Public Assessment Report

Decentralised Procedure

Levonorgestrel 1.5 mg tablet

UK/H/5787/001/DC

PL 04854/0136

Gedeon Richter Plc.
LAY SUMMARY

This is a summary of the public assessment report (PAR) for Levonorgestrel 1.5 mg tablet. It explains how Levonorgestrel 1.5 mg tablet was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Levonorgestrel 1.5 mg tablet.

For practical information about using Levonorgestrel 1.5 mg tablet, patients should read the package leaflet or contact their doctor or pharmacist.

What is Levonorgestrel 1.5 mg tablet and what is it used for?
Levonorgestrel 1.5 mg tablet is an emergency contraceptive that can be used within 72 hours (3 days) of unprotected sex or if the usual contraceptive method has failed.

How does Levonorgestrel 1.5 mg tablet work?
Levonorgestrel is thought to work by stopping the ovaries from releasing an egg and preventing sperm from fertilising any egg that may have already been released.

Levonorgestrel can only prevent pregnancy if taken within 72 hours of unprotected sex. It does not work in women who are already pregnant. It will not stop women from becoming pregnant who have unprotected sex after taking levonorgestrel.

How is Levonorgestrel 1.5 mg tablet used?
The tablet should be taken as soon as possible, preferably within 12 hours and no later than 72 hours (3 days), after unprotected sex. Levonorgestrel can be taken at any time of the menstrual cycle.

The tablets should be swallowed whole with water. The tablet works better the sooner it is taken after unprotected sex.

Women who are regularly using methods of contraception, such as the contraceptive pill, should continue to take these at the regular times.

If another unprotected intercourse takes place after the use of the tablets (also if this is during the same menstrual cycle), the tablet will not exert its contraceptive effect and there is again the risk of pregnancy.

The medicine can be obtained from a pharmacy with a prescription.

What benefits of Levonorgestrel 1.5 mg tablet have been shown in studies?
Studies were performed that showed that a single dose of Levonorgestrel 1.5 mg tablet is equally effective in the prevention of pregnancy after unprotected sex as two doses of the already-authorised medicine, Levonorgestrel 0.75 mg tablet, given 12 hours apart.

What are the possible side effects of Levonorgestrel 1.5 mg tablet?
The most common side effects associated with Levonorgestrel 1.5 mg tablet (which may affect more than 1 in 10 people) are feeling sick (nausea), irregular bleeding until the next period after taking the tablet, abdominal pain, tiredness and headache.
For the full list of all side effects reported with Levonorgestrel 1.5 mg tablet, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

**Why is Levonorgestrel 1.5 mg tablet approved?**
The MHRA decided that the benefits of Levonorgestrel 1.5 mg tablet are greater than its risks and recommended that they be approved for use.

**What measures are being taken to ensure the safe and effective use of Levonorgestrel 1.5 mg tablet?**
A risk management plan has been developed to ensure that Levonorgestrel 1.5 mg tablet is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Levonorgestrel 1.5 mg tablet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Levonorgestrel 1.5 mg tablet**
The Marketing Authorisation for Levonorgestrel 1.5 mg tablet was granted in the UK on 2 July 2015.

This summary was last updated in August 2015.

The full PAR for Levonorgestrel 1.5 mg tablet follows this summary.
### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th></th>
<th>I Introduction</th>
<th>Page 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II Quality aspects</td>
<td>Page 6</td>
</tr>
<tr>
<td></td>
<td>III Non-clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td></td>
<td>IV Clinical aspects</td>
<td>Page 10</td>
</tr>
<tr>
<td></td>
<td>V User consultation</td>
<td>Page 23</td>
</tr>
<tr>
<td></td>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>Page 23</td>
</tr>
</tbody>
</table>

Annex 1 - Table of content of the PAR update for MRP and DCP: Page 24
I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Levonorgestrel 1.5 mg tablet could be approved. This is a Pharmacy (P) medicine.

Levonorgestrel 1.5 mg tablet is indicated in adults and adolescents > 16 years of age for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Finland as Concerned Member State (CMS). This application was made under Article 8(3) of Directive 2001/83/EC, as amended.

The precise mode of action of levonorgestrel as an emergency contraceptive 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. Levonorgestrel is not effective once the process of implantation has begun.

