AUSTRALIAN PRODUCT INFORMATION

POSTRELLE-1

Levonorgestrel tablet

1 NAME OF THE MEDICINE

Levonorgestrel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Postrelle-1 tablet contains 1.5 milligrams of levonorgestrel.

Postrelle-1 also contains sugars (as lactose). For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Postrelle-1 tablets: Round, white to off-white, uncoated flat tablets debossed '145' on one side and other side plain.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Postrelle-1 is an oral emergency contraceptive indicated for use within 72 hours of unprotected intercourse. It should be used only as an emergency measure. Women who present for repeated courses of emergency contraception should be advised to consider long-term methods of contraception.

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral administration.

One 1.5 milligram tablet to be taken as soon as possible (and not later than 72 hours) after unprotected intercourse.

The highest efficacy is achieved if the tablet is taken as early as possible. Therefore treatment should not be delayed as efficacy declines with time.

If the patient vomits within two hours of taking the tablet, she should return to her pharmacist, doctor or clinic where an additional tablet may be given.

Postrelle-1 can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

Children: Postrelle-1 is not recommended in children.
Only limited data are available in young women of child-bearing potential aged 14-16 years. No data are available about use in young women aged less than 14 years or children.

4.3 CONTRAINDICATIONS

Postrelle-1 should not be given to pregnant women. If menstrual bleeding is overdue, if the last menstrual period was abnormal in timing or character or if pregnancy is suspected for any other reason, pregnancy should be excluded (by pregnancy testing or pelvic examination) before treatment is given.

If a woman has had unprotected intercourse more than 72 hours earlier in the same menstrual cycle, conception may have already occurred. Treatment with Postrelle-1 following the second act of intercourse may therefore be ineffective in preventing pregnancy. While the consensus is that levonorgestrel is not teratogenic, no guarantee can be given that pregnancy will result in a normal baby.

Progestogen-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Postrelle-1 regimen consisting of the emergency use of one 1.5 mg tablet.

Traditionally many of the contraindications to combined hormonal contraception have been applied to progestogen-only contraception. Since the contraindications largely apply to estrogen this is inappropriate. In their Medical Eligibility Criteria, The World Health Organisation advises that the only absolute contraindications to high dose progestogen-only contraception are unexplained vaginal bleeding, current breast cancer, pregnancy or hypersensitivity to any of the ingredients of the preparation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Conditions which are regarded as relative contraindications include severe hypertension (BP >180+/110+), diabetes mellitus with nephropathy, retinopathy, neuropathy or vascular disease, ischaemic heart disease, stroke, or a past history of breast cancer. Since exposure to levonorgestrel with Postrelle-1 is brief, the risks of pregnancy in all women, including those with pre-existing medical conditions, are almost certainly greater than those associated with Postrelle-1. In individual cases the risk-benefit ratio should be assessed by the practitioner in discussion with the patient.

Postrelle-1 is not as effective as conventional regular methods of contraception and is suitable only as an emergency measure. Women who present for repeated courses of emergency contraception should be advised to consider a long-term method of contraception.

Emergency contraception does not protect against sexually transmitted infections.

Precautions before use

- Exclude pregnancy if suspected clinically
- Breast or pelvic examinations are not routinely necessary. Perform such examinations only if indicated by the patient's history
- Blood pressure may be measured before prescribing Postrelle-1. An elevated BP is not a contraindication to treatment but indicates the need for further investigation
- No routine laboratory testing is required
- Explain the importance of follow-up and the possibility of an early or late onset of the next menstrual period to the patient. Advise the practice of abstinence or careful use of a barrier method until the onset of the next period. Follow-up should be offered 3 weeks after administration of therapy to assess the effectiveness of the method, to discuss future management if a period has not occurred, and to counsel the patient about future contraception
- Women should be warned that if pregnancy occurs after treatment with Postrelle-1, there is a possibility of an ectopic pregnancy.

