

**Public Assessment Report**  
**Mutual Recognition Procedure**

**Levonelle 1500 microgram Tablet**

**UK/H/803/01**

**Medimpex UK Limited**

## TABLE OF CONTENTS

Module 1: Information about initial procedure	Page	3
Module 2: Summary of Product Characteristics	Page	4
Module 3: Product Information Leaflets	Page	10
Module 4: Labelling	Page	14
Module 5: Scientific Discussion	Page	16
1 Introduction		
2 Quality aspects		
3 Non-clinical aspects		
4 Clinical aspects		
5 Overall conclusions		

## Module 1

<b>Product Name</b>	Levonelle
<b>Type of Application</b>	Known active substance Initial application Full dossier, Article 8.3(i) Chemical substance Prescription only
<b>Active Substance</b>	Levonorgestrel
<b>Form</b>	Tablet
<b>Strength</b>	1500 microgram
<b>MA Holder</b>	Medimpex UK Limited
<b>RMS</b>	United Kingdom
<b>CMS</b>	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Lithuania, Luxembourg, The Netherlands, Norway, Poland, Portugal, Spain and Sweden
<b>Procedure Number</b>	UK/H/803/01
<b>Timetable</b>	Day 90 1/11/2005

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1. NAME OF THE MEDICINAL PRODUCT

Levonelle 1500 microgram tablet

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The tablet contains 1500 microgram of levonorgestrel.  
For excipients see section 6.1.

#### 3. PHARMACEUTICAL FORM

Tablet

The tablet is round and white with an impressed mark of “G00 on one 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 use. 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 vomiting occurs within three hours of taking the tablet, another tablet should be taken immediately.

Levonelle 1500 can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

After using emergency contraception it is recommended to use a barrier method (e.g. condom, diaphragm or cap) until the next menstrual period starts. The use of Levonelle 1500 does not contraindicate the continuation of regular hormonal contraception.

*Children:* Levonelle 1500 is not recommended in children.

Very limited data are available in women under 16 years of age.

### 4.3 Contraindications

Hypersensitivity to the active substance levonorgestrel or any of the excipients.

### 4.4 Special warning 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 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 Levonelle 1500 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 excluded.

If pregnancy occurs after treatment with Levonelle 1500, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as Levonelle 1500 prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

Therefore, Levonelle 1500 is not recommended for patients who are at risk of ectopic pregnancy (previous history of salpingitis or of ectopic pregnancy).

Levonelle 1500 is not recommended in patients with severe hepatic dysfunction.

Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of Levonelle 1500.

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.

After Levonelle 1500 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 be advised to make a medical appointment to initiate or adopt a method of regular contraception. If no withdrawal bleed occurs in the next pill-free period following the use of Levonelle 1500 after regular hormonal contraception, pregnancy should be ruled out.

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

Levonelle 1500 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.

### 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.

Drugs suspected of having the capacity to reduce the efficacy of levonorgestrel containing medication include barbiturates (including primidone), phenytoin, carbamazepine, herbal medicines containing *Hypericum perforatum* (St. John's Wort),

rifampicin, ritonavir, rifabutin, griseofulvin.

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

#### 4.6 Pregnancy and lactation

Pregnancy

**Levonelle 1500 should not be given to pregnant women. It will not interrupt a pregnancy. In the case of continued pregnancy, limited epidemiological data indicate no adverse effects on the fetus 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.).**

Lactation

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 following Levonelle 1500 administration.

#### 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. The following undesirable effects were observed in two different studies<sup>1, 2</sup>.

*Reproductive system and breast disorders*

Very Common (>1/10): Bleeding not related to menses\*

Common (>1/100, <1/10): Delay of menses more than 7 days \*\*,  
Irregular bleeding and spotting

*Nervous system disorders*

Very Common (>1/10): Headache

Common (>1/100, <1/10): Dizziness

*Gastrointestinal disorders*

Very Common (>1/10): Nausea, Low abdominal pain

Common (>1/100, <1/10): Diarrhoea, Vomiting

*Reproductive system and breast disorders*

Common (>1/100, <1/10): Breast tenderness

*General disorders and administration site conditions*

Very Common (>1/10): Fatigue

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.

<sup>1</sup> Task Force on post-ovulatory Methods of Fertility Regulation. Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet*, 1998; 352:428-

433

(n=977; data on 0.75 mg levonorgestrel tablet taken as two doses with a 12-hour interval)

<sup>2</sup> Herten et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. Lancet. 2002; 360:1803-1810

(n=1,359; data on Levonelle 1500 taken as a single dose of 1.5 mg)

\* n=1,011 out of 1,359

\*\* n=1,334 out of 1,359

*From Post-marketing surveillance additionally, the following adverse events have been reported:*

*Skin and subcutaneous tissue disorders*

Very rare (<1/10,000): rash, urticaria, pruritus, face edema

## 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:

**PROGESTOGENS**

**ATC code: G03AC03**

The precise mode of action of Levonelle 1500 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 preovulatory phase, when the likelihood of fertilisation is the highest. It may also cause endometrial changes that discourage implantation. Levonelle 1500 is not effective once the process of implantation has begun.

*Efficacy.*

Results from a recent clinical study (Lancet 2002; 360: 1803-1810) showed that a 1500 microgram single dose of levonorgestrel (taken within 72 hours of unprotected sex) prevented 84% of expected pregnancies (compared with 79% when the two 750 microgram tablets were taken 12 hours apart).

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

### 5.2 Pharmacokinetic properties

Levonorgestrel: orally administered levonorgestrel is rapidly and almost completely absorbed.

Following ingestion of one tablet of Levonelle 1500 maximum drug serum levels of levonorgestrel of 18.5 ng/ml were found at 2 hours. 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. The biotransformation follows the known pathways of steroid metabolism, the levonorgestrel is hydroxylated in the liver and the metabolites are excreted as glucuronide conjugates. No pharmacologically active metabolites are known.

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.

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

About 0.1% of the maternal dose can be transferred via milk to the nursed infant.

### **5.3 Preclinical safety data**

Animal experiments with levonorgestrel have shown virilisation of female fetuses 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 section of the SPC.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Potato starch,  
Maize starch,  
Colloidal silica anhydrous,  
Magnesium stearate,  
Talc,  
Lactose monohydrate.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

### **6.4 Special precautions for storage**

Store in original packaging in order to protect from light.

### **6.5 Nature and contents of container**

PVC/Aluminium-blister containing one tablet. The blister is packaged in a folded carton.

### **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

- 8.     MARKETING AUTHORISATION NUMBER**
  
- 9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**
  
- 10.    DATE OF REVISION OF THE TEXT**

## **Module 3**

# **Product Information Leaflet**

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 1

**Levonelle® 1500**  
Levonorgestrel 1500 microgram tablet

**SCHERING**

Hauptpharma AG

Karl-Ludwig-Str. 29  
D-65205 Wiesbaden  
Tel. +49 6381 39-111  
Fax +49 6381 39-3333  
E-Mail: info@levonelle.com

Distributors: **Novartis (UK) Limited**  
One Watlington Way  
Watlington, Oxford OX4 9DQ  
Tel: +44 (0)1865 861100  
Fax: +44 (0)1865 861101  
E-mail: novartis@novartis.co.uk

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 1

▶ **Levonelle® 1500** microgram tablet  
This booklet tells you about your Levonelle 1500 tablet. Please read it carefully as it contains important information and keep it in a safe place as you may like to read it again if there is

---

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 9

**2 Product licence holder and manufacturer**  
The product licence holder is Novartis UK Limited  
137 Stratford Road  
London  
W5 2ER

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 9

▶ **If you are worried about security**

5 How to take Levonelle 1500

- ▶ Take one tablet every day
- ▶ Take it at the same time every day
- ▶ Take it with or without food
- ▶ Take it with water

---

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 9

Levonelle 1500 is made by:  
Schering AG or Schering GmbH & Co.  
Berlin  
Germany  
Mölnbeim  
Germany  
MS 2ER

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 9

▶ **After you have taken Levonelle 1500**

7 What are the possible side effects?

8 Where to keep your Levonelle 1500

9 Further information

---

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 10

Levonelle 1500 is distributed in the UK by:  
Schering Health Care Limited  
The Brook  
Burgess Hill  
West Sussex  
BN15 2NE