No new non-clinical data were submitted, which is acceptable given that levonorgestrel been in clinical use for over 10 years.

The applicant has submitted a report of one bioequivalence study and two efficacy/safety studies. Assurance has been provided that the study has been conducted according to the principles of Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the pharmacovigilance system, as described by the MA holder, fulfils the requirements and provides adequate evidence that the MA holder has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. The MA holder has provided a Risk Management Plan (RMP).

The applicant has conducted an in depth environmental risk assessment based upon data in the literature, which is acceptable.

The RMS and CMS considered that the application could be approved at Day 210 of the procedure on 2 June 2015. After a subsequent national phase, the Marketing Authorisation was granted in the UK on 2 July 2015.
II  Quality aspects

II.1  Introduction
The tablets are almost-white, flat and rimmed. Each tablet measures 8 mm in diameter and has an impressed mark of “G00” on one side.

Each tablet contains 1.5 mg of levonorgestrel and the excipients potato starch, maize starch, silica colloidal anhydrous, magnesium stearate, talc and lactose monohydrate.

A single tablet is packaged in a PVC/aluminium blister stored in a cardboard carton.

II.2  Drug Substance
INN:    Levonorgestrel
Chemical name: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
Structure:

![Structure of Levonorgestrel]

Molecular formula: C₂₁H₂₈O₂
Molecular weight: 312.5

Levonorgestrel is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the drug substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

II.3  Medicinal Product
Pharmaceutical development
The aim of the pharmaceutical development of Levonorgestrel 1.5 mg tablet was to develop a single dose emergency contraceptive pill with similar efficacy to two doses of the 750 microgram tablet.

The formulation of the product is based on that of the 750 microgram tablet.

All excipients comply with their respective Ph Eur monograph requirements.

Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

The lactose monohydrate is sourced from milk from animals suitable for human consumption, in accordance with current requirements. None of the other excipients are of animal or human origin.
Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years when the storage precaution ‘Store in the original package in order to protect from light’ is applied.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

II.5 SmPC, PIL and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER</strong></td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Levonorgestrel 1.5 mg Tablet</td>
</tr>
<tr>
<td>levonorgestrel</td>
</tr>
<tr>
<td>2. NAME OF THE MARKETING AUTHORISATION HOLDER</td>
</tr>
<tr>
<td>Gedeon Richter Plc.</td>
</tr>
<tr>
<td>(RG emblem)</td>
</tr>
<tr>
<td>3. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP:</td>
</tr>
<tr>
<td>4. BATCH NUMBER</td>
</tr>
<tr>
<td>Batch:</td>
</tr>
<tr>
<td>5. OTHER</td>
</tr>
<tr>
<td>PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
</tbody>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

Levonorgestrel 1.5 mg Tablet
levonorgestrel

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Each tablet contains 1.5 mg of levonorgestrel.

3. **LIST OF EXCIPIENTS**

Also contains lactose monohydrate. See the package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

1 tablet

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

For oral use.
Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

This medicine is not recommended for use in children under 12 years of age.
If you under 16, you must take the tablet under supervision of your doctor.

8. **EXPIRY DATE**

EXP:

9. **SPECIAL STORAGE CONDITIONS**
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder:
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest, Hungary

(RG logo)

12. MARKETING AUTHORISATION NUMBER(S)

PL 04854/0136

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

P

15. INSTRUCTIONS ON USE

Indication:
Levonorgestrel 1.5 mg Tablet is an emergency contraceptive that can be used within 72 hours (3 days) of unprotected sex or if your usual contraceptive method has failed.

Usual dosage:
Take the tablet as soon as possible, preferably within 12 hours, and no later than 72 hours (3 days) after you have had unprotected sex.

Read the package leaflet before use.

16. INFORMATION IN BRAILLE

levonorgestrel 1.5 mg tablet
III Non-clinical aspects

III.1 Introduction
Levonorgestrel is a widely-used, well-established drug substance. This is reflected in the applicant’s non-clinical overview, which has been written by an appropriately qualified person and is satisfactory.

III.2 Pharmacology
No new pharmacology data have been submitted, which is acceptable since levonorgestrel is a widely-used, well-established drug substance.

III.3 Pharmacokinetics
No new pharmacokinetic data have been submitted, which is acceptable since levonorgestrel is a widely-used, well-established drug substance.