Precautions after use

- If pregnancy occurs after treatment with Postrelle-1, the possibility of an ectopic pregnancy should be considered.

Vomiting, severe diarrhoea or other causes of malabsorption, such as Crohn’s disease, might impair the efficacy of Postrelle-1. Women suffering from conditions associated with possible malabsorption should be referred for medical consultation as consideration should be given to the taking of another tablet. If the patient vomits within two hours of taking the tablet, she should return to her pharmacist, doctor or clinic where an additional tablet may be given (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in Hepatic Impairment

Postrelle-1 is not recommended in patients with severe hepatic dysfunction.

Use in the Elderly

No data available.

Paediatric Use

Postrelle-1 is not indicated for use in children. Only limited data are available in young women of child-bearing potential aged 14 to 16 years. No data is available about use in young women aged less than 14 years or in children (see also Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The metabolism of levonorgestrel can be enhanced by concomitant use of medicines which induce CYP3A4, one of the families of liver enzymes. This may reduce the effectiveness of Postrelle-1 in preventing pregnancy.

Medicines suspected of having the capacity to reduce the efficacy of levonorgestrel containing medications include barbiturates (including primodone), phenytoin, carbamezipine, herbal medicines containing Hypericum perforatum (St John's Wort), rifampicin, ritonavir, rifabutin, griseofulvin and efavirenz.

Levonorgestrel has the ability to decrease glucose tolerance when it is used in the longer term. However, use of levonorgestrel as an emergency contraceptive is not thought to induce significant modification of carbohydrate metabolism.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy (Category D)

Postrelle-1 is not to be used during an existing or suspected pregnancy. Research has found no significant effects on fetal development associated with the long-term use of contraceptive doses of combined oral steroids before pregnancy or taken inadvertently during early pregnancy. There have been an insufficient number of pregnancies in patients using levonorgestrel-only oral contraceptives to rigorously evaluate the potential for developmental toxicity; however, based on the combined oral contraceptive experience, an increase in abnormalities is not expected. If taken by the mother at or after 8 weeks post conception, progestogens such as levonorgestrel can cause virilisation of the female fetus. This is a dose dependent effect. Prior to 8 weeks post conception, they have no virilising effects. There are no studies of the effect of the high levonorgestrel doses used in Postrelle-1 on pregnancy and embryo/fetal development.

Use in Lactation

Progestogens do not appear to affect the quantity or quality of breast milk. However, levonorgestrel has been identified in the breast milk following oral administration to lactating women. Women should be advised not to breast-feed within 3 days after taking Postrelle-1.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The adverse events reported with an incidence of greater than 1% in the Ho and Kwan and the Pivotal Studies (two 750 microgram tablets taken 12 hours apart) are included in **Table 1.**

Table 1. Adverse events reported in the Ho and Kwan study and the pivotal study

Adverse Events	Ho and Kwan Study		Pivotal Study	
	LNG[a] N = 410 %	Yuzpe N = 424 %	LNG[a] N = 977 %	Yuzpe N = 979 %
Body, whole				
Fatigue	23.9[b]	36.8	16.9	28.5
Flu syndrome	-	-	1.0	- (0.9)
Gastrointestinal				
Abdominal pain	-	-	17.6	20.9
Nausea	16.1[b]	46.5	23.1[b]	50.5
Vomiting	2.7[b]	22.4	5.6[b]	18.8
Diarrhoea	-	-	5.0	6.5
Neurological				
Dizziness	18.5	23.1	11.2	16.6
Headache	-	-	16.8	20.2
Reproductive				
Breast tenderness	15.9	20.8	10.7	12.1
Increased bleeding	-	-	13.8	12.2
Vaginal haemorrhage	3.4	4.2	1.0	1.2

a LNG = Levonorgestrel
b Significantly different to Yuzpe group

Side effects did not result in any discontinuations in either study. No ectopic pregnancies or congenital abnormalities were reported in either study. However, such a possibility must always be considered, as there have been rare reports of ectopic pregnancies reported during post-marketing surveillance. Cutaneous reactions have also been reported from post-marketing surveillance on rare occasions.