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 10

▶ **What is in this booklet?**

1 What is Levonelle 1500?

2 How does Levonelle 1500 work?

3 How does Levonelle 1500 work?

4 What to tell your doctor...

5 How to take Levonelle 1500

6 What to do if you are worried about security

7 What are the possible side effects?

8 Where to keep your Levonelle 1500

9 Further information

---

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 12

**3 How does Levonelle 1500 work?**  
Levonelle 1500 prevents about 99% of expected pregnancies when taken within 72 hours of unprotected sex.  
Levonelle 1500 will not prevent a pregnancy if every residue that the tablet is made effective the

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 12

▶ **What to tell your doctor...**

- ▶ If you are pregnant
- ▶ If you are on any other medicine
- ▶ If you are taking any other medicines

---

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 12

▶ **What to tell your doctor...**

- ▶ If you are pregnant
- ▶ If you are on any other medicine
- ▶ If you are taking any other medicines

7564593\_3.qxd 24.07.2004 9:44 Uhr Seite 12

▶ **What to tell your doctor...**

- ▶ If you are pregnant
- ▶ If you are on any other medicine
- ▶ If you are taking any other medicines

75646593\_R\_004 24.07.2004 9:44 Uhr Seite 1

**Levonelle® 1500**  
Levonorgestrel 1500 microgram Tablet



**2 Product licence holder and manufacturer**

The product licence holder is Mediplex UK Limited  
127 Ferndale Road  
London  
W5 2EP

75646593\_R\_004 24.07.2004 9:44 Uhr Seite 2

anything that you do not understand or if you need to know anything else, you should ask your pharmacist, doctor, practice nurse or family planning clinic.

**2**

75646593\_R\_004 24.07.2004 9:44 Uhr Seite 3

**1. What is this tablet?**

Levonelle 1500 is an emergency contraceptive that can be used after unprotected sex or where a contraceptive method has failed. This type of contraceptive is often called the 'morning-after pill'. Each pack of Levonelle 1500 contains a complete

**3**

75646593\_R\_004 24.07.2004 9:44 Uhr Seite 4

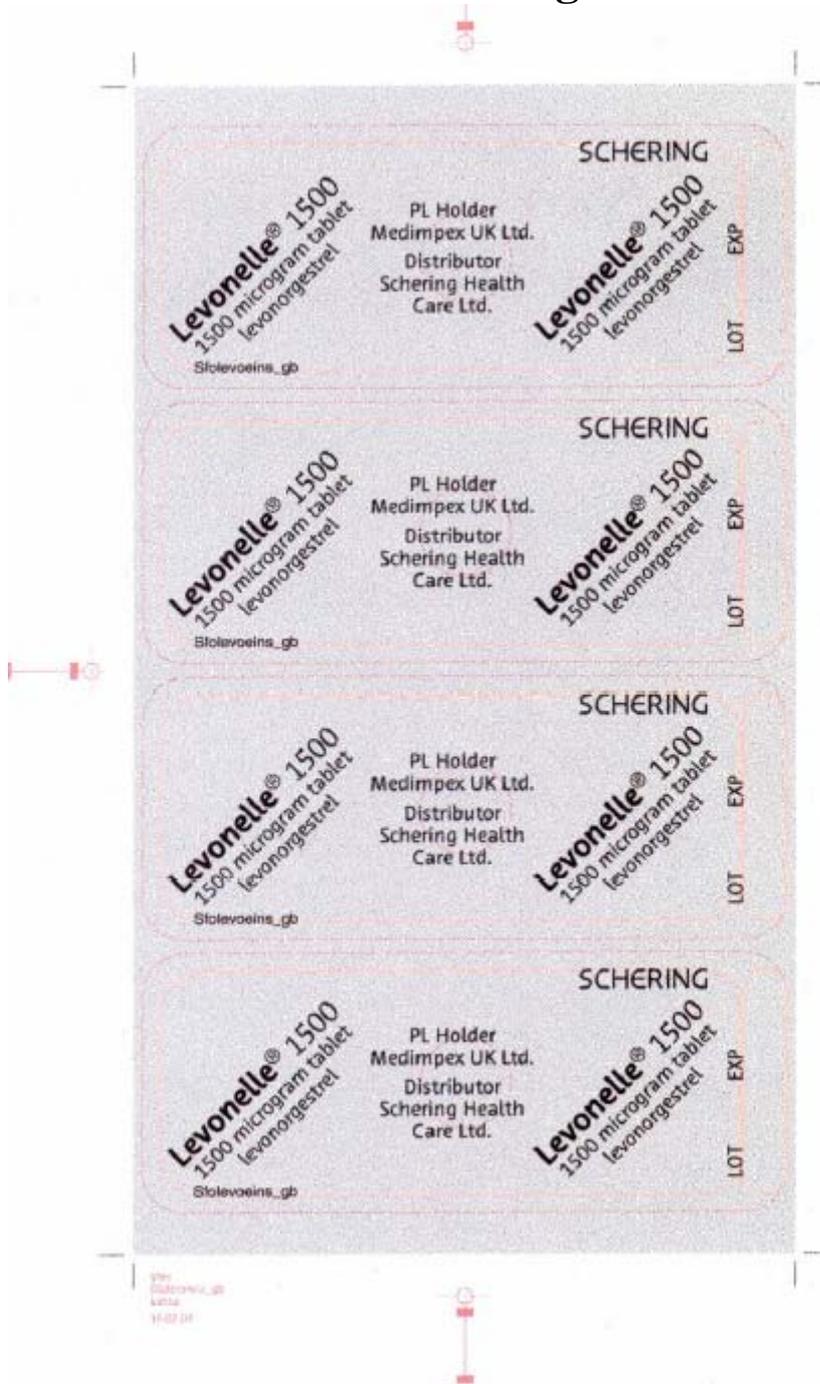
**3 How does Levonelle 1500 work?**

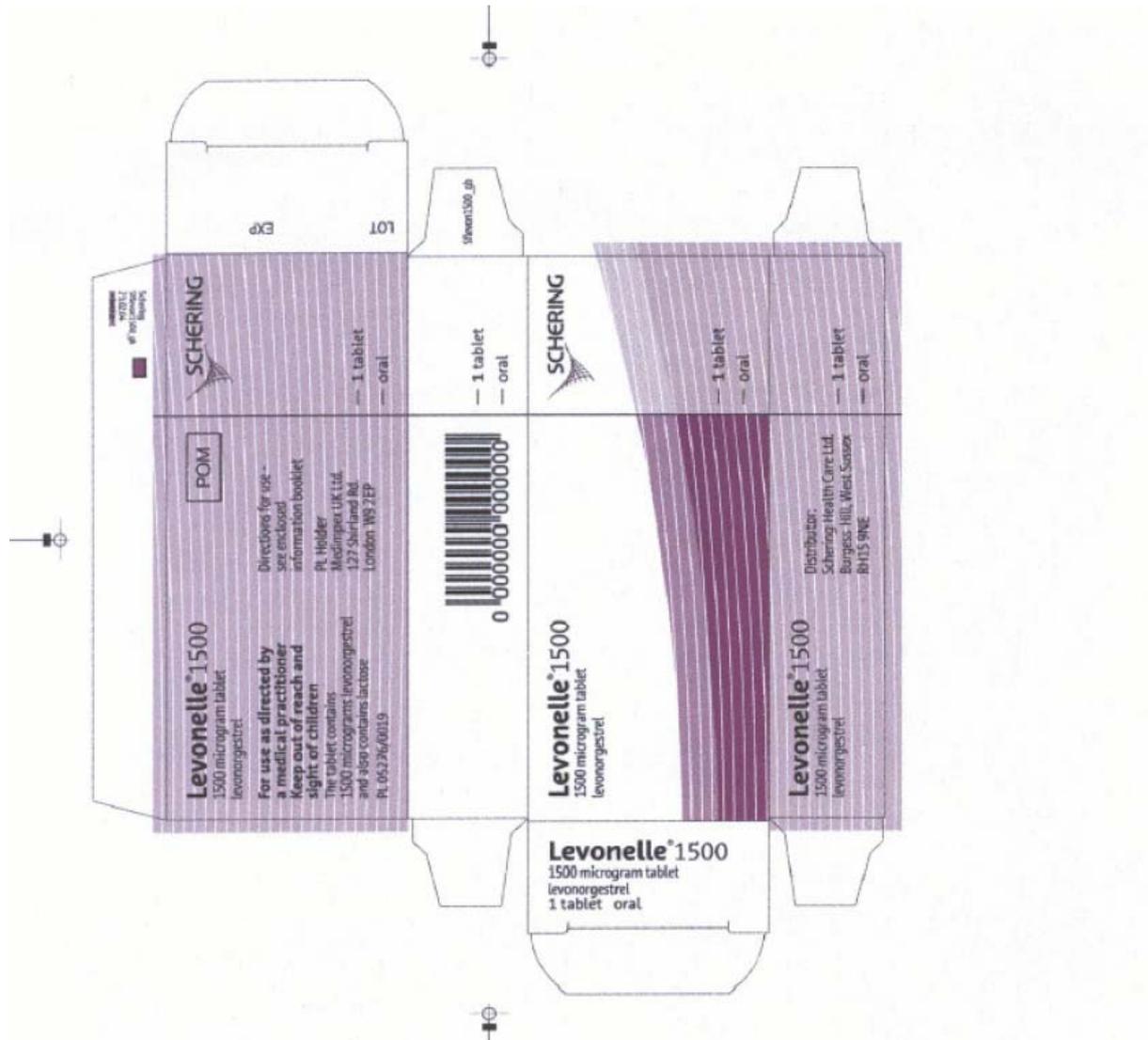
Levonelle 1500 prevents about 85% of expected pregnancies when it is taken within 72 hours (3 days) of unprotected sex. Levonelle 1500 will not prevent a pregnancy in every instance but the tablet is more effective the

<p>7564693_3.qxd 24.02.2004 9:44 Uhr 9a11e112</p> <p><b>Deliver your emergency contraception as soon as possible after unprotected sex. It is better to take it within 72 hours rather than delay until the third day.</b></p> <p>Levonelle 1500 is thought to work by:</p> <ul style="list-style-type: none"> <li>▶ stopping your ovaries from releasing an egg</li> <li>▶ preventing sperm from fertilising any egg you may have already released, or</li> </ul>	<p>51</p> <p>▶ your period is late, or your last period was irregular at all</p> <ul style="list-style-type: none"> <li>▶ you have had unprotected sex which was more than 72 hours ago, and since your last period (if pregnancy may have already occurred and the treatment won't work)</li> <li>▶ you have a degree of your small bowel such as</li> </ul>	<p>52</p> <p>▶ stopping a fertilised egg from attaching itself to your womb or ovary</p> <p>▶ Levonelle 1500 stops a pregnancy before it is established. It does not work if you are already pregnant.</p>	<p>53</p> <p><b>4 Before you take Levonelle 1500</b></p> <p>When you should not use Levonelle 1500 go on red, and Levonelle 1500 is not for you if you are allergic to any of the ingredients of this medicine</p>
<p>7564693_3.qxd 24.02.2004 9:44 Uhr 9a11e112</p> <p><b>Deliver your emergency contraception as soon as possible after unprotected sex. It is better to take it within 72 hours rather than delay until the third day.</b></p>	<p>57</p> <p>If any of these apply to you, Levonelle 1500 may not be suitable for you, or other types of emergency contraception may be better for you.</p> <p><b>If you are pregnant</b></p> <p>You should not take this medicine if you are already pregnant. If you have had unprotected sex which was more than 72 hours ago, and already pregnant, it is important that you see your doctor.</p>	<p>58</p> <p>Colony's disease. It can interfere with the digestion of your food</p> <ul style="list-style-type: none"> <li>▶ you have been told by your doctor that you have an intestinal or some signals, as Levonelle 1500 contains 142.5 mg lactose</li> <li>▶ you have severe liver problems</li> <li>▶ you are taking any of the medicines listed</li> </ul>	<p>59</p> <p>Below are these medicines may prevent Levonelle 1500 from working properly</p> <ul style="list-style-type: none"> <li>- barbiturates and other medicines used to treat epilepsy (for example, phenytoin, phenobarbital, and carbamazepine)</li> <li>- medicine used to treat tuberculosis (for example, rifampicin, rifabutin)</li> </ul>
<p>7564693_3.qxd 24.02.2004 9:44 Uhr 9a11e112</p> <p><b>Deliver your emergency contraception as soon as possible after unprotected sex. It is better to take it within 72 hours rather than delay until the third day.</b></p>	<p>61</p> <p>There is no evidence that Levonelle 1500 will have a long-term effect on your fertility. However, if you are pregnant or have just become pregnant, you should see your doctor. If you do become pregnant after taking this medicine, it is important that you see your doctor.</p>	<p>62</p> <p>If you are taking any other medicines tell your doctor if you are taking any of the medicines listed in the section "What to tell your doctor".</p> <p>If you are not sure about anything, check with your pharmacist, doctor, practice nurse or family planning clinic.</p>	<p>63</p> <p><b>5 How to take Levonelle 1500</b></p> <ul style="list-style-type: none"> <li>▶ Take the tablet as soon as possible, preferably within 12 hours of unprotected sex.</li> <li>▶ If you have had unprotected sex, swallow the tablet whole with water if necessary. Do not chew, crush or break the tablet. The</li> </ul>
<p>7564693_3.qxd 24.02.2004 9:44 Uhr 9a11e112</p> <p><b>Deliver your emergency contraception as soon as possible after unprotected sex. It is better to take it within 72 hours rather than delay until the third day.</b></p>	<p>65</p> <p>not thought to be harmful to the baby, but if you are worried you can take your tablet immediately after a breast-feed. In this way you are taking your tablet well before the next feed and reducing the amount of active ingredient your baby may take in with the breast milk.</p>	<p>66</p> <p>If you are worried about sexually transmitted diseases this medicine will not protect you against sexually transmitted diseases, only condoms can do this. Ask your doctor, nurse, family planning clinic or pharmacist for advice if you are worried about this.</p>	<p>67</p> <p><b>What to tell your doctor</b></p> <p>If any of these apply to you, tell your doctor before you take Levonelle 1500 as emergency contraception may not be suitable for you.</p> <ul style="list-style-type: none"> <li>▶ you are pregnant or think you may already be pregnant</li> </ul>
<p>7564693_3.qxd 24.02.2004 9:44 Uhr 9a11e112</p> <p><b>Deliver your emergency contraception as soon as possible after unprotected sex. It is better to take it within 72 hours rather than delay until the third day.</b></p>	<p>68</p> <p>stop pregnancy, fetal pain like surgery or placental infarction disease.</p> <p>When to take special care with Levonelle 1500</p> <p>If you are breast-feeding</p> <p>Very small amounts of the active ingredient of this medicine may appear in your breast milk. This is</p>	<p>69</p> <p>stop pregnancy, fetal pain like surgery or placental infarction disease.</p> <p>When to take special care with Levonelle 1500</p> <p>If you are breast-feeding</p> <p>Very small amounts of the active ingredient of this medicine may appear in your breast milk. This is</p>	<p>70</p> <p>stop pregnancy, fetal pain like surgery or placental infarction disease.</p> <p>When to take special care with Levonelle 1500</p> <p>If you are breast-feeding</p> <p>Very small amounts of the active ingredient of this medicine may appear in your breast milk. This is</p>

# Module 4

## Labelling





## Module 5

### Scientific discussion during initial procedure

#### 1 Introduction

The company has provided the following Product Profile:

Levonelle 1500 microgram tablets were granted a Market Authorisation in accordance with Commission Regulation (EC) No 541/95 Annex II 3 (iii). Levonorgestrel 1.5 mg tablet is a progestogen only emergency contraceptive. The initial product is 0.75 mg levonorgestrel emergency contraceptive (Levonelle, Postinor-2, Postinor, Postinor Duo).

#### *Chemical and pharmacokinetic properties*

The composition of the preparation is the following:

- 1.5 mg levonorgestrel in each tablet

Levonorgestrel (Fig.1.) is a progestin type steroid substance.

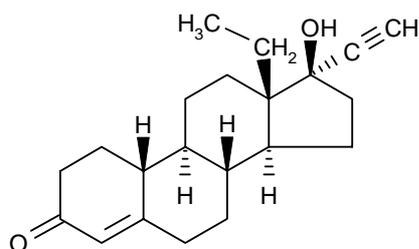


Figure 1.

Chemical Abstracts Registry Number: [797-63-7]

13-Ethyl-17-hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one

Levonorgestrel is a white or almost white, crystalline powder, practically insoluble in water, sparingly soluble in methylene chloride, slightly soluble in alcohol. The finished product is a conventional immediate release tablet for oral administration.

#### *Indication*

Emergency contraception. One tablet should be taken within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

The term 'emergency contraception' refers to contraceptive methods that women can use after unprotected intercourse to prevent pregnancy. Results of studies (Ho and Kwan; WHO/HRP 1998 - Study 92908) sponsored by Programme of Research, Development and Research Training in Human Reproduction (HRP) of WHO proved that levonorgestrel was an effective emergency contraceptive with a favourable safety profile. Based on these results WHO/HRP designed and sponsored a multicenter, double-blind, randomized, controlled trial to compare the efficacy and side effects of three types of hormonal method of emergency contraception. Women requesting emergency contraception were given either single dose of 10 mg mifepristone or two doses of 0.75 mg levonorgestrel taken 12 hours apart or single dose of 1.5 mg levonorgestrel. The regimens were given within 120 hours after unprotected intercourse. It was found that the two levonorgestrel regimens have similar efficacy and side effects profile. The major clinical advantage of the single dose of 1.5 mg levonorgestrel is that it simplifies the treatment and may improve acceptability and compliance.

*The pharmacological and therapeutic classification of the active substance, defining the mode of action*

Levonorgestrel is a gestagen (19-nortestosterone derivate). It has a strong progestational and no estrogenic activity. The precise mode of action of 1.5 mg of levonorgestrel is not known. At the recommended regimen, levonorgestrel is thought to work mainly by preventing ovulation and fertilisation if the intercourse has taken place in the preovulatory phase, when the likelihood of fertilisation is the highest. It may also cause endometrial changes that discourage implantation. It is not effective once the process of implantation has begun.

*Precautions*

Emergency contraception is an occasional method. It should in no instance replace a regular contraceptive method. Emergency 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 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 excluded.

If pregnancy occurs after treatment, the possibility of an ectopic pregnancy should be considered, especially in those women who present with abdominal/pelvic pain or collapse and those with a history of ectopic pregnancy, fallopian tube surgery or pelvic inflammatory disease. The preparation is not recommended to patients with severe hepatic dysfunction. Severe malabsorption syndromes, such as Crohn's disease, might impair the efficacy of the preparation. Menstrual periods sometimes occur earlier or later than expected by a few days. It is recommended to make a medical appointment to initiate or adapt a method of regular contraception. If no menstrual period occurs in the next pill-free period following the use of the preparation after regular hormonal contraception, pregnancy should be ruled out. 1.5 mg of levonorgestrel 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.

*List of any post-marketing surveillance*

There were eleven Periodic Safety Update Reports, and three Summary Bridging Safety Reports on 0.75 mg levonorgestrel emergency contraceptive tablets compiled for Regulatory Authorities by Gedeon Richter Ltd. These reports summarised all relevant safety data received by Medical Affairs of Gedeon Richter Ltd. from world-wide sources during the period of 1993-2004.

*Marketing authorisation*

The initial product (0.75 mg levonorgestrel tablet) is on the market in most of the EU countries and several other countries all over the world including the USA, Africa, Far- and Middle-East.

## Background

This application was submitted by Medimpex UK Limited based upon Mutual Recognition of United Kingdom Product Licence (UK MA PL 05276/0019 ) held by the applicant, which was approved on 14<sup>th</sup> June 2004.

Levonelle is indicated for: *Emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.*

The applicant now has Marketing Authorisation in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Lithuania, Luxembourg, The Netherlands, Czech Republic, Norway, Poland, Portugal, Spain and Sweden. The product names are:

Concerned member states	Product Name
<b>Austria</b>	Postinor Tablette 1500 Mikrogramm
<b>Belgium</b>	Postinor 1500 microgram comprimé Postinor 1500 microgram tablet
<b>Czech Republic</b>	Escapelle tablety
<b>Denmark</b>	Levonelle tabletter 1500 mikrogram
<b>Finland</b>	Postinor 1500 mikrogram tabletti
<b>France</b>	Levonelle 1500microgram comprimé
<b>Germany</b>	Levogynon Tablette 1500 Mikrogramm
<b>Greece</b>	Postinor 1500 microgram tablet
<b>Iceland</b>	Postinor 1.5 mgtaflan
<b>Ireland</b>	Levonelle 1500 microgram tablet
<b>Italy</b>	Levonelle 1500 microgrammi compresse
<b>Luxembourg</b>	Postinor 1500 microgram tablet
<b>Lithuania</b>	Escapelle tablettes
<b>The Netherlands</b>	Postinor 1500 microgram tablet
<b>Norway</b>	Postinor 1.5 mg tabletter
<b>Poland</b>	Escapelle tabletki 1500 mikrogramów
<b>Portugal</b>	Levonelle-1 1500 microgramas comprimido
<b>Spain</b>	Postinor-1 1500 microgramos comprimido
<b>Sweden</b>	Postinor 1.5 mg tablett

### *Overall Benefit/Risk Assessment*

No new preclinical studies were conducted, which is acceptable given that this product is a direct scale-up of the Levonelle 750 microgram already well established in clinical use.

Clinical studies on Levonelle were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Levonelle provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All product related texts (SPC, PIL and labels) are satisfactory from the clinical, preclinical and pharmaceutical point of view for a product of this nature.

The quality of the product is satisfactory in relation to its safety and efficacy. The data have demonstrated the efficacy and safety of the product to the extent that the overall risk/benefit of the product is favourable for the proposed indications.

## 2. Quality Aspects

Composition and function of ingredients

Ingredient	Function	Reference Standard
Levonorgestrel	Active ingredient	Ph Eur
Silica, colloidal anhydrous	Glidant	Ph Eur
Magnesium stearate	Lubricant	Ph Eur
Talc	Glidant	Ph Eur
Potato starch	Binder	Ph Eur
Maize starch	Diluent	Ph Eur
Lactose monohydrate	Diluent	Ph Eur

This product is a direct scale-up of the Levonelle 750microgram formulation marketed throughout Europe. The formulation is based on conventional excipients and consists mainly of lactose monohydrate and maize starch as diluents. Further ingredients are talc and colloidal anhydrous silica as glidants, potato starch as a binding agent and magnesium stearate as a lubricant. The product is presented in aluminium/PVC blister packs.

### CLINICAL TRIAL BATCH

The efficacy of a single dose of 1500micrograms levonorgestrel was tested in a randomised, double-blind, multinational study by WHO in 1998. The formulation in the WHO study was two Postinor-2 tablets of 750micrograms levonorgestrel taken as a single dose. The initial formulation was changed to delete gelatine and replace it with a small amount of maize starch.

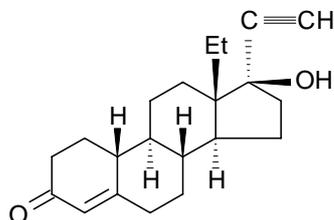
### Development Pharmaceutics

The rationale for this application is to enable the therapeutic dosage of levonorgestrel to be administered as a single tablet rather than the existing two tablet regimen. The Applicant is of the view that this would simplify the treatment and increase compliance and acceptability. Ensuring that both tablets were actually taken would decrease the failure of this mode of emergency contraception.

Three full scale production batches of the 1500microgram tablet have been manufactured in accordance with the manufacturer's Validation Master Plan and Process Validation Plan.

### 3. Control Of Starting Materials

#### 3.1 Active substances - Levonorgestrel (rINN) - D-Norgestrel



13 $\beta$ -ethyl-17 $\beta$ -hydroxy-18,19-dinor-17 $\alpha$ -pregn-4-en-20-yn-3-one  
C<sub>21</sub>H<sub>28</sub>O<sub>2</sub> MW: 312.5

Practically insoluble in water, soluble in chloroform, sparingly soluble in ethanol and methylene chloride. Levonorgestrel has six asymmetric carbons and therefore theoretically 64 isomers. Only the D,L-Norgestrel and Levonorgestrel (D-Norgestrel) forms are used in pharmaceutical products. No evidence of polymorphism has been seen. Levonorgestrel melts in the range 232-239°C.

The active ingredient is manufactured by and complies with the European Pharmacopoeia monograph for levonorgestrel. The active ingredient is covered by a Certificate of Suitability.

The CEP certifies that the quality of the substance is suitably controlled by the current Ph Eur monograph when supplemented by the following tests for related substances and residual solvents. A retest period of 5 years has been assigned to the active substance when stored in double polyethylene bags, sealed and placed into fibre drums, protected from light.

The product is manufactured according to GMP principles and appropriate certificates have been provided.

#### 3.2 other ingredients

##### TSE aspects

Confirmation has been provided that lactose monohydrate (manufactured from whey with calf rennet), is obtained from milk sourced from healthy cows in the same conditions as milk obtained for human consumption. The magnesium stearate is certified as of vegetable origin.

#### 3.3 Packaging Material (Immediate Packaging)

Satisfactory specifications have been provided for the PVC and hard aluminium foil used in manufacture of the blister packs. Representative Certificates of Analysis have been provided for typical batches of the packaging components.

### 4. Control Tests On Intermediate Products

No intermediate products are formed.

## **5. Control Tests On The Finished Medicinal Product**

### **General Description of Tests performed on the Finished Product**

1. Standard pharmacopoeial tests for friability, hardness and uniformity were carried out on Levonelle tablets
2. The amount and purity of the active substance was also determined
3. Standard pharmacopoeial tests for disintegration, dissolution and uniformity of content were also carried out.

## **6. Stability**

### **Stability tests on the finished medicinal product**

The shelf-life for Levonelle 1500 microgram Tablets is 2 years when stored in the original container with no specific temperature conditions. Data has been provided to support the proposed shelf-life and parameters tested include: appearance, disintegration, dissolution, assay, and related substances.

## **7. Bioequivalence**

Bioequivalence was investigated comparing 1500 microgram Levonelle Tablets with 2 x 750 microgram Levonelle in a pharmacokinetic study. Bioequivalence was demonstrated satisfactorily.

## **8. Expert Report**

The report is satisfactory

## **9. Summary Of Product Characteristics**

The SPC is satisfactory see Module 2 of this Public Assessment Report.

## **10. Discussion / Conclusions**

This applicant seeks marketing authorisations for a new strength of Levonelle which will allow the therapeutic dose to be administered as a single tablet rather than two 750 microgram tablets. The formulation is a direct scale-up of the lower strength tablet and uses the same manufacturing process. Production scale batches have already been manufactured and there are no concerns about the manufacturing process.

The active ingredient complies with the Ph Eur monograph for levonorgestrel and is covered by a CEP with additional tests and limits for residual solvents and impurities. The CEP authorises a re-test period of 5 years.

The finished product specification is in line with that for the lower strength and is satisfactory.

Sufficient stability data have been presented for this strength to support the 2 year shelf-life.

A pharmacokinetic study has been undertaken comparing the 1500 microgram tablet with 2 750 microgram tablets. Comparative dissolution data have been presented for the batches used in the pharmacokinetic study.

A market authorisation was granted.

### **PART III PRECLINICAL ASSESSMENT**

No new preclinical studies were conducted, which is acceptable as this product is a direct scale up of Levonelle -2 tablet of 750 micrograms levonorgestrel content..

## Clinical Aspects

### 1. INTRODUCTION

This marketing authorisation is for the emergency contraceptive, Levonelle 1500 microgram tablets, containing levonorgestrel (LNG) as the active substance.

A type II variation was granted for Levonelle tablets authorising the updated posology of taking two 750 microgram tablets at the same time rather than 12 hours apart. This product simplifies the regimen as the patient would be required to take just one tablet instead of two.

The application was submitted in accordance with Article 8.3(i) of Directive 2001/83/EC.

The application was submitted by Medimpex UK Ltd.

### 2. BACKGROUND

Emergency contraception is used as an emergency procedure to prevent pregnancy following unprotected coitus and is not a routine approach to contraception.

Levonelle 1500 microgram tablets, because they involve administration of a single tablet, rather than two tablets, are considered to have the advantage of being more acceptable to the patient and are likely to be associated with better compliance and hence efficacy.

### 3. INDICATIONS

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

### 4. DOSE & DOSE SCHEDULE

For oral administration: 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 vomiting occurs within three hours of taking the tablet, another tablet should be taken immediately.

Levonelle 1500 can be used at any time during the menstrual cycle unless menstrual bleeding is overdue.

After using emergency contraception it is recommended to use a barrier method (e.g. condom, diaphragm or cap) until the next menstrual period starts. The use of Levonelle 1500 does not contraindicate the continuation of regular hormonal contraception.

Children: Levonelle 1500 is not recommended in children.  
Very limited data are available in women under 16 years of age.

## 5. TOXICOLOGY

There are no new toxicological issues.

## 6. CLINICAL PHARMACOLOGY

### PHARMACOKINETICS

The Pharmacokinetics for LNG has previously been discussed in the Levonelle dossier.

### PHARMACODYNAMICS

ATC-CODE: G03AC03

(Hormonal contraceptives for systemic use, progestogens)

#### Mode of Action

The mechanism of action has not been fully elucidated and post-coital administration of LNG may interfere with any or some of the following, and may depend on the phase of the cycle in which treatment is given:

- Ovulation
- Release of pituitary gonadotrophins
- Sperm transport through cervical mucus and fallopian tubes
- Implantation.

The Clinical Expert Report (CER) summarises published studies which indicate that postcoital administration of high doses of LNG suppress or delay ovulation if given early enough in the cycle. However, other published studies have demonstrated an alteration in endometrial histology which might inhibit implantation via an effect on factors required for implantation such as integrins and steroid receptors. This is an area of on-going research and a study is being conducted in Chile looking at the effects of a single dose of 1500 microgram of LNG on follicular growth and ovulation.

Studies have shown little effect on sperm function at the proposed LNG dose.

Whatever the precise mechanism, there is good evidence that emergency contraception works prior to fertilisation as studies, including the WHO/HRP 1998 – Study 97902, show that efficacy is inversely related to the elapsed time since unprotected intercourse, the cut-off for protection being around 4/5 days post coitus.

### BIOEQUIVALENCE

The PK profile of the single 1500 microgram tablet was compared with that of the established regimen, namely two 750 microgram tablets given 12-hours apart.

A single-centre, open-label, randomised, cross-over bioequivalence study was carried out. The PK profile of the single 1500 microgram tablet was compared with that of the established regimen, namely two 750 microgram tablets given 12-hours apart.

16 healthy women aged between 18 and 35 years were enrolled and the study was divided into two study periods of 10 days each, which were separated by an adequate 28-day washout period.

Dosing was conducted after an overnight fast and blood samples were taken pre-dose, then at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, and 216 hours post-dose. The following PK parameters were derived:  $C_{max}$ ,  $T_{max}$ ,  $K_{el}$ ,  $T_{1/2el}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ , and residual area.

The data show that under fasting conditions, one 1500 microgram LNG tablet demonstrates a higher rate but slightly lower extent of absorption, compared to two 750 microgram LNG tablets taken 12 hours apart. In this study both formulations were well tolerated, with no serious adverse events, and no relevant differences in safety profiles were observed between the preparations, particularly with respect to the number and pattern of adverse events.

*Assessor's comment: as the Pivotal Study (discussed in Section 3) did not show any difference between the efficacy or safety of LNG 750 microgram tablet and LNG 1500 microgram tablet the Applicant does not consider the difference in PK profile between the two regimens is clinically relevant and the assessor concurs with this.*

## **EFFICACY**

### **Introduction**

There have been no formal dose-ranging studies for LNG emergency post-coital contraception. Early efficacy studies showed acceptable crude failure rates using doses between 0.6 to 1.0mg. The ovulation inhibition dose, i.e. the dose of contraceptive steroid which prevents ovulation in all women when given alone on a daily basis, is 0.06mg/day for LNG or 1.68mg/cycle of 28 days. This is approximately equal to 1500 microgram LNG, the established dose for the previously registered products Levonelle 750 microgram tablets and Levonelle-2 tablets (the only change being that one 1500 microgram tablet, rather than two containing 750 microgram each, is proposed in this application).

This application is supported by a Pivotal WHO/HRP-sponsored study. The study was designed to find emergency contraception which would be better tolerated and more effective than currently available methods. The study was based on the findings from two previous trials, also conducted by WHO/HRP:

Project 92903 – single dose of 10mg mifepristone was effective

Project 92908 – LNG given as two 750 microgram doses 12 hours apart was more effective than the Yuzpe regimen

and the consensus that a single-dose of 1500 microgram LNG would be more convenient and more likely to be complied with (and hence more effective) compared with two 750 microgram tablets 12 hours apart.

In addition, the results of a supportive Nigerian study are also supplied.

## Pivotal Efficacy Trial

### WHO/HRP Project 97902

#### Methods

This was a double-blind, randomised study conducted in 15 centres in Sweden, India, Hungary, Slovenia, Switzerland, Hong Kong, UK, China, USA, Mongolia and Finland.

#### Study Participants

Young women who required emergency contraception following unprotected coitus.