III.4 Toxicology
No new toxicology data have been submitted, which is acceptable since levonorgestrel is a widely-used, well-established drug substance.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Although Levonorgestrel 1.5 mg tablet will be used in place of another product, the drug substance (or active metabolite) is likely to act as an endocrine disruptor. For this reason the applicant conducted an in depth environmental risk assessment (ERA) based upon data in the literature.

Based on this ERA it was concluded that although a risk to the environment cannot be completely excluded, overall, if Levonorgestrel 1.5 mg tablet is used as proposed, it should not pose a significant risk to the environment.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV Clinical aspects

IV.1 Introduction
A randomised, 2-way crossover, bioavailability study comparing Levonorgestrel 1.5 mg tablet (Gedeon Richter Plc) administered as 1 x 1.5 mg single dose and Levonorgestrel 0.75 mg tablet (Gedeon Richter Plc) administered as 1 x 0.75 mg given twice was conducted in healthy female subjects under fasting conditions.

The study drug was administered with 240 ml water after an overnight fast. 26 blood samples were collected pre-dose and at intervals up to 192 hours after administration of each product.

The drug administrations were separated by a wash-out period of 28 days.

Blood samples for SHBG were collected prior to drug administration and at intervals up to 192 hours post-dose in each period.
16 volunteers were entered in the study and one subject was withdrawn. Therefore, samples from 15 subjects were considered in the pharmacokinetic analysis and the results are presented below:

**Table**: Summary of the ratios of pharmacokinetic parameters of the levonorgestrel 1.5 mg tablet vs. levonorgestrel 0.75 mg tablet

<table>
<thead>
<tr>
<th>Ratio1</th>
<th>AUC0-1</th>
<th>AUC0-inf</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% geometric C.I.2</td>
<td>80.67% to 89.50%</td>
<td>80.90% to 89.61%</td>
<td>122.49% to 146.74%</td>
</tr>
<tr>
<td>Intra-Subject CV</td>
<td>8.03%</td>
<td>7.90%</td>
<td>14.00%</td>
</tr>
</tbody>
</table>

1. Calculated using least-squares means according to the formula $\frac{\text{levonorgestrel 1.5 mg tablet (A)}}{\text{levonorgestrel 0.75 mg tablet (B)}}$
2. 90% geometric confidence interval using ln-transformed data

Based on these results, it can be concluded that the single dose of the 1.5 mg levonorgestrel tablet demonstrates a higher rate and a lower extent of absorption compared to two doses of the 0.75 mg levonorgestrel tablets taken 12 hours apart, under fasting conditions. The pharmacokinetic parameters all fall within the standard bioequivalence criteria of 80 to 125% apart from the Cmax. This is not considered clinically relevant as efficacy studies have also been conducted.

**IV.3 Pharmacodynamics**

No new pharmacodynamic data are required for this application and none have been submitted.

**IV.4 Clinical efficacy**

The efficacy data is comprised of a pivotal WHO/HRP-sponsored study and a supportive study.

**Pivotal WHO/HRP-sponsored study**

A double blind, randomised, multicentre study was performed to compare the efficacy and safety of three different regimens for emergency contraception.

**Methods**

4,136 women requesting emergency contraception following unprotected intercourse participated in the study. The inclusion and exclusion criteria for the study were acceptable.

Subjects were separated into three treatment groups:

**One-dose group**

First dose: two tablets of 0.75 mg levonorgestrel, two tablets of mifepristone placebo
Second dose: one tablet of levonorgestrel placebo

**Two-dose group**

First dose: one tablet of 0.75 mg levonorgestrel, one tablet of a levonorgestrel placebo and two tablets of mifepristone placebo
Second dose: one tablet of 0.75 mg levonorgestrel
Levonorgestrel 1.5 mg tablet

Mifepristone group
First dose: two tablets of mifepristone and two tablets of levonorgestrel placebo
Second dose: one tablet of levonorgestrel placebo

Participants were given their treatments orally; the first and second doses were administered 12 hours apart and the first dose was taken within 120 hours after unprotected intercourse.

The primary outcome measurement was pregnancy; the two following measures of efficacy were calculated for each group:

• Pregnancy rate (PR) and its confidence limits: the percentage of women in the analysis population who become pregnant
• Prevented fraction (PF) and its confidence limits: the proportion of expected pregnancies prevented by treatment, calculated as 100 X [1-(number of observed pregnancies/number of expected pregnancies)]

The sample size calculation, randomisation, blinding and statistical methods appear adequate and are acceptable.

Results
4136 subjects were enrolled in the trial: 1379 were assigned to 1.5 mg levonorgestrel x 1, 1377 were assigned to 0.75 mg levonorgestrel x 2 and 1380 to mifepristone. All volunteers received the first dose of treatment. 61 subjects were lost to follow-up and four women were withdrawn from the study.

All subjects 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 4071 women who completed the study (1359 from the mifepristone group, 1356 from the one-dose group and 1356 from the two-dose group).

Restricted ITT data set: This comprised the sub-population of the full ITT population excluding protocol violations (1282 from the mifepristone group, 1293 from the one-dose group and 1275 from the two-dose group).

PP data set: This comprised the sub-population excluding those with treatment non-compliance and volunteers who used prohibited concomitant medication (1272 from the mifepristone group, 1276 from the one-dose group and 1258 from the two-dose group).

Efficacy analysis was performed for all data sets

Primary efficacy analysis
Pregnancy rate
Of the 4071 women who were included in the full ITT set, 65 were found to be pregnant; 1.5% from the mifepristone group, 1.5% from the one-dose group and 1.8% from the two-dose group. There were 48 pregnancies after excluding major protocol
violators; 0.8% from the mifepristone group, 1.4% from the one-dose group and 1.6% from the two-dose group.

The PP population demonstrated similar results.

Prevented fraction
Based on the pooled-recognisable conception probabilities, if no treatment had been given, it was estimated that there would have been a total of 108 pregnancies in the full ITT population in the mifepristone group, 111 in the one-dose group and 106 in the two-dose group.

Among women receiving the following treatments the % of the pregnancies prevented was:
Mifepristone: 80.6% (CI: 70.3 to 88%)
Levonorgestrel 1.5 mg: 81.9% (CI: 72.1 to 88.9%)
Levonorgestrel 0.75 mg x 2: 77.3% (CI: 66.3 to 85.5%).

The prevented fraction in the restricted ITT population:
Mifepristone: 90.3% (CI: 82.1 to 95.3%)
Levonorgestrel 1.5 mg: 82.9% (CI: 73.0 to 89.9%)
Levonorgestrel 0.75 mg x 2: 80.1% (CI: 69.3 to 87.8%).

The PP population demonstrated similar results.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Observed Pregnancies (%)</th>
<th>Expected Pregnancies (%)</th>
<th>Expected Pregnancies (%) TM*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>Rate 95%LL 95%UL</td>
<td>#</td>
<td>PF 95%LL 95%UL</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>1359</td>
<td>21 1.6453 0.9590 2.3524</td>
<td>108.1 80.57 70.31 87.68</td>
<td></td>
</tr>
<tr>
<td>Lng 1ds</td>
<td>1356</td>
<td>20 1.4749 0.9032 2.2688</td>
<td>110.5 81.90 72.05 88.94</td>
<td></td>
</tr>
<tr>
<td>Lng 2ds</td>
<td>1356</td>
<td>24 1.7699 1.1372 2.6221</td>
<td>105.8 77.32 66.25 85.47</td>
<td></td>
</tr>
<tr>
<td>All groups</td>
<td>4071</td>
<td>65 1.9657 1.2344 2.0306</td>
<td>324.4 79.97 74.45 84.54</td>
<td></td>
</tr>
</tbody>
</table>

Table 11-12: Efficacy results of the full ITT Population

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Observed Pregnancies (%)</th>
<th>Expected Pregnancies (%)</th>
<th>Expected Pregnancies (%) TM*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>Rate 95%LL 95%UL</td>
<td>#</td>
<td>PF 95%LL 95%UL</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>1283</td>
<td>10 0.7800 0.3747 1.4291</td>
<td>102.9 82.26 62.08 86.33</td>
<td></td>
</tr>
<tr>
<td>Lng 1ds</td>
<td>1293</td>
<td>19 1.3921 0.8274 2.1912</td>
<td>106.4 82.82 73.00 69.87</td>
<td></td>
</tr>
<tr>
<td>Lng 2ds</td>
<td>1275</td>
<td>20 1.5686 0.6607 2.4123</td>
<td>100.5 80.10 59.26 67.64</td>
<td></td>
</tr>
<tr>
<td>All groups</td>
<td>3550</td>
<td>48 1.2448 0.9205 1.6497</td>
<td>308.5 84.44 76.37 88.53</td>
<td></td>
</tr>
</tbody>
</table>

