraceptive method can be started immediately after the use of [RH068 trade name] emergency contraceptive pills. If the woman starts a hormonal contraceptive:

- she needs to abstain from sexual intercourse or use barrier contraception for 7 days
- she should be advised to have a pregnancy test if she does not have a withdrawal bleed within 3 weeks.

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

[RH068 trade name] is not as effective 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 emergency contraception does not replace the necessary precautions against sexually transmitted diseases.

Excipients

[RH068 trade name] contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance when using it.

It is important to consider the contribution of excipients from all the medicines that the patient is taking

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.

Drugs suspected of having the capacity to reduce the efficacy of levonorgestrel include barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing St. John's wort (*Hypericum perforatum*), rifampicin, ritonavir, rifabutin, bosentan, felbamate, oxcarbazepine and griseofulvin.

Significant changes (increase or decrease) in the plasma levels of the progestogen have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. The potential interaction may require close monitoring, alteration of drug dosage or timing of administration.

For women who have used enzyme-inducing drugs in the past 4 weeks and need emergency contraception, a double-dose of levonorgestrel should be taken (see section 4.2).

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

4.5 Fertility, pregnancy and breastfeeding

Pregnancy

[RH068 trade name] should not be given to pregnant women. It will not interrupt the pregnancy.

In case of failure of this emergency contraception and developing pregnancy, epidemiological studies indicate no adverse effects of progestogens on the fetus. There are no clinical data on the potential consequences if doses greater than 1.5 mg 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 tablets immediately after feeding and avoids nursing following each [RH068 trade name] administration.

Fertility

Levonorgestrel increases the possibility of menstrual cycle disturbances which can sometimes lead to earlier or later ovulation date. These changes can result in modified fertility date; however there are no fertility data in the long term.

4.6 Effects on ability to drive and use machines

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

4.7 Undesirable effects

The most commonly reported undesirable effect was nausea.

All adverse drug reactions are listed by system, organ class and frequency.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	**Frequency of adverse reactions**		
	Very common	**Common**	**Very rare**
Gastrointestinal disorders	Nausea Lower abdominal pain	Diarrhoea Vomiting	
General disorders and administration site conditions	Fatigue		Face oedema
Nervous system disorders	Headache	Dizziness	
Reproductive system and breast disorders	Bleeding not related to menses*	Delay of menses more than 7 days** Menstruation irregular Breast tenderness	Pelvic pain Dysmenorrhoea

Skin and subcutaneous tissue disorders			Rash Urticaria Pruritus

* 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.

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. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.8 Overdose

There have been no reports of any serious damage to health caused by an overdose.

The symptoms that may occur in such a case include: nausea, vomiting and mild vaginal bleeding. There is no specific antidote. 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 mode of action of levonorgestrel is not known.

At the recommended regimen, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if intercourse has taken place in the pre-ovulatory phase, when the likelihood of fertilisation is the highest. It is not effective once the process of implantation has begun.

Clinical efficacy and safety

Efficacy: 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 two 750-microgram tablets were taken 12 hours apart).

It is therefore, recommended that levonorgestrel is taken as soon as possible (and no later than 72 hours) after unprotected intercourse.

At the recommended regimen, levonorgestrel is not expected to significantly modify blood clotting factors, or lipid and carbohydrate metabolism.

Safety: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A double-blind, controlled clinical trial in 1,955 evaluable women compared the efficacy and safety of Levonorgestrel (one 0.75 mg tablet of levonorgestrel taken within 72 hours of unprotected intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets each containing 250 micrograms levonorgestrel and 50 micrograms ethinylestradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later).

There are limited and inconclusive data on the effect of high body-weight/BMI on the contraceptive efficacy. In three WHO studies, no trend for a reduced efficacy with increasing body-weight/BMI was observed), 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. 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.

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

No pharmacokinetic data are available for [RH068 trade name]. A bioequivalence study was conducted with a product containing levonorgestrel 1.5 mg that is essentially the same as [RH068 trade name] in qualitative terms and with respect to the ratio of active and other ingredients."

The absorption characteristics of levonorgestrel 1.5 mg [RH069 trade name] have been determined after administration of single tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Arithmetic mean ± standard deviation (*)**
	Levonorgestrel
Maximum concentration (C_{max})	19.5 ± 5.8 (18.7)
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	315 ± 133
Time to attain maximum concentration (t_{max})	2.0 ± 0.9

***** Geometric mean

Pharmacokinetics of levonorgestrel

Absorption	
Oral bioavailability	Rapid and near complete absorption
Food effect	NA
Distribution	
Volume of distribution (mean)	106 L
Plasma protein binding *in vitro*	33.5% bound to serum albumin and 65% bound to sex hormone binding globulin
Tissue distribution	0.1% of dose transferred to breast milk
Metabolism	
	Metabolism follows the known pathways of steroid metabolism. 100% metabolized by liver.
Active metabolite(s)	None known.
Elimination	
Elimination half life	26 hours
Mean systemic clearance (Cl/F)	1.0 - 1.5 mL/minute/kg
% of dose excreted in urine	Levonorgestrel metabolites are excreted in about equal proportions with urine and faeces.
% of dose excreted in faeces	Levonorgestrel metabolites are excreted in about equal proportions with urine and faeces.

*Information not available

Pharmacokinetics in obese women

A pharmacokinetic study showed that levonorgestrel concentrations are decreased in obese women (BMI ≥ 30 kg/m^2) (approximately 50% decrease in C_{max} and AUC_{0-24}), compared to women with normal BMI (< 25 kg/m^2) (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

Non-clinical data reveal no special hazard for humans based on conventional studies of chronic toxicity, mutagenicity and carcinogenicity potential, beyond the information included in other sections of the SmPC.

Animal experiments with levonorgestrel have shown virilisation of female foetuses at high doses.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline cellulose
Lactose monohydrate
Poloxamer
Croscarmellose sodium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30ºC. Avoid excursions above 30ºC

6.5 Nature and contents of container

Clear to slightly opaque PVC/PVdC-aluminium blister. Each blister card contains 2 tablets. One such blister card is packed in a carton box.

6.6 Special precautions for disposal

No special requirements.

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

7. SUPPLIER

Laboratorios Leon Farma SA
La Vallina s/n
Poligono Industrial Navatejera
Villaquilambre
Leon 24008
Spain

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

RH068

9. DATE OF PREQUALIFICATION

05 February 2021

10. DATE OF REVISION OF THE TEXT

March 2021

References

General references

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Sections 4.4 and 5.2

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Section 5.1

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Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines