Public Assessment Report

Decentralised Procedure

RAMONNA 1500 MICROGRAM TABLETS

(Levonorgestrel)

Procedure No: UK/H/4569/001/DC

UK Licence No: PL 04854/0105

GEDEON RICHTER PLC
LAY SUMMARY

On 19 January 2012, Bulgaria, the Czech Republic, Estonia, Lithuania, Latvia, Poland, Romania, Slovenia, Slovakia and the UK agreed to grant a Marketing Authorisation to Gedeon Richter Plc for the medicinal product Ramonna 1500 microgram tablets (PL 04854/0105; UK/H/4569/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 15 February 2012. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P).

Ramonna 1500 microgram tablets is an emergency contraceptive that can be used within 72 hours (3 days) of unprotected sex or if a usual contraceptive method has failed.

This medicine contains a synthetic hormone-like active substance called levonorgestrel. It prevents about 85% of expected pregnancies when it is taken within 72 hours of having unprotected sex. It will not prevent a pregnancy every time and is more effective if it is taken as soon as possible after unprotected sex. It is better to take it within 12 hours rather than delay until the third day.

Ramonna 1500 microgram tablets are thought to work by:
- stopping the ovaries from releasing an egg;
- preventing sperm from fertilising any egg that may have already been released.

Ramonna 1500 microgram tablets can only prevent you becoming pregnant if you take it within 72 hours of unprotected sex. It does not work if you are already pregnant. If you have unprotected sex after taking this medicine, it will not stop you from becoming pregnant.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ramonna 1500 microgram tablets outweigh the risks and a Marketing Authorisation was granted.
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## Module 1

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<th><strong>Product Name</strong></th>
<th>Ramonna 1500 microgram tablets</th>
</tr>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Full dossier, Article 8.3</td>
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<tr>
<td><strong>Active Substances</strong></td>
<td>Levonorgestrel</td>
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<tr>
<td><strong>Form</strong></td>
<td>Tablet</td>
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<tr>
<td><strong>Strength</strong></td>
<td>1.5 mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Gedeon Richter Plc</td>
</tr>
<tr>
<td></td>
<td>Győmrői út 19-21, H-1103 Budapest, Hungary</td>
</tr>
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<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<tr>
<td><strong>Concerned Member State (CMS)</strong></td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/4569/001/DC</td>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ramonna 1500 microgram tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 1500 micrograms of levonorgestrel.

Excipient with known effect: 142.5 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet.

Almost white, flat, rimmed tablet of about 8 mm diameter 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.

Levonorgestrel is not recommended for use by young women under 16 years of age without medical supervision.

4.2 Posology and method of administration
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.

Ramonna 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 local barrier method (e.g. condom, diaphragm, spermicide, cervical cap) until the next menstrual period starts. The use of levonorgestrel does not contraindicate the continuation of regular hormonal contraception.

Paediatric population:
Ramonna 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 or to any of the excipients listed in section 6.1.

4.4 Special warnings 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 levonorgestrel 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 levonorgestrel, the possibility of an ectopic pregnancy should be considered. The absolute risk of ectopic pregnancy is likely to be low, as
levonorgestrel prevents ovulation and fertilisation. Ectopic pregnancy may continue, despite the occurrence of uterine bleeding.

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

Levonorgestrel is not recommended in patients with severe hepatic dysfunction. Severe malabsorption syndromes, such as Crohn’s disease, might impair the efficacy of levonorgestrel.

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 levonorgestrel 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 levonorgestrel 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.

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.

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 cyclosporin metabolism.

Women taking such drugs should be referred to their doctor for advice.

4.6 Fertility, pregnancy and lactation

Pregnancy
Levonorgestrel 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.).

Breast-feeding
Levonorgestrel is secreted into breast milk. Potential exposure of an infant to levonorgestrel can be reduced if the breast-feeding woman takes the tablet immediately after feeding and avoids nursing at least 8 hours following levonorgestrel administration.

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

4.7 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.
## Frequency of adverse reactions

<table>
<thead>
<tr>
<th>System Organ Class MedDRA 14.1</th>
<th>Very common (≥10%)</th>
<th>Common (≥1% to &lt;10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain lower</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Bleeding not related to menses*</td>
<td>Delay of menses more than 7 days **</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Menstruation irregular</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast tenderness</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td></td>
</tr>
</tbody>
</table>

* Bleeding patterns may be temporarily disturbed, but most women will have their next menstrual period within 5-7 days of the expected time.
** If the next menstrual period is more than 5 days overdue, pregnancy should be excluded.

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

- **Gastrointestinal disorders**
  - Very rare (<1/10,000): abdominal pain
- **Skin and subcutaneous tissue disorders**
  - Very rare (<1/10,000): rash, urticaria, pruritus,
- **Reproductive system and breast disorders**
  - Very rare (<1/10,000): pelvic pain, dysmenorrhoea
- **General disorders and administration site conditions**
  - Very rare (<1/10,000): face oedema

### 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: Sex hormones and modulators of the genital system, emergency contraceptives, ATC code: G03AD01

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.

**Efficacy.**

Results from a randomised, double-blind clinical study conducted in 2001 (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 two 750 microgram tablets were taken 12 hours apart). There was no difference between pregnancy rates in case of women who were treated on the third or the fourth day after the unprotected act of intercourse (p>0.2).

Another study conducted in 1997 (Lancet 1998; 352: 428–33) showed that two 750 microgram doses taken 12 hours apart prevents 85% of expected pregnancies.

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
Orally administered levonorgestrel is rapidly and almost completely absorbed.

The results of a pharmacokinetic study carried out with 16 healthy women showed that following ingestion of a single dose of 1.5 mg levonorgestrel maximum drug serum levels 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. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenicity potential, beyond the information included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Potato starch,
Maize starch,
Silica, colloidal anhydrous,
Magnesium stearate,
Talc,
Lactose monohydrate.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
5 years

6.4 Special precautions for storage
Store in the original package in order to protect from light.

6.5 Nature and contents of container
One tablet in PVC/aluminium blister and cardboard cartons.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Gedeon Richter Plc.
Győmrői út 19-21,
H-1103 Budapest
Hungary

8 MARKETING AUTHORISATION NUMBER(S)
PL 04854/0105
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15/02/2012

10 DATE OF REVISION OF THE TEXT
15/02/2012
Module 3
Patient Information Leaflet
The following text is the approved patient Information leaflet (PIL) text. No PIL mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the PIL mock-ups has been obtained.

Package leaflet: Information for the user

Ramonna 1500 microgram tablet
Levonorgestrel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
Always take this medicine exactly as described in this leaflet or as your pharmacist has told you.
- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is this leaflet:
1. What Ramonna 1500 microgram tablet (hereinafter Ramonna) is and what it is used for
2. What you need to know before you take Ramonna
3. How to take Ramonna
4. Possible side effects
5. How to store Ramonna
6. Contents of the pack and other information

1. What Ramonna is and what it is used for

Ramonna is an emergency contraceptive that can be used within 72 hours (3 days) of unprotected sex or if your usual contraceptive method has failed.

Ramonna contains a synthetic hormone-like active substance called levonorgestrel. It prevents about 85% of expected pregnancies when you take it within 72 hours of having unprotected sex. It will not prevent a pregnancy every time and is more effective if you take it as soon as possible after unprotected sex. It is better to take it within 12 hours rather than delay until the third day.

Ramonna is thought to work by:
• stopping your ovaries from releasing an egg;
• preventing sperm from fertilising any egg you may have already released.

Ramonna can only prevent you becoming pregnant if you take it within 72 hours of unprotected sex. It does not work if you are already pregnant. If you have unprotected sex after taking Ramonna, it will not stop you from becoming pregnant.

2. What you need to know before you take Ramonna

Do not use Ramonna
- if you are allergic to levonorgestrel or any of the other ingredients of this medicine listed in section 6.

Warnings and precautions
If any of the following applies to you, talk to your doctor before taking Ramonna as emergency contraception may not be suitable for you. Your doctor may prescribe another type of emergency contraception for you.
• If you are pregnant or think that you may already be pregnant. This medicine will not work if you are already pregnant. If you are already pregnant, Ramonna cannot terminate pregnancy, so Ramonna is not an “abortion pill”.
• You may already be pregnant if:
  - your period is more than 5 days late, or you have experienced unusual bleeding when your next period is due
- you have had unprotected sex more than 72 hours ago, and since your last period.
- Levonorgestrel is not recommended for young women under 16 years of age without medical supervision.

The use of Ramonna is not advised if:
- you have a disease of your small bowel (such as Crohn’s disease) that inhibits the absorption of the drug
- you have severe liver problems
- you have a history of ectopic pregnancy (where the baby develops somewhere outside the womb)
- you have ever had a disease called salpingitis (inflammation of the Fallopian tubes).

A previous ectopic pregnancy or previous infection of the fallopian tubes increases the risk of a new ectopic pregnancy.

If you are worried about sexually transmitted diseases
If you did not use a condom (or if it has been torn or slid down) during the intercourse, it might be possible that you have caught a sexually transmitted disease or the HIV virus.
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.

Other medicines and Ramonna
Tell your pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines may prevent Ramonna from working properly, these include:
- barbiturates and other medicines used to treat epilepsy (for example, primidone, phenytoin, and carbamazepine)
- medicines used to treat tuberculosis (for example, rifampicin, rifabutin)
- a treatment for HIV infection (ritonavir)
- a medicine used to treat fungal infections (griseofulvin)
- herbal remedies containing St John’s wort (Hypericum perforatum)
- a medicine called ciclosporin (suppresses the immune system).
Consult a doctor or pharmacist before using Ramonna if you use any of the above mentioned medicine.

How often can you use Ramonna
You should only use Ramonna in emergencies and not as a regular method of contraception. If Ramonna is used more than once in a menstrual cycle, it is less reliable and it is more likely to upset your menstrual cycle (period).
Ramonna does not work as well as regular methods of contraception. Your doctor, practice nurse or family planning clinic can tell you about long-term methods of contraception which are more effective in preventing you from getting pregnant.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking any medicine.

Pregnancy
You should not take this medicine if you are already pregnant. If you do become pregnant even after taking this medicine, it is important that you see your doctor. There is no evidence that Ramonna will harm a baby that develops in your uterus/womb if you use Ramonna as described. Nevertheless, your doctor may want to check that the pregnancy is not ectopic (where the baby develops somewhere outside the womb). This is especially important if you develop severe abdominal pain after taking Ramonna or if you have previously had an ectopic pregnancy, Fallopian tube surgery or pelvic inflammatory disease.

Breast-feeding
Very small amounts of the active ingredient of this medicine may appear in your breast milk. This is not thought to be harmful to the baby, but if you are worried you can take your tablet immediately after a breast-feeding and avoid nursing at least 8 hours following tablet taking. 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.

*Fertility*
Ramonna increases the possibility of menstruation disturbances which can sometimes lead to earlier or later ovulation date. These changes can result in modified fertility date, however there are no fertility data in the long term.

*Driving and using machines*
Your Ramonna tablet is unlikely to affect your ability to drive a car or use machines. However, if you feel tired or dizzy do not drive or operate machinery.

*Ramonna contains lactose*
In case of milk sugar (lactose) intolerance it should be considered that each Ramonna tablet also contains 142.5 mg lactose monohydrate.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. **How to take Ramonna**

Always use this medicine exactly as described in the leaflet or as your pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

*Use in children and adolescents*
This medicine is not recommended for use in children. If you are under 16, you must visit your doctor or family planning clinic to get emergency contraception.

- 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. Ramonna can be taken at any time in your menstrual cycle assuming you are not already pregnant or think you may be pregnant. Do not chew but swallow the tablet whole with water. Do not delay taking the tablet. The tablet works better the sooner you take it after having unprotected sex.
- If you are already using a regular method of contraception such as the contraceptive pill, you can continue to take this at your regular times.

If another unprotected intercourse takes place after the use of Ramonna (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.

**What to do if you are sick (vomit)**
If you are sick (vomit) within three hours of taking the tablet, you should take another tablet. You will need to contact your pharmacist, doctor, practice nurse or family planning clinic immediately for one more tablet.

**After you have taken Ramonna**
After you have taken Ramonna, if you want to have sex, and are not using the contraceptive pill, you should use condoms or a cap plus spermicide until your next menstrual period. This is because Ramonna won’t work if you have unprotected sex again, before your next period is due.

After you have taken Ramonna, you are advised to make an appointment to see your doctor about three weeks later, to make sure that Ramonna has worked. If your period is more than 5 days late or is unusually light or unusually heavy, you should contact your doctor as soon as possible. If you do become pregnant even after taking this medicine, it is important that you see your doctor.
Your doctor can also tell you about longer-term methods of contraception which are more effective in preventing you from getting pregnant.

If you continue to use regular hormonal contraception such as the contraceptive pill and you do not have a bleed in your pill-free period, see your doctor to make sure you are not pregnant.

**Your next period after you took Ramonna**

After the use of Ramonna, your period is usually normal and will start at the usual day; however sometimes, this will be a few days later or earlier. If your period starts more than 5 days later than expected, an ‘abnormal’ bleeding occurs at that time or if you think that you might be pregnant, you should check whether you are pregnant by a pregnancy test.

**If you take more Ramonna than you should**

Although there have been no reports of serious harmful effects from taking too many tablets at once, you may feel sick, actually be sick (vomit), or have vaginal bleeding. You should ask your pharmacist, doctor, practice nurse or family planning clinic for advice, especially if you have been sick, as the tablet may not have worked properly.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common (may affect more than 1 in 10 people):**
- Feeling sick (nausea)
- You might have some irregular bleeding until your next period
- You might have lower abdominal pain
- Tiredness
- Headache

**Common (may affect up to 1 in 10 people):**
- Being sick (vomiting). If you are sick, read the section ‘What to do if you are sick (vomit )’.
- Your period might be different. Most women will have a normal period at the expected time, but some may have their period later or earlier than normal. You might also have some irregular bleeding or spotting until your next period. If your period is more than 5 days late or is unusually light or unusually heavy, you should contact your doctor as soon as possible.
- You might have tender breasts, diarrhoea, feel dizzy after taking this medicine.

**Very rare effects (may affect up to 1 in 10000 people):**
- Rash, urticaria, pruritus, swelling of the face, pelvic pain, painful period.

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

5. **How to store Ramonna**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Ramonna contains

The active substance is levonorgestrel. Each tablet contains 1500 micrograms of levonorgestrel.

The other ingredients are:
Potato starch,
Maize starch,
Silica, colloidal anhydrous,
Magnesium stearate,
Talc,
Lactose monohydrate.

What Ramonna looks like and contents of the pack

Tablet: almost white, flat, rimmed tablet of about 8 mm diameter with an impressed mark of “G00” on one side.

Packaging: one tablet in PVC//aluminium blister and cardboard cartons.

Marketing Authorisation Holder and Manufacturer

Gedeon Richter Plc,
Gyömrői út 19-21,
H-1103 Budapest
Hungary

This medicinal product is authorised in the Member States of the EEA under the following names:

- Bulgaria: Ramonna
- Czech Republic: Ramonna
- Estonia: RAMONNA
- Lithuania: RAMONNA
- Latvia: Ramonna
- Poland: Ramonna
- Romania: Ramonna
- Slovenia: Ramonna
- Slovakia: Ramonna
- United Kingdom: Ramonna

This leaflet was last revised in [02/2012].
Module 4
Labelling

The following text is the approved labelling text as agreed during EU procedure number UK/H/4569/001/DC. No labelling mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the labelling mock-up has been obtained.

<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON &lt;THE OUTER PACKAGING&gt; &lt;AND&gt; &lt;THE IMMEDIATE PACKAGING&gt;</th>
</tr>
</thead>
</table>

1. **NAME OF THE MEDICINAL PRODUCT**

   Ramonna 1500 micrograms tablet
   levonorgestrel

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

   Each tablet contains 1500 micrograms 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.

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.
Győrnői út 19-21.
1103 Budapest, Hungary

((RG logo))

### 12. MARKETING AUTHORISATION NUMBER(S)

PL 04854/0105

### 13. BATCH NUMBER

Batch:

### 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product not subject to medical prescription.

### 15. INSTRUCTIONS ON USE

**Indication:**
Ramonna 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

Ramonna

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### MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

#### 1. NAME OF THE MEDICINAL PRODUCT

Ramonna 1500 micrograms tablet
levonorgestrel

#### 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

((RG emblem))

#### 3. EXPIRY DATE

Exp.:

#### 4. BATCH NUMBER

Batch:
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Ramonna 1500 microgram tablets (PL 04854/0105; UK/H/4569/001/DC) could be approved. This product is licensed for sale in pharmacies, under the supervision of a pharmacist (legal status P).

Ramonna 1500 microgram tablets is indicated as emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method. It is not recommended for use by young women under 16 years of age without medical supervision.

This is a full-dossier application for a known active substance submitted via the decentralised procedure in accordance with Article 8.3 of 2001/83/EC, as amended. This application is a duplicate of existing Marketing Authorisations held by the same Marketing Authorisation Holder within the EEA. This is acceptable and in line with Co-ordination Group for Mutual Recognition and Decentralised Procedures-Human [CMD(h)] advice (http://www.hma.eu/227.html; see question 1). The UK acted as Reference Member State (RMS) and Bulgaria, the Czech Republic, Estonia, Lithuania, Latvia, Poland, Romania, Slovenia and Slovakia were Concerned Member States (CMS).

Levonorgestrel is a progestogen-only emergency contraceptive used by women after unprotected sexual intercourse to prevent pregnancy. Its precise mode of action 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 studies were conducted or provided, which is acceptable given that the application is for the known active substance levonorgestrel, for which the pharmacodynamic, pharmacokinetic and toxicological properties are well-known.

The clinical studies (including one bioequivalence study) were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practise (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 19 January 2012. After a subsequent national phase, the licence was granted in the UK on 15 February 2012.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ramonna 1500 microgram tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Levonorgestrel</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Sex hormones and modulators of the genital system, emergency contraceptives, (ATC code: G03AD01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>1.5 mg tablets</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/4569/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member State</td>
<td>Bulgaria, Czech Republic, Estonia, Lithuania, Latvia, Poland, Romania, Slovenia and Slovakia</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 04854/0105</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Gedeon Richter Plc Győmőrői út 19-21, H-1103 Budapest, Hungary</td>
</tr>
</tbody>
</table>
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Active substance
INN: Levonorgestrel
Chemical names: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one
Structure:

![Chemical structure of Levonorgestrel]

Molecular formula: $C_{21}H_{28}O_2$
Molecular mass: 312.5
Appearance: Levonorgestrel is a white or almost white crystalline powder. It is practically insoluble in water; sparingly soluble in methylene chloride and slightly soluble in alcohol.

Levonorgestrel is the subject of a European Pharmacopoeia monograph.

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

P. Medicinal Product
Other Ingredients
Other ingredients consist of the pharmaceutical excipients potato starch, maize starch, colloidal anhydrous silica, magnesium stearate, talc and lactose monohydrate.

All excipients comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk collected for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development
The objective of the development program was to produce a product that is a dose proportional modification of Levonorgestrel 0.75 mg Tablets (Gedeon Richter Plc) which has been manufactured since 1980.

Satisfactory product development data were submitted.
Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

Finished Product Specification
The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in polyvinylchloride/aluminium blister strips containing one tablet.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

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

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is satisfactory.

Expert report (Quality Overall Summary)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of levonorgestrel are well-known, no new non-clinical studies are required and none have been provided.
The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended to provide the same daily dosage of active substance for the treatment of the same indications as other levonorgestrel-containing products that are currently marketed, no additional environmental burden is anticipated. Thus, the applicant’s justification is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

INTRODUCTION

In support of this application, the marketing authorisation holder has submitted one bioequivalence study and two efficacy studies (one pivotal and one supportive study).