Table 11-13: Efficacy results of the restricted ITT Population

Secondary efficacy analysis
The crude relative risk (RR)

Full ITT set
Levonorgestrel 1.5 mg x 1 compared with levonorgestrel 0.75 mg x 2: 0.83 (CI: 0.46 to 1.50)

Restricted ITT and PP set
Levonorgestrel 1.5 mg x 1 compared with levonorgestrel 0.75 mg x 2: 0.89 (CI: 0.47 to 1.67)
The 95% CI includes 1, indicating that the levonorgestrel regimens have the same effectiveness.

The risk of pregnancy following treatment with levonorgestrel 1.5 mg compared with levonorgestrel 0.75 mg x 2, adjusted for the expected pregnancies in each group was

**Full ITT set**

0.80 (0.42 to 1.51)

**Restricted ITT and PP set**

0.85 (CI: 0.43 to 1.70)

Mifepristone was more effective than the levonorgestrel regimens.

<table>
<thead>
<tr>
<th>Groups Compared</th>
<th>Crude Ratio with CI</th>
<th>Pooled Ratio with CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR  95%LL 95%UL</td>
<td>RR  95%LL 95%UL</td>
</tr>
<tr>
<td>Lng 1ds vs Lng 2ds</td>
<td>0.833 0.4628 1.5013</td>
<td>0.7982 0.4180 1.5082</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1ds</td>
<td>1.0477 0.5705 1.9238</td>
<td>1.0733 0.5536 2.0877</td>
</tr>
<tr>
<td>Mifepristone vs Lnd 2ds</td>
<td>0.8731 0.4884 1.5606</td>
<td>0.8567 0.4533 1.6061</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1+2ds</td>
<td>0.9524 0.5687 1.5952</td>
<td>0.9552 0.5391 1.6415</td>
</tr>
</tbody>
</table>

**Table 11-15: Efficacy results of the full ITT Population**

The PP population and restricted ITT population demonstrated similar results.

**Additional efficacy analyses**

**Efficacy by interval between intercourse and treatment**

The analysis stratified by interval between intercourse and treatment showed that the shorter intervals were associated with lower pregnancy rates in both groups. For the three treatment arms combined, women who were treated after 96 hours had significantly higher pregnancy rates than those treated within 96 hours. The difference was significant in each efficacy set (p=0.030, p=0.049, p=0.047). There was no difference in pregnancy rates between women who were treated on the third or the fourth day after unprotected intercourse (p>0.2).

For the two levonorgestrel arms combined, women who were treated after 72 hours had higher pregnancy rates than women who were treated within 72 hours. The difference was not significant in each efficacy set (p=0.17, p=0.18, p=0.18). The pregnancy rates on days 1, 2, 3, 4 and 5 were 1.6% (10/622), 0.5% (2/377), 2.0% (4/199), 1.1% (1/87) and 4.8% (3/63) in the full ITT population for the levonorgestrel one-dose group. The results were similar for the levonorgestrel two-dose group. For all treatment groups combined there was a significant trend in pregnancy rates in the 5 successive days from the time of unprotected intercourse in each efficacy set, showing an increase in pregnancy rates by days elapsed from unprotected intercourse. For the two levonorgestrel regimens combined a similar trend was found.

**Efficacy by further acts of unprotected intercourse**

Having further acts of intercourse between treatment and expected menstruation resulted in higher pregnancy rates: in the levonorgestrel groups of full ITT population
a total of 2651 women reported not having had any further acts of intercourse between treatment and expected menstruation, while 61 women reported at least one.

Among women who had not had further acts of intercourse the pregnancy rate in the one-dose levonorgestrel group was 1.36% (95% CI 0.80% to 2.13%), while in the two-dose levonorgestrel group it was 1.66% (95% CI 1.04% to 2.50%).

