

## NEW MEDICINES ON THE MARKET

Evaluated Information for NHS Managers, Budget Holders and Prescribers.

### LEVONORGESTREL

#### Summary

- Levonelle-2 is the first progestogen-only oral preparation to be licensed for use as an emergency contraceptive in the UK. It contains 750mcg levonorgestrel, a synthetic derivative of the hormone progesterone.
- Levonelle-2 is thought to prevent pregnancy by various mechanisms dependant on the stage of the cycle. It suppresses ovulation, inhibits fertilisation of any eggs released and also causes changes to the endometrium to prevent implantation of the fertilised egg.
- Results from a large WHO study has demonstrated that Levonelle-2 has improved efficacy compared to the Yuzpe regimen of combined oestrogen and progestogen. The levonorgestrel-only regimen prevented 85% of expected pregnancies, compared to 57% in the Yuzpe group.
- Levonorgestrel-only regimens have also been shown to have a better tolerability and safety profile compared to the Yuzpe regimen. Nausea and vomiting, often a cause of non-compliance with the Yuzpe regimen has been found to be significantly reduced in women given levonorgestrel-only post-coital contraception.
- The lack of an oestrogen component in Levonelle-2 results in fewer restrictions and contraindications to its use, therefore making oral emergency contraception more accessible to a larger number of women for whom previously this method was not advised (e.g those with cardiovascular complications).
- Levonelle-2 is more expensive than the licensed Yuzpe regimen, Schering PC4. However the improved reliability and tolerability, and potentially improved compliance may offset this cost and the cost to the NHS of pregnancy. Schering Health Care has applied for a non-prescription status for Levonelle-2, so it may supersede PC4 and become the first postcoital preparation available without a prescription.

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## LEVONORGESTREL

<b>APPROVED NAME:</b>	Levonorgestrel
<b>BRAND NAME:</b>	Levonelle-2 (Schering Health Care Limited)
<b>PRESENTATION:</b>	A blister pack of 2 tablets, each containing 750 micrograms of levonorgestrel.
<b>THERAPEUTIC CLASS:</b>	Emergency Contraception [BNF 7.3.1].
<b>LICENSED INDICATIONS:</b>	Emergency contraceptive for use within 72 hours of unprotected intercourse.
<b>DOSAGE &amp; ADMINISTRATION:</b>	One 750 microgram tablet to be taken as soon as possible (and not later than 72 hours) after unprotected intercourse, followed by one additional 750 microgram tablet 12 hours later.
<b>THERAPEUTIC COMMENT:</b>	First progestogen-only (PO) product licensed for postcoital contraception in UK. There is a move towards the use of PO postcoital contraceptives because of their improved efficacy & side effect profile compared to the Yuzpe regimen. Schering Health Care has also applied for non-prescription status for Levonelle-2.
<b>SECTOR:</b>	Hospital [Y] <span style="float: right;">Primary Care [Y]</span>
<b>COST/COURSE:</b>	£5 for two tablet pack
<b>TREATMENT ALTERNATIVES:</b>	(Prices from MIMS February 2000)

Preparation	Type	Dose	Cost
Schering PC4 [Ethinylestradiol 50mcg + Levonorgestrel 250mcg]	Oestrogen/ progestogen combination	Two tablets taken as soon as possible after unprotected intercourse (up to max of 72hrs) then two tablets 12hrs later	£1.60 (4)
Levonelle-2 [Levonorgestrel 750 mcg]	Progestogen	One tablet taken as soon as possible after unprotected intercourse (up to max of 72hrs) then another tablet 12hrs later	£5.00 (2)
Gynefix* [Copper-containing intrauterine device]	Intrauterine device	Inserted by a specially trained doctor not more than 5 days from the most probable calculated date of ovulation. It can be removed after during the next menstrual bleed.	£24.75

\*Gynefix is the only IUD licensed for emergency contraceptive use. Cheaper IUDs are available.

## INTRODUCTION

Emergency contraception is a well-tolerated and effective way of preventing accidental pregnancy after unprotected intercourse.

There are three emergency contraceptive methods used in the UK; the licensed oral combined hormonal preparation (Schering PC4), also known as the Yuzpe regimen; the postcoital insertion of a copper-containing coil (IUD); and the use of oral progestogen-only preparations [1].

The choice of emergency contraception should be made in light of the clinical circumstances, in consultation with the patient.

The most widely used method is the Yuzpe method, a combination of ethinylestradiol and levonorgestrel. It was first described in the 1970s and little has changed since that time in how it is used. The Yuzpe regimen also has the same contraindications associated with the long-term use of combined oral contraceptives, which can sometimes restrict its use [1].

The copper-bearing IUD is a highly effective postcoital contraceptive, with failure rates of less than 1%. In the UK it is used for up to 5 days after the earliest estimated day of ovulation. It is particularly appropriate for women who wish to use the IUD as a long-term method of contraception. However, most women requesting emergency contraception are young and nulliparous, and it can be difficult to insert a device if the uterus is small [1].

Up until the launch of Levonelle-2, there were no licensed progestogen-only postcoital preparations available in the UK. Previously when this method was preferred, large numbers of PO pills (e.g 25 x Microval) were given.

## PHARMACOLOGY

Levonorgestrel is a synthetic derivative of the hormone progesterone. It is thought to prevent pregnancy in three different ways, depending on the stage of the menstrual cycle at which unprotected intercourse occurs: it suppresses ovulation, inhibits the fertilisation of any egg already released, and may also cause changes to the endometrium to prevent a fertilised egg implanting [2].

## PHARMACOKINETICS

Orally administered levonorgestrel is rapidly and almost completely absorbed with an absolute bioavailability of almost 100%. Following ingestion of one tablet of 750 micrograms, maximum drug serum levels of 14.1ng/ml were found at 1.6hrs. The mean elimination half-life ranges from 9-14.5hrs. Levonorgestrel is excreted as metabolites in equal proportions with urine and faeces. These metabolites are not thought to be pharmacologically active [2].

## EFFICACY

There have been two published studies which compare the efficacy and tolerability of levonorgestrel-only regimens with Yuzpe regimens when used for emergency contraception [3,4].

The largest of these two studies build on the results reported by the earlier study which demonstrated that levonorgestrel is similar in efficacy to the Yuzpe regimen but is associated with an improved side effect profile [3]. The more recent study undertaken by a WHO Task Force on Postovulatory Methods of Fertility Regulation confirms the improved tolerability of levonorgestrel but also demonstrated an improved efficacy compared with the Yuzpe regimen [4]. The multicentre, international, double-blind, randomised controlled trial sought to compare the efficacy of the two methods when started within 72 hours of unprotected intercourse.

# LEVONORGESTREL

The study enrolled a total of 1998 women from 21 centres world-wide. All women included in the study had requested emergency contraception after a single act of unprotected intercourse [4]. Of the 1998 participants enrolled in the study, 1001 were randomised to 750mcg levonorgestrel (repeated 12 hours later) and 997 to the Yuzpe regimen, 100mcg ethinylestradiol + 500mcg levonorgestrel (repeated 12 hours later). Outcomes were unknown in 2.2% (n=43) and the final number of women in the study were 1955 (976 - levonorgestrel and 979 - Yuzpe). Follow-up was conducted 1 week after the expected onset of their next menses, and the women kept diaries of side effects, bleeding patterns and any further acts of intercourse. Unintended pregnancy was the primary outcome measured using both crude and adjusted pregnancy rates. Secondary outcomes included reduction in expected pregnancies, side effects, and changes in bleeding patterns [4]. The calculated pregnancy rate was 1.1% (95%CI 0.6-2.0) for the levonorgestrel group and 3.2% (95%CI 2.2-4.5) for the Yuzpe group. Relative risk of pregnancy was 0.36 (95%CI 0.18-0.7) [4]. This pregnancy rate for the Yuzpe regimen was greater than the overall pregnancy rate of 1.8% reported in a review of 11 studies published in 1989. However it is within the range of pregnancy rates reported for the individual studies [5]. Calculations of the number of pregnancies that could have occurred if no treatment had been given showed that levonorgestrel had prevented 85% (95%CI 74-93) of unintended pregnancies as compared to 57% (95% CI 39-71) with the Yuzpe regimen [4]. The efficacy of the Yuzpe regimen in this trial, is considerably lower than the 76% average efficacy which has been reported previously [6-7] and this difference has not been fully explained. The WHO study also demonstrated that the

efficacy of both regimens was increased if the treatment was provided within 24 hours of intercourse and that efficacy decreased as time of treatment approached 72 hours (p=0.1) [4].

Coitus-treatment interval	Percentage of expected pregnancies prevented (%)	
	Levonorgestrel-only	Yuzpe Regimen
24 hours or less	95	77
25-48 hours	85	36
49-72 hours	58	31

Table1. Effect of coitus to treatment interval [4]

## PROMOTIONAL DATA

The company are promoting Levonelle-2 on the basis that it is more effective and better tolerated than PC4 or other Yuzpe regimens and this is in fact borne out in the 1998 WHO trial.

## ADVERSE EFFECTS

Nausea occurs in about 25% of women taking Levonelle-2 and vomiting occurs in about 5%. Other side effects are breast tenderness, headache, dizziness & fatigue [2].

The WHO trial [4] concluded that the levonorgestrel-only method of postcoital contraception was better tolerated than the Yuzpe regimen with nausea, vomiting, dizziness and fatigue significantly less common among the women who received the levonorgestrel-only regimen.

Side effect	Levonogestrel-only regimen	Yuzpe Regimen	P
Nausea	23.1%	50.5%	<0.01
Vomiting	5.6%	18.8%	<0.01
Dizziness	11.2%	16.7%	<0.01
Fatigue	16.9%	28.5%	<0.01

Table 2. Percentage of women with symptoms after the levonorgestrel-only method of postcoital contraception & the Yuzpe regimen [4]

Bleeding patterns may be temporarily disturbed. Some women may experience early or delayed onset of menses (pregnancy should be excluded if the next menstrual period is more than seven days late) [2].

The effects on the menstruation have been found to be similar for women who have taken the levonorgestrel method of postcoital contraception or the Yuzpe regimen. The average duration of the next menses was 4.7 days for both the levonorgestrel-only group and the Yuzpe group [4].

## CONTRAINDICATIONS

See SPC for full details.

Levonelle-2 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 test or pelvic examination) before treatment is given [2].

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 [2].

Conditions which are regarded as relative contraindications include severe hypertension (BP>180+/110+), diabetes mellitus with neuropathy, retinopathy or vascular disease, ischaemic heart disease, stroke, or a past history of breast cancer [2].

## PRECAUTIONS

See SPC for full special warnings and special precautions for use.

Vomiting, severe diarrhoea or other cases of malabsorption, such as Crohn's disease, might impair the efficacy of Levonelle-2. Consideration should be given to the taking of more tablets [2].

### Drug Interactions

As with other oral contraceptives, it is thought the efficacy of Levonelle-2 may be reduced by concomitant use with various drugs, which include barbiturates, phenytoin, carbamazepine, phenylbutazone, rifampicin, ritonavir, griseofulvin and other antibiotics [2].

### Pregnancy/Lactation

The effect of Levonelle-2 on the fetus is not known. Although the consensus opinion among teratologists is that known teratogens will not produce malformations before organogenesis starts (which is later than 72 hours after fertilisation), Levonelle-2 should not be given to pregnant women [2].

Minute amounts (~0.1%) of active substance are excreted with the milk, however there is no evidence to show that taken in an emergency situation, Levonelle-2 diminishes milk yield [2].

## References

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