In the additional studies conducted to compare dosing with two 750 microgram tablets taken as a single dose and taking the two tablets 12 hours apart, the adverse events recorded were mostly similar to the above studies, as detailed in the following table:

Table 2. Adverse events reported in the pivotal study and Arowojolu et. al. study

Adverse Events	Pivotal Study		Arowojolu et al	
	Single dose N = 1379 %	Two tabs 12 hours apart N = 1377 %	Single dose N = 544 %	Two tabs 12 hours apart N = 518 %
Body, whole				
Fatigue	13.3	13.2	-	-
Gastrointestinal				
Abdominal pain	13.3	14.4	15.6	18.3
Nausea	13.7	14.5	24.3	22.9
Vomiting	1.4	1.4	7.8	8.4
Diarrhoea	3.8	3.2	-	-
Neurological				
Dizziness	9.6	9.2	12.6	13.9
Headache	10.3	9.4	21.3*	14.5

Reproductive				
Breast tenderness	8.2	8.4	12.9*	8.8
Bleeding	30.9	30.9	-	-
Delay of menses >7 days	4.5	4.5	-	-
Heavy menses	-	-	15.5	10.5

* Significantly different ($p<0.05$) to two tablets 12 hours apart for same study (Arowojolu)

One ectopic pregnancy was observed in the pivotal study and none in the supporting (Arowojolu) study.

Overall, there was no indication that taking the full 1.5 milligram dose at the one time resulted in an adverse event profile of greater concern than that for the regimen when the two 750 microgram tablets were taken 12 hours apart.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Serious ill 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.

As strategies for the management of overdose are continually evolving, it is advisable to contact the Poisons Information Centre to determine the latest recommendations for the management of an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Postrelle-1 is an emergency oral contraceptive tablet containing the synthetic progestogen, levonorgestrel.

The precise mode of action of levonorgestrel is not known. Emergency hormonal contraception is thought to work mainly by preventing ovulation and fertilisation by altering tubal transport of sperm and/or ova. It may also cause endometrial changes that discourage implantation.

Clinical Trials

Efficacy. From earlier studies where two levonorgestrel tablets (each 750 micrograms) have been taken 12 hours apart, it has been estimated that levonorgestrel prevents 85% of expected pregnancies. Efficacy appears to decline with time after intercourse (95% within 24 hours, 85% 24-48 hours, 58% if used between 48 and 72 hours).

In an additional study to compare taking the two tablets 12 hours apart versus taking a total dose of 1.5 mg after unprotected intercourse, similar rates of prevention of pregnancy were observed when taken within 72 hours. In this study, it was also observed that efficacy declined with increasing time of taking the medication after intercourse.

In further studies to compare the bioavailability of the single 1.5 mg tablet to two 750 microgram tablets, it has been determined that the efficacy would be similar.

Two large controlled studies of levonorgestrel using 750 microgram tablets (two tablets taken 12 hours apart), for emergency contraception have been undertaken. The first of these is referred to as the Ho and

Kwan study and the second, which included larger numbers, as the Pivotal study. Both studies compared this treatment regime to the Yuzpe regimen (ethinylestradiol 100 micrograms plus levonorgestrel 500 micrograms, repeated 12 hours later).

The Ho and Kwan study was a single centre and open-label (age range 18-45 years) while the Pivotal study was multi-centre, randomised and double-blind (age range 14-47 years), with both including women requiring emergency contraception resulting from no contraception used during intercourse or contraception method failure. The regimens were similar with two exceptions:

- The Ho and Kwan study allowed treatment to be initiated up to 48 hours post intercourse whereas the Pivotal study allowed a 72 hour gap between treatment initiation and intercourse.
- The treatment regimen in both studies used two tablets, the second taken 12 hours after the first. In the Pivotal study only, women in each of the two groups were provided with replacement medication to take should vomiting occur within four hours of either dose.

The efficacy results from the efficacy population analysis from the two studies are summarised in the following table:

Table 3. Efficacy results from the Ho and Kwan study and the pivotal study

Parameter	Ho and Kwan Study		Pivotal Study	
	LNG[a]	Yuzpe	LNG[a]	Yuzpe
Number of women	410	424	976	979
Number of pregnancies	12	15	11	31
Pregnancy rate (%)	2.9	3.5	1.1	3.2
Number of Observed/ Expected Pregnancies	8/19.8[b]	9/22.0[b]	11/76.3	31/74.2
Prevented fraction (%)	60	59	86[c]	58

a LNG = Levonorgestrel
b Among 331 (LNG) and 341 (Yuzpe) women who had reliable menstrual dates
c Significantly greater than in the Yuzpe group

The relative risk of pregnancy in the Pivotal study for the Yuzpe versus levonorgestrel regimens was 2.8 with a lower one-sided 95% confidence bound of 1.53.

Stratified analyses of the data showed no significant effect for age or ethnicity. For intervals between intercourse and initiation of treatment, shorter intervals were associated with lower pregnancy rates.

Two further studies have been conducted in order to determine whether taking two 750 microgram tablets at the same time (as a single dose) was as efficacious as taking the two tablets 12 hours apart.

The pivotal study for this comparison was a double blind, randomised, double dummy multicentre study, conducted by the WHO/HRP across 10 countries. This study included women ranging in age from 14 to 52 years, and allowed for enrolment up to 120 hours after intercourse.

A supporting study (Arowojolu et al, 2002) for this comparison was conducted in Nigeria at a single centre. A total of 1118 women were assessed for efficacy in this study.

The efficacy results from the data analysis for the two treatment regimes from both studies are summarised in the following table:

Table 4. Efficacy results from the pivotal study and Arowojolu et. al. study

Parameter	Pivotal study		Arowojolu et al, 2002	
	Two 750 microgram tablets taken as a single dose	Two 750 microgram tablets taken 12 hours apart	Two 750 microgram tablets taken as a single dose	Two 750 microgram tablets taken 12 hours apart
Number of women	1356	1356	545	573
Number of pregnancies	20	24	4	7
Pregnancy rate (%)	1.5	1.8	0.7	1.3
Number of Observed / Expected Pregnancies	20/111	24/106		
Prevented fraction (%)	81.9 [1]	77.3 [1]	93.4 [2]	87.5 [2]

[1] Prevented fraction over 5 days – calculated from Number of Observed / Expected Pregnancies (Pivotal study)

[2] Prevented fraction calculated using British conception probabilities (Arowojolu et al study)

There was no significant difference in efficacy between the two levonorgestrel treatment groups in the pivotal study. Shorter intervals between intercourse and treatment were associated with lower pregnancy rates in both groups.

The authors of the supporting study (Arowojolu et al, 2002) concluded that both treatment regimes were effective – the single two tablet dose appeared to be more effective than when the two tablets were taken 12 hours apart and that the earlier the medication is taken after unprotected intercourse, the better the efficacy.

Adverse events reported in these two studies were similar for both treatment groups (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

No specific clinical trials investigating pregnancy outcome have been conducted on the single 1.5 mg tablet. Evidence for its efficacy is based on the 1.5 mg tablet and two 750 microgram tablets taken at the same time having the same pharmacokinetic profile.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

A study compared the pharmacokinetics of a 1.5 mg levonorgestrel tablet taken as a single dose with that of two 750 microgram tablets taken 12 hours apart. Following ingestion of one 1.5 mg tablet, maximum plasma drug levels of 18.5 ng/mL were found at 2 hours. Thereafter, levonorgestrel plasma levels decreased with a half life of approximately 26 hours. In this study, the C_{max} was higher for the single 1.5mg tablet, but plasma levels over a 24 hour period were similar, as were the T_{max} and half life.