##### *Inclusion criteria:*

- within 120 hours (5 days) of unprotected coitus.
- only one act of unprotected coitus during the current cycle
- negative pregnancy test
- regular spontaneous cycles (24 – 42 days)
- in those who had recently discontinued hormonal contraception or who had a recent abortion or delivery - at least one spontaneous cycle of normal length before the current cycle
- willing to terminate the pregnancy if treatment failed

##### *Exclusion criteria:*

- pregnant or breast feeding
- using hormonal methods of contraception during the current cycle (i.e. those requesting emergency contraception after forgetting to take one or more contraceptive pills)
- rhythm or ovulation method of natural family planning
- coitus earlier in the same cycle
- unsure of date of last menstrual period
- Those in whom study drug was contra-indicated (adrenal pathology, steroid-dependence, cancer)

#### Treatments

Patients were randomly allocated to one of three treatment groups:

- Group 1 – 1500 microgram LNG
- Group 2 – 2 x 750 microgram LNG, administered 12 hours apart
- Group 3 – 10mg mifepristone

#### Objectives

To compare the efficacy and safety of the three treatment regimens.

#### Outcomes/endpoints

*Efficacy:* The primary endpoint was unintended pregnancy, as determined by pregnancy rate and prevented fraction.

*Safety:* incidence of side-effects expressed as the %age of women reporting an adverse events within 7 days of treatment.

## Sample Size

This was based on previous studies involving emergency contraception and was planned to be large enough to show a clinically relevant difference between treatments, if it existed. It was calculated that, assuming a 2.9% failure rate in the LNG group, a sample size of 1,340 subjects per group (total 4,020) would give an 80% power to detect a significant difference at the 5% level. For practical reasons the recruitment target for the whole study was 4,200 women i.e. 1,400 per treatment group (providing a power of 82%).

## Statistical methods

Demographic and other baseline characteristics were summarised descriptively for the ITT population (number of women, number of missing values, minimum and maximum values, means, standard deviations).

To compare efficacy, the ratio of observed to expected pregnancies, the prevented fraction and its 95% confidence interval in each group and relative risks were calculated.

The prevented fraction, defined as the proportion of expected pregnancies prevented by the treatment, was calculated as  $100 \times [1 - (\text{number of observed pregnancies} / \text{number of expected pregnancies})]$ . The expected number was calculated by multiplying the number of women having unprotected coitus on each cycle day by the estimated probability of conception on that day.

The cycle day was determined relative to the estimated day of ovulation, which was defined by subtracting 14 days from the expected date of the next menstrual period. The risk at different days of the cycle was taken as the conception probabilities obtained by the two methods of Dixon et al 1980 and Wilcox et al 1995 – modified to restrict conception probabilities to non-chemical pregnancies (Trussel et al 1998).

The comparison between observed and expected numbers of pregnancies was made using the indirect method of standardisation as described by Gardner and Altman in 1989 by dividing the number of observed pregnancies by the expected number and calculating its 95% CI using a Poisson distribution.

For safety assessment, numbers and percentages of women with adverse events were calculated by group for all centres combined using chi-square (see Section 8.Safety).

No adjustments for covariates were planned or performed during the study.

Missing values were not imputed in the statistical analysis.

## RESULTS

### Recruitment and Participant flow

See Table 3. A total of 4,200 subjects were planned and 4,136 were enrolled (122-447 per centre). They were randomised to receive study medication as follows:

- 1,379 - LNG 1500 microgram x 1 dose
- 1,377 – LNG 750 microgram x 2
- 1,380 – mifepristone

All received the first dose of treatment. Overall, 61 patients (1.5%) were lost to follow-up and outcome of treatment was therefore unknown. Four (0.1%) who requested emergency contraception were subsequently found to have had unprotected coitus *after* missed menses; they were therefore withdrawn and excluded from efficacy analysis. The final study population therefore consisted of 4,071 women (98.4%) who completed the study and took part in the efficacy analysis (Study Population).

### **Conduct of the Study**

The study was designed according to WHO scientific and ethical policy. The study was approved by the Secretariat Committee on Research into Human Subjects (SCRIHS), the Steering Committee of the Task Force on Postovulatory Methods for Fertility Regulation, the Toxicology Group and the Scientific and Ethical Review Group. WHO/HRP designed the protocol and ran the study in accordance with GCP. Gideon Richter Ltd. Provided the study medication.

### **Baseline data**

There was no difference in baseline characteristics between the groups at admission. Mean age was 27 years, mean weight 56kg, and mean cycle length 29.3 days. 54% were Chinese, 34% were Caucasian and 12% Asian or Black in each treatment group.

Women in the three treatment groups had a similar obstetric and contraceptive history; about a quarter had used emergency previously. Over half (61%) had had a previous pregnancy, but there was a large variation between centres. 8% of women in Helsinki had been pregnant before but the figure was 92% in one Shanghai centre. The percentage of induced abortion varied between 6-77% in the same centres.

About half (52%) requested emergency contraception because they had not used any contraception at coitus, about 38% reported a failure of the condom and 10% had other contraceptive failure. 45% requested treatment within 24 hours, 73% within 48 hours and 89% within 72 hours. The distributions of the interval between intercourse and estimated date of ovulation were similar between the three groups.

26% had used emergency contraception in the past and about 60% had had a previous pregnancy. 44% requested treatment within 24 hours, 73% within 48 hours, 89% within 72 hours and 96% within 96 hours. Approximately as many women had coitus before ovulation as after it.

### **Numbers analyses**

All the women who had been randomised and for whom any assessment of efficacy was available were included in the ITT analysis.

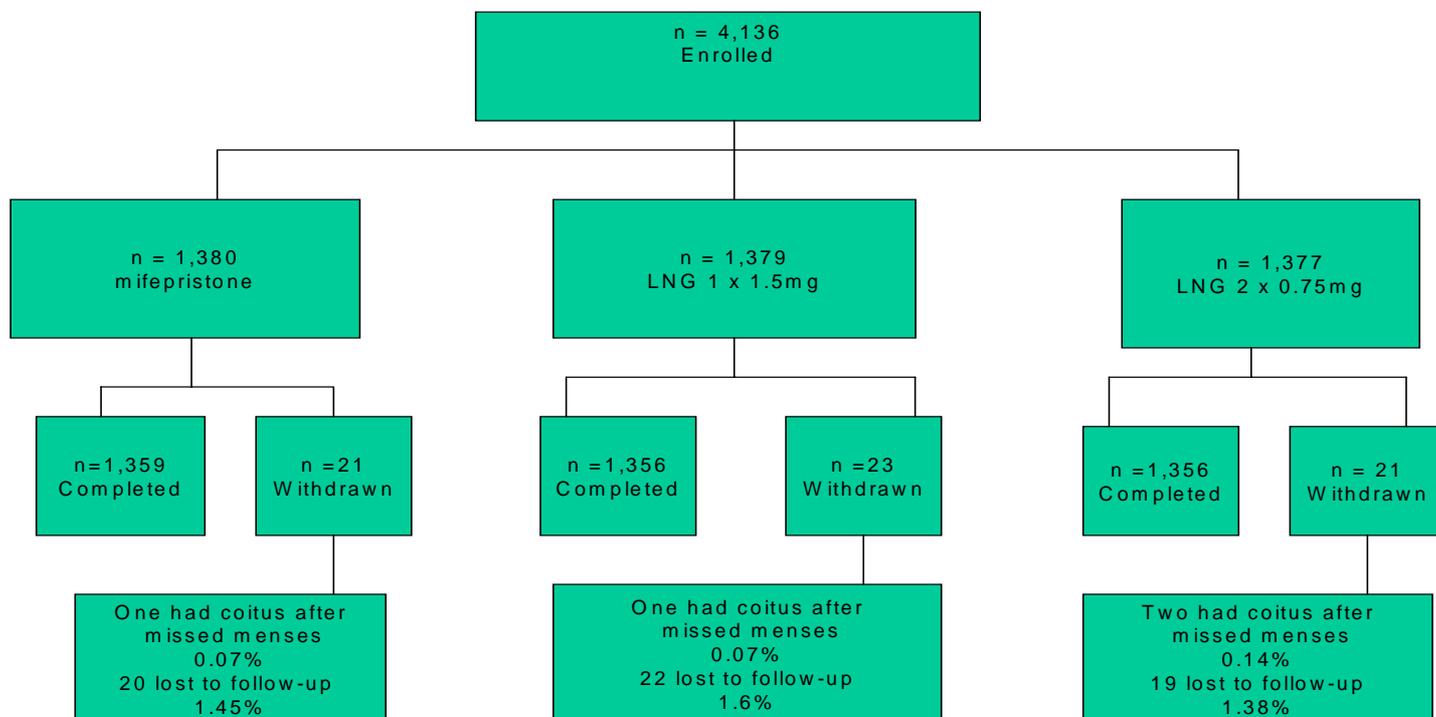
Full ITT data set: This comprised the 4,071 women who completed the study (1,359 on mifepristone, 1,356 in the LNG one dose and 1,356 in the LNG two dose group).