Among women with further acts of intercourse the pregnancy rates were 6.45% (95% CI 0.79% to 21.42%), and 6.67% (95% CI 0.81% to 22.07%) in the one-dose, and two-dose groups, respectively. Pregnancy rates were lower if further acts of unprotected intercourse had not occurred.

**Efficacy by ethnicity**
Chinese subjects became pregnant more frequently than non-Chinese subjects, but the difference was not significant (p>0.2) for all sets.

**Efficacy conclusions**
Mifepristone, levonorgestrel 1.5 mg x 1 and levonorgestrel 0.75 mg x 2 are effective for emergency contraception.

The relative risk of pregnancy of following treatment with levonorgestrel 1.5 mg x 1 compared to levonorgestrel 0.75 mg x 2 was 0.83 (CI: 0.46 – 1.50) for the full ITT population and 0.89 (CI: 0.46 – 1.67) for the restricted ITT and PP populations. Therefore, a single dose of levonorgestrel 1.5 mg is as effective as two doses of levonorgestrel 0.75 mg taken 12 hours apart.

Both levonorgestrel regimens were demonstrated to be effective in preventing pregnancy when taken within 72 hours of unprotected intercourse and also when not followed by further acts of unprotected intercourse.

**Supportive study**
A double-blind, comparative, randomised study was carried out in Nigeria to find an acceptable levonorgestrel regimen for emergency contraception in the Nigerian community; levonorgestrel 0.75 mg x 2 given 12 hours apart and levonorgestrel 1.5 mg x 1 were studied.

1160 healthy women who requested emergency contraception, did not take any contraceptives and had been sexually exposed within 72 hours of presentation at the family planning clinic were enrolled in the study.

Group A comprised 560 women who were given levonorgestrel 0.75 mg x 2 and Group B comprised 600 women who were given levonorgestrel 1.5 mg x 1.

An intention to treat analysis was carried out. Pregnancy rates and crude relative risks with 95% confidence interval 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 calculated.
Also, the effectiveness of each regimen was calculated using the method developed by Trussell et al. The days of ovulation was estimated by subtracting 14 days from the expected date of the next period. British, North Carolina, and pooled conception probabilities was used to estimate effectiveness rate.

### Table 10: Number of Women in Each Analysis Population, by Group

<table>
<thead>
<tr>
<th>Population</th>
<th>LNG 0.75 mg</th>
<th>LNG 1.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population 1: Enrolled population</td>
<td>380</td>
<td>600</td>
</tr>
<tr>
<td>Population 2: Efficacy Population</td>
<td>345</td>
<td>573</td>
</tr>
<tr>
<td>Includes all women in Population 1 except:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final pregnancy status unknown (lost to follow-up)</td>
<td>15</td>
<td>27</td>
</tr>
<tr>
<td>Population 3: Safety population</td>
<td>518</td>
<td>544</td>
</tr>
<tr>
<td>Includes all women who takes minimum one tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results

11 intrauterine pregnancies (seven in group A and four in group B) were recorded. There were no ectopic pregnancies. Three women in group A and one in group B continued with their pregnancies and delivered live healthy babies.

The pregnancy rate in group A was 1.28% (0.34-2.2, 95% CI) and in group B was 0.69% (0.02-1.38, 95% CI). There was no significant difference in the crude relative risk of pregnancy between the two groups (RR=0.71; 0.32-1.55, 95% CI; p>0.05). Analysis of the prevented fraction gave results that were conclusively similar to those for pregnancy rates.

The estimated effectiveness rate using different conception probabilities showed a significantly lower (p<0.05) effectiveness rate for group A than for group B.

The relative risk of pregnancy in group A compared to group B increased from 0.68 (0.14-3.36, 95% CI) for≤24 hour delay in treatment to 0.82 (0.30-2.23, 95% CI) for 49-72 hour delay in treatment. The relative risk of pregnancy for a delay between 24-48 hour before treatment was 0.47 (0.09-2.59, 95% CI). These differences were not significant (p>0.05).

Further acts of sexual intercourse increased the pregnancy rates in each of the two groups (1.7% versus 1.1% in group A, and 1.1% versus 0.5% in group B).