Pharmacokinetics

The applicant has provided the following bioequivalence study in support of this application:

An open-label, randomised, two-way crossover study to compare the pharmacokinetics of the test product Ramonna 1500 microgram tablets (Gedeon Richter Ltd) versus the reference product levonorgestrel 0.75 mg tablet (Gedeon Richter Ltd) in healthy adult female volunteers under fasted conditions.

All volunteers received a 1.5 mg oral dose of levonorgestrel as a single dose of 1 x 1.5 mg of the test product or 2 x 0.75 mg (with a 12-hour interval between doses), of the reference product, administered with 240 ml of water after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 192 hours post dose. The washout period between treatment periods was at least 28 days.

The pharmacokinetic results for levonorgestrel are presented below:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Levonorgestrel 1.5 mg tablet (A)</th>
<th>Levonorgestrel 0.75 mg tablet (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0,4&lt;/sub&gt; (pg h/mL)</td>
<td>Mean ±SD CV (%)</td>
<td>Mean ±SD CV (%)</td>
</tr>
<tr>
<td>304981.1 ±83134.1 7</td>
<td>27.26</td>
<td>359853.8 ±99782.42 4</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0,inf&lt;/sub&gt; (pg h/mL)</td>
<td>Mean ±SD CV (%)</td>
<td>Mean ±SD CV (%)</td>
</tr>
<tr>
<td>310182.5 ±84025.6 6</td>
<td>27.09</td>
<td>365129.9 ±100282.54 5</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>18465.40 ±4719.96 25.56</td>
<td>13776.98 ±3517.93 25.53</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>1.72 ±0.52 30.25</td>
<td>1.52 ±0.65 42.52</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.00 ±2.00</td>
<td>2.00 ±12.50</td>
</tr>
<tr>
<td>K&lt;sub&gt;el&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.0296 ±0.0098 33.14</td>
<td>0.0301 ±0.0114 37.95</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2el&lt;/sub&gt; (h)</td>
<td>26.11 ±9.40 35.99</td>
<td>26.19 ±9.78 37.55</td>
</tr>
</tbody>
</table>

*Medians and interquartile ranges are presented instead of means and SD.
Based on these results, it can be concluded that the single dose of one levonorgestrel 1.5 mg tablet demonstrates a higher rate and a lower extent of absorption compared to two doses of levonorgestrel 0.75 mg tablets taken 12 hours apart, under fasting conditions.

With the exception of $C_{\text{max}}$, the 90% confidence intervals for the pharmacokinetic parameters for test versus reference product for levonorgestrel are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). It is not considered clinically relevant that the 90% confidence intervals for the pharmacokinetic parameter $C_{\text{max}}$, for test versus reference product, are outside the predefined acceptance criteria as an efficacy study has also been submitted to support this application (see below).

**Pharmacodynamics**

No new pharmacodynamic data were submitted which is acceptable. It is acknowledged that the exact mechanism of action for levonorgestrel as an emergency contraception depends on the phase of the menstrual cycle in which the treatment is given.

**Efficacy**

The efficacy data submitted for this application is comprised of a pivotal UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (WHO/HRP) sponsored study and a supportive Nigerian study.

**PIVITOL WHO/HRP-sponsored study (project 97902)**

The applicant has provided the following pivotal study in support of this application:

A double-blind, randomised, multicentre study to compare the efficacy and safety of three different regimens for emergency contraception. The three treatments were;

1) **Mifepristone group.**
   10 mg dose of mifepristone (First dose: two tablets of mifepristone and two placebo tablets of levonorgestrel. Second dose: one placebo tablet of levonorgestrel).

2) **One dose group.**
   Levonorgestrel administered in one dose of 1.5mg (First dose: Two tablets of 0.75mg levonorgestrel, two tablets of mifepristone placebo . Second dose: one placebo tablet of levonorgestrel).

3) **Two dose group.**

**Table 2: Summary of the ratios of pharmacokinetic parameters of the levonorgestrel 1.