- Efficacy analysis was performed for the ITT sets.

## **OUTCOMES AND ESTIMATION**

### Pregnancy rate

The findings for the two ITT data sets are summarised in Table 4 below.

**Table 3: Patient Disposition****Table 4**

Full ITT data set				
	Mifepristone N=1,359	LNG 1.5mg x 1 N=1,356	LNG 0.75mg x 2 N= 1,356	Overall Number of pregnancies N=4,071
Number of pregnancies (%)	21 (1.5%)	20 (1.5%)	24 (1.8%)	65 (1.6%)

**Prevented fraction:**

Based on the pooled-recognisable conception probabilities, if no treatment had been given the results are summarised in Table 5.

**Table 5: Efficacy results for the Full ITT population**

Group	n	Observed Pregnancies (%)				Expected Pregnancies (%)				Expected Pregnancies (%) TM*			
		#	Rate	95% LL	95% UL	#	PF	95%Ll	95%U L	#	PF	95%Ll	95%UL
Mifepristone	1359	21	1.55	0.96	2.35	108.1	80.57	70.31	87.98	108.1	80.57	76.70	83.80
LNG 1.5mg x1	1356	20	1.47	0.90	2.27	110.5	81.90	72.05	88.94	110.5	81.90	78.27	84.93
LNG 0.75mg x2	1356	24	1.77	1.14	2.62	105.8	77.32	66.26	85.47	105.8	77.32	72.60	81.24
All groups	4071	65	1.60	1.23	2.03	324.4	79.97	74.46	84.54	324.4	79.97	77.26	82.35

The four women who were excluded from the efficacy analysis because they requested emergency contraception after the expected date of menses were not pregnant.

### **Secondary efficacy analysis**

The crude relative risk (RR) of pregnancy for LNG 1500 microgram x 1 compared with LNG 750 microgram x 2 was 0.83 (CI: 0.46-1.50) in the full ITT set. The 95% CI around the relative risk included 1 which indicates that both LNG regimens are similarly effective. The risk of pregnancy for LNG 1500 microgram x 1 compared with LNG 750 microgram x 2, adjusted for the expected pregnancies in each group, was 0.80 (0.42-1.51) in the full ITT group.

### **Additional efficacy analyses**

#### *Efficacy by interval between coitus and treatment*

Data stratified in this way showed that shorter intervals were associated with lower pregnancy rates in all analysis sets in all groups. For the three treatment arms combined, women who were treated after 96 hours (i.e. after 4 days) had significantly higher pregnancy rates than women who were treated within 96 hours.

#### *Efficacy by further acts of unprotected coitus*

Using this stratification, there was a statistically significant effect in the mifepristone group ( $p < 0.0001$ ). In the two LNG groups, pregnancy rates were significantly lower than in the mifepristone group ( $p = 0.049$ ).

#### *Efficacy by ethnicity*

Chinese women became pregnant more frequently than non-Chinese, but the difference was not significant ( $p > 0.2$ ) for all sets.

## **EFFICACY CONCLUSIONS**

A single once daily 1500 microgram dose of LNG is as effective as the currently licensed 2x 750 microgram LNG doses taken 12 hours apart. The relative risk of pregnancy of LNG 1500 microgram x1 compared to LNG 750 microgram x2 was 0.83 (CI:0.46 – 1.50) for the full ITT population. Thus, 1500 microgram x 1 of LNG has been shown to have the same efficacy as the currently marketed 750 microgram x 2 LNG regimen.

### **Nigerian Efficacy Trial**

There is no formal study report available but the study has been published in *Contraception* and a reprint is included in Part IV, vol II pg 1-6 “*Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians*”.

This was a double-blind, randomised, comparator study conducted in Nigeria. The study was designed to compare the efficacy and safety profile of the standard emergency contraceptive regimen (2x750 microgram LNG taken 12 hours apart) with the single 1500 microgram LNG regimen. Women were therefore randomised into two groups:

Group A            Standard therapy: 2 x 750 microgram LNG separated by 12 h  
Group B            Proposed therapy: 1x 1500 microgram LNG

Entry criteria included if a regular menstrual cycle of 21-35 days and unprotected coitus during the ovulation period. Women were excluded if they were not available for follow-up,

were found to be pregnant or had contraindications to the use of oral contraceptive agents. The study population had similar admission characteristics and around 33% had used emergency contraception before and >30% had had a previous pregnancy that ended in abortion or live birth. Timing of coitus relative to expected ovulation was similar in the two groups. In 60% of the women, treatment was given within 24 hours, and between 24 and 48 hours for 10% of them. Out of the 1,160 women, 42 (3.6%) were lost to follow-up and were withdrawn from the final analysis. Of the 1,118 women (96.4%) analysed, 545 women were in Group A and 573 were in Group B. The mean age of Group A was 27.4 years and of Group B 26.6 years.

ITT analysis was carried-out. Pregnancy rates and crude relative risks with 95% CIs were compared by standard methods. The expected number of pregnancies in each group was estimated by multiplying the number of women having unprotected coitus in each day of the menstrual cycle by the probability of conception on each cycle day and the estimated reduction in expected pregnancies was calculated. Also, the effectiveness of each regimen was calculated using the method developed by Trussell et al. The days of ovulation were estimated by subtracting 14 days from the expected date of the next period. British, North Carolina and pooled conception probabilities were used to estimate effectiveness rate.

*Results:* 11 pregnancies (7 in standard regimen Group A and 4 in proposed regimen Group B) were recorded. Three women in Group A and one in Group B continued with their pregnancies and delivered live healthy babies. Pregnancy rate in Group A was 1.28% (95% CI 0.34-2.2) and in Group B it was 0.69% (95% CI 0.02-1.38). There was no significant difference in the crude relative risk of pregnancy in the two groups (RR=0.71; 95% CI 0.32-1.55; p>0.05). Analysis of the prevented fraction gave results that were similar to those for pregnancy rates. The effectiveness rates for the two regimens using the conception probabilities for all conceptions and recognised conceptions calculated from pooled British and North Carolina data are shown in Table 8:

**Table 8**

Day	Cycles	Pregnancies		British	NC-ac	NC-rc	Pooled-ac	Pooled-rc
<b>LNG Regimen A</b>								
-7	70	0	Observed pregs	7	7	7	7	7
-6	29	0	(var)	6.71	6.71	6.71	6.71	6.71
-5	30	0	Expected pregs	56.15	65.80	43.99	61.49	53.05
-4	32	0	(var)	58.6	69.22	30.45	31.40	26.76
-3	44	0	Effectiveness rate	87.53%	89.36%	84.09%	88.62%	86.80%
-2	50	0	(var)	0.00242	0.00173	0.00386	0.00188	0.00255
-1	50	0	(var)	0.00242	0.00173	0.00386	0.00188	0.00255
-1	57	0	Lower 95% CI	73.00%	77.11%	65.78%	75.98%	72.07%
0	61	2	Upper 95% CI	94.24%	95.06%	92.60%	94.61%	93.77%
1	54	3						
2	32	1						
3	35	1						
4	545	7						
<b>LNG Regimen B</b>								
-7	73	0						
-6	32	0						
-5	35	0	Observed pregs	4	4	4	4	4
-4	38	0	(var)	3.88	3.88	3.88	3.88	3.88
-3	48	0	Expected pregs	60.55	68.31	47.16	65.20	57.05
-2	53	0	(var)	66.70	71.46	33.05	34.19	30.02
-1	63	0	Effectiveness rate	93.39%	94.14%	91.52%	93.87%	92.99%
0	54	2	(var)	0.00114	0.00088	0.00185	0.00094	0.00124
1	65	1	Lower 95%CI	82.03%	84.16%	77.07%	83.63%	81.25%
2	35	1	Upper 95% CI	97.57%	97.84%	96.86%	97.70%	97.38%
3	35	1						
4	40	0						
<b>Total</b>	573	4						

Using the British conception probabilities, the effective rate was 87.53% (95% CI 73.00-94.24%) for standard regimen A and 93.39% (95% CI 82.03-97.57) for proposed regimen B.