### Overall conclusions on clinical efficacy

The results of the pivotal and supportive study demonstrate that levonorgestrel given as one 1.5 mg dose and two 0.75 mg doses taken 12 hours apart are equally effective in the prevention of pregnancy after unprotected intercourse. The results also demonstrated a reduction in efficacy when there is a delay beyond 72 hours for both of these treatment groups. There was also a reduction in efficacy with further acts of unprotected intercourse.

Overall, levonorgestrel 1.5 mg has been demonstrated to be effective when used as an emergency contraceptive.

### IV.5 Clinical safety

All subjects who had received at least one dose of study medication were included in the safety analysis.
**Patient exposure**

According to the summary of clinical safety, 1359 women in the levonorgestrel one-dose group and 1361 women in the levonorgestrel two-dose group were assessed. 22 women in the one-dose group and 21 women in the two-dose group did not take the second dose of the study medication.

In the Nigerian study 1062 subjects (518 who took 0.75 mg levonorgestrel x 2 and 544 who took 1.5 mg levonorgestrel) were assessed.

The number of the total population analysed for safety was 3782, out of which 1903 women were given a single dose of 1.5 mg levonorgestrel and 1879 women took two doses of 0.75 mg levonorgestrel.

**Adverse events**

**Pivotal study**

There was a total of 6261 adverse events (2035 in the mifepristone group, 2120 in the levonorgestrel one-dose group, and 2106 in the levonorgestrel two-dose group) observed during the study. A total of 2012 women reported at least one adverse event (624 in the mifepristone group, 695 in the levonorgestrel one-dose group, and 693 in the levonorgestrel two-dose group).

The most common adverse events included nausea, fatigue and vaginal bleeding. Vomiting was negligible in all treatment groups; about 1.2% of women reported this adverse event on average.

While bleeding disturbances were reported by 31% of subjects, delay of menses occurred in 4.5% of subjects in the levonorgestrel groups. The corresponding data in the mifepristone group were 18.7% and 8.6%, respectively.

There was significant difference in the incidence of bleeding between the mifepristone and the two levonorgestrel groups (18.6% in the mifepristone group, 30.9% and 31.0% in the two levonorgestrel groups, p<0.01). There was also a difference in the delay of menses between mifepristone and levonorgestrel groups. This effect was significantly more common in the mifepristone group than in the levonorgestrel groups (8.6% in the mifepristone group, 4.5% in the levonorgestrel groups, p<0.01). There was no statistically significant difference in the incidence of adverse events between the two levonorgestrel groups.
Supportive study
The side effects observed after treatment were nausea, vomiting, dizziness, headache, breast tenderness, lower abdominal pain, and menorrhagia. Women in group A (two-dose regimen 0.75 mg levonorgestrel 12 hours apart) had more vomiting, dizziness, and lower abdominal pain, and less nausea, headache, breast tenderness, and increased menstrual flow than those in group B (single dose 1.5 mg levonorgestrel).

Significant differences (p < 0.05) were seen for headache, breast tenderness, and heavy menstrual flow only.

Menstruation resumed after a similar interval in the two groups. It was early (>7 days before expected menses) for about 25% of the women, unchanged for 20%, and delayed (>7 days after expected menses) for 18%. Areas of significant differences are shown on table below.

Table 13: Side effects reported by women who gave complete information in each group
Serious adverse events and deaths
No subjects died during the studies.

There were five reports of serious adverse events in the pivotal study. One case of corpus luteum cyst, one case of acute appendicitis and one case pyelonephritis (requiring hospitalisation) was reported. One subject in the mifepristone group had two tender nodules in her right breast. One subject had an ectopic pregnancy in the levonorgestrel two-dose group.

No serious adverse events were reported in the supportive study.