In another study, a comparison of the pharmacokinetics with two 750 microgram tablets taken together (as a single dose) or 12 hours apart showed similar levels of serum levonorgestrel over a 24 hour period, and similar terminal half lives (43.7 versus 43.3 hours). The C_{max} was about 50% higher when the two tablets were taken together than when they were taken 12 hours apart (12.3 versus 7.9 ng/mL, p=0.03), and this occurred at 2.5 and 1.8 hours, respectively, after the (first) dose.

When the bioavailability of a single 1.5 mg levonorgestrel tablet was compared to two 750 microgram tablets taken at the same time, AUC and C_{max} were found to be the same with both treatments. In this study, maximum plasma drug levels of 19.1 ng/mL were found at 1.7 hours following the ingestion of one 1.5 mg tablet. Thereafter, levonorgestrel plasma levels decreased with a half life of approximately 27 hours.

In general, it is recognised that the pharmacokinetics of levonorgestrel can be quite variable.

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

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.

Metabolism and Excretion

Levonorgestrel is not excreted in unchanged form but as metabolites. Levonorgestrel metabolites are excreted in about equal proportions in urine and faeces. The biotransformation follows the known pathways of steroid metabolism with levonorgestrel being hydroxylated in the liver and the metabolites then excreted as glucuronide conjugates. No pharmacologically active metabolites are known.

About 0.1% of the maternal dose can be transferred via milk to the breast-fed infant.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No studies of the mutagenic potential of levonorgestrel have been performed.

Carcinogenicity

No studies of the carcinogenic potential of levonorgestrel have been performed. Numerous epidemiological studies have been performed to determine the incidence of breast, endometrial, ovarian and cervical cancer in women using combination oral contraceptives. Some studies suggest that combination oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV). Evidence in the literature suggests that use of combination oral contraceptives is not associated with an increased risk of developing breast cancer in the overall population of users. However, some of these same studies have shown an increased relative risk of breast cancer in certain subgroups of combination-oral- contraceptive users, although no consistent pattern of findings has been identified. Benign hepatic adenomas have been found to be associated with the use of oral contraceptives containing levonorgestrel. Although benign, hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The contribution of the progestin component of oral contraceptives to the development of hepatic adenomas is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Povidone, lactose monohydrate, maize starch, magnesium stearate and silicon dioxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Do not remove from the primary pack except immediately before use.

6.5 NATURE AND CONTENTS OF CONTAINER

Postrelle-1 is supplied in blister packs (PVC/PVDC/Aluminium) containing 1 tablet.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

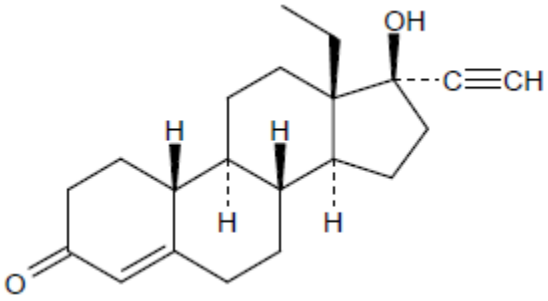
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name: (-)-13β- ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Structural formula:



Molecular formula: $C_{21}H_{28}O_2$

Molecular Weight: 312.45

Levonorgestrel is a white or almost white, odourless or almost odourless, crystalline powder. Practically insoluble in water; slightly soluble in alcohol, in acetone, and in ether; soluble in chloroform; sparingly soluble in methylene chloride.

CAS Number

797-63-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

S3 – Pharmacist Only Medicine

8 SPONSOR

Alphapharm Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

03/04/2014

10 DATE OF REVISION

07/02/2020

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat to align with the new form for providing product information
2	Addition of statement regarding excipient with known effect
4.3, 5.1, 6.1	Update to ingredient names to align with International Harmonisation of Ingredient Names

2, 3, 4.8, 5.1, 5.3, 8, 4.4	Editorial changes
6.5	Addition of blister material information

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