Using North Carolina conception probabilities, standard regimen A had an effectiveness rate of 89.36% (95% CI 77.11-92.06%) for all conceptions and 84.09% (95% CI 65.78-92.60%) for recognised conceptions. The corresponding effectiveness rates for proposed regimen B were 94.14% (95% CI 84.16-97.84%) and 91.52% (95% CI 77.07-96.86%), respectively. The effectiveness for the two regimens using the conception probabilities for all conceptions and recognised conceptions calculated from pooled British and North Carolina data showed very similar results and are shown in Table 8.

*Conclusions:* the findings indicated that regimen B, i.e. a single 1500 microgram dose of LNG, was significantly more effective than the standard, divided dose, regimen A ( $p < 0.05$ ). Both regimens were more effective the earlier they were taken before ovulation.

This study can be considered supportive but not pivotal. A publication alone cannot be regarded as an adequate basis on which to assess the quality of this trial. A full study report and protocol are necessary to verify the important features of the study. Therefore levels of statistical significance and estimates of effect size should be interpreted with care.

#### *Assessor's overall conclusions on efficacy*

LNG 1500 microgram tablet has been shown in a well-controlled clinical trial to be as effective as the established regimen of two doses of 750 microgram LNG taken 12 hours apart. In addition, the proposed single tablet offers the advantage simplicity for the patient and should increase compliance and acceptability. These findings are consistent with the supportive Nigerian study.

Treatment appears to be most effective when given within 3 days of unprotected coitus, with a non-significant trend to reduced efficacy if delayed 4-5 days post coitus and this reduced efficacy became significant if treatment were delayed beyond 4 days. These findings are consistent with a previous WHO study (WHO/HRP Study 92908) and with the supportive Nigerian study. It is agreed that a treatment window of 72 hours should be retained in the product literature for the proposed line-extensions in order to discourage any delay.

## CLINICAL SAFETY

### Introduction

The total number of women included in the safety analysis was 3,818, of which 1,923 received a single 1500 microgram LNG dose and 1,895 received two 750 microgram LNG doses.

### Patient Exposure

#### Clinical Studies

Study	Evaluable Patients	Patients exposed to standard 2x0.75mg LNG	Patients exposed to the proposed 1.5mg x 1 LNG dose regimen
97902 (Pivotal)	2,756	1,377	1,379
Nigerian Study	1,062	518	544

**Pivotal Study 97902:** All women who had received at least one dose of study medication were included in the safety analysis i.e. n = 4,136. All women took the 1st dose of study medication, thus 1,379 women were involved in the safety analysis in the LNG single dose group and 1,377 in the LNG divided-dose group.

### Supportive Nigerian Efficacy Trial:

There is no formal study report available but the study has been published in *Contraception* and a reprint is included in Part IV, vol II pg 1-6 “*Comparative evaluation of the effectiveness and safety of two regimens of levonorgestrel for emergency contraception in Nigerians*”.

1,062 women (518 in the LNG divided-dose group and 544 in the single-dose group) were assessed.

### Post-Marketing Data – see Section 8.5

#### Adverse Events (AEs)

##### Pivotal Study

These were collected for seven days. Study medication was well tolerated; the most frequently reported AE being menstrual disturbances. 17% in those receiving 1500 microgram LNG and in 16% of those in the LNG divided dose group experienced a change in their bleeding pattern during the study period. 4.5% of women had menses >7 days after the expected time. More than half the women had menses within two days of the expected time. In most cases the characteristics of the bleeding were similar to their normal menstruation.

>10% reported nausea, fatigue, lower abdominal pain and headache in each treatment group. <10% reported breast tenderness, dizziness, delayed menses (>7days), diarrhoea and vomiting.

The occurrence of vomiting was negligible in all treatment groups; it occurred in 1.4% of women who had taken LNG-containing regimens. Nausea was experienced by 13.7% of women in the LNG single-dose group and 14.5% in the divided-dose group. Diarrhoea occurred in 3.8% and 3.2% respectively. No significant differences were seen between the two LNG regimens.

##### Nigerian Study

42 women (3.6%) were lost to follow-up. In the evaluable patients, AEs are summarised in Table 10.

**Table 10: AEs from women who provide complete information in each group**

AEs	Group A (divided LNG dose) %	Group B (single 1.5mg LNG dose) %
Nausea	22.9	24.3
Vomiting	8.4	7.8
Dizziness	13.9	12.6
Headache	14.5	21.3*
Breast tenderness	8.8	12.9*
Lower abdominal pain	18.3	15.6
Menorrhagia	10.5	15.5

\*significant difference ( $p < 0.05$ )  
some women reported >one AE.

Vomiting occurred in 8.4% in the divided LNG dose group and in 7.8% of the single LNG dose group. Nausea was reported in 22.9 and 24.3%, respectively.

*Assessor's comment: the findings are generally consistent between the two studies and are consistent with the product literature for the currently marketed LNG emergency contraceptive products. Vomiting was seen more frequently in the Nigerian study – in the Pivotal study its occurrence was negligible in all treatment groups: 1.4% in the LNG containing regimens. Headache and breast tenderness appeared to be more commonly associated with the 1500 microgram LNG regimen in the supportive Nigerian study, but this was not seen in the pivotal study. In any case such non-serious findings would not be a cause for clinical concern with this “one-off” emergency therapy.*

Menstruation resumed after a similar delay in the two groups (Table 11).

**Table 11: Time to Resumption of menstruation after Treatment in Each Group**

Day of onset of menstruation relative to expected 1 <sup>st</sup> day of menses	Group A (divided LNG dose) %	Group B (single 1.5mg LNG dose) %
<-7 days	29.9	19.9*
-7 to 4 days	14.9	14.8
-3 to +3 days	25.5	30.4*
+4 to +7 days	9.9	9.9
>+7 days	14.9	19.9*
No information	4.9	5.1

\*significant difference ( $p < 0.05$ )

### Serious Adverse Events (SAEs)

#### Pivotal Study

Three were reported. Two occurred in the proposed 1500 microgram LNG group; they were both considered unrelated to therapy:  
one woman required surgery for a ruptured corpus luteum cyst between treatment and follow-up  
acute appendicitis

In the established divided dose regimen group there was one SAE:

- Ectopic pregnancy – this was considered treatment-related.

It has been shown, from post-marketing data, that if pregnancy occurs after treatment with LNG emergency contraception, the possibility of an ectopic pregnancy should be considered. This is reflected in the product literature of the currently marketed LNG emergency contraceptive products and is included in that of the proposed product.

#### Nigerian Study

None was reported.

### Pregnancy Outcome

#### Pivotal study

There was one ectopic pregnancy in the divided LNG dose group. 44 intra-uterine pregnancies were reported: 20 in the single-dose LNG group and 24 in the LNG divided-dose group and these were all terminated.

#### Nigerian study:

Of the 11 pregnancies reported, 3 women in the divided dose LNG group and one in the LNG single-dose group continued with their pregnancies and delivered live healthy babies. The other women were lost to follow-up and outcome is unknown.

### **Post-Marketing Data**

No new safety concerns have arisen.

### **ON-GOING STUDIES**

A study is being conducted in Chile (mentioned in 6.1, Pharmacodynamics) to investigate the effects of a single dose of 1500 microgram of LNG on follicular growth and ovulation. PK, as well as the levels in endometrial tissue, will be examined after oral and vaginal administration of this dose.

A WHO/HRP sponsored seven-centre, double-blind, randomised trial in Nigeria to investigate efficacy and safety of single doses of 1500 microgram LNG compared with a two dose regimen (2x 750 microgram 24h apart).

A WHO/HRP sponsored double-blind, multicenter study in China to investigate whether the 12-hour interval between the two 750 microgram tablets could be increased to 24 hours.

### **PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**

The patient information leaflet and labelling are both satisfactory

### **MEDICAL CONCLUSION**

The provision of emergency contraception is a clinical necessity in order to avoid the risk of unwanted pregnancy and/or need for abortion in women after a single occasion of unprotected coitus.

The pivotal study, supported by the Nigerian study, show that the LNG 1500 microgram tablet is safe and effective in this context. Efficacy and safety of the single 1500 microgram dose is at least as good as the established regimen of two tablets, each containing 750 microgram of LNG, taken 12 hours apart.

As for divided dose regimens, treatment should be taken within 72 hours of unprotected coitus to maximise efficacy – this is stipulated in the SPC. A single tablet regimen is likely to be more acceptable to patients and the compliance issue of remembering to take a second tablet within a 12-hour interval is avoided.

#### **Overall risk-benefit ratio**

These products are therefore considered to have a positive risk-benefit profile and marketing authorisation has been granted.