IV.6 Risk Management Plan
The applicant has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Levonorgestrel 1.5 mg tablet. Routine pharmacovigilance activities and risk minimisation measures should be adequate for this product, which contains a widely used active substance with a well-established safety profile.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| #1. Pregnancy after post-coital contraception (contraceptive failure)         | Appropriate labelling (SmPC and PIL) Text in SmPC:  
- Section 4.2 provides guidance on the appropriate use of the product  
- Section 4.4 contains warnings regarding the possibility of emergency contraception failure resulting in an unintended pregnancy and describes the possible reasons for the contraceptive failure.  
- Section 4.5 states that the concomitant use of liver enzyme inducers may also decrease the efficacy of levonorgestrel.  
- Section 4.8 also contains a warning that pregnancy should be excluded if the next menstrual period is more than 5 days overdue.  
- Section 5.1 contains information concerning limited and inconclusive data on the effect of high body weight on the contraceptive efficacy.  
Prescription only medicine | No additional risk minimisation activities are planned. |
| #2. Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption, vomiting) | Appropriate labelling (SmPC and PIL) Text in SmPC:  
- Section 4.2 contains a warning on the necessity of another Levonorgestrel 1.5 mg tablets intake in case of vomiting within three hours after the product administration.  
- Section 4.4 contains a warning regarding severe malabsorption syndromes, which might impair the efficacy of levonorgestrel.  
Prescription only medicine | No additional risk minimisation activities are planned. |
<p>| #3. Use more than 72 hours after the sexual intercourse                        | Appropriate labelling (SmPC and PIL) Text in SmPC: | No additional risk minimisation |</p>
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Section 4.1</em> highlights the indication and the appropriate timing of the intake of Levonorgestrel 1.5 mg tablets.</td>
<td>activities are planned.</td>
</tr>
<tr>
<td></td>
<td><em>Section 4.2</em> clearly describes the correct use of the product.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Section 4.4</em> contains information about the appropriate timing of the drug intake and warnings on possibility of contraceptive failure if the timing of Levonorgestrel 1.5 mg tablets administration is incorrect.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Section 5.1</em> contains information regarding the efficacy of the product in clinical studies.</td>
<td></td>
</tr>
<tr>
<td>#4. Ectopic pregnancy</td>
<td><strong>Appropriate labelling (SmPC and PIL)</strong>&lt;br&gt;&lt;i&gt;Text in SmPC:&lt;/i&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Section 4.4</em> warns for the possibility of ectopic pregnancy after contraceptive failure and highlights that the product is not recommended for woman who are at risk of ectopic pregnancy.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Section 4.8</em> contains a warning that pregnancy should be excluded if the next menstrual period is more than 5 days overdue.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine</td>
<td></td>
</tr>
<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>#5. Abortion spontaneous</td>
<td><strong>Appropriate labelling (SmPC and PIL)</strong>&lt;br&gt;&lt;em&gt;Text in SmPC&lt;/em&gt;:&lt;br&gt;• <em>Section 4.6</em> highlights that the product is not recommended in case of an existing pregnancy because no effect will present, as levonorgestrel is not abortive. It is also stated that there is no clinical evidence on that levonorgestrel could harm the developing foetus; however no clinical data are available on the potential consequences of doses greater than 1.5 mg levonorgestrel.&lt;br&gt;• <em>Section 5.1</em> states that levonorgestrel is not effective once the process of implantation has begun. Prescription only medicine</td>
<td>No additional risk minimisation activities are planned.</td>
</tr>
<tr>
<td>#6. Drug exposure during pregnancy</td>
<td><strong>Appropriate labelling (SmPC and PIL)</strong>&lt;br&gt;&lt;em&gt;Text in SmPC&lt;/em&gt;:&lt;br&gt;• <em>Section 4.6</em> states that limited epidemiological data indicate no adverse effects on the foetus, but no clinical data are available on the potential consequences of doses greater than 1.5 mg levonorgestrel. It is also stated that the product should not be given to pregnant woman.&lt;br&gt;• <em>Section 5.3</em> states that animal experiments with levonorgestrel suggest virilisation of female foetuses at high doses; otherwise preclinical data reveal no special hazard for humans, beyond information included in other sections of the SmPC. Prescription only medicine</td>
<td>No additional risk minimisation activities are planned.</td>
</tr>
<tr>
<td>#7. Drug interactions</td>
<td><strong>Appropriate labelling (SmPC and PIL)</strong>&lt;br&gt;&lt;em&gt;Text in SmPC&lt;/em&gt;:&lt;br&gt;<em>Section 4.5</em> warns that concomitant use of liver enzyme inducers may reduce the efficacy of levonorgestrel. This section also contains a warning on the possibility of</td>
<td>No additional risk minimisation activities are planned.</td>
</tr>
</tbody>
</table>
IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V User consultation
The package leaflet is based on that for another product, Escapelle 1500 microgram tablet, which has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The results show that the package leaflet meets the criteria for readability, as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levonorgestrel is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
Annex 1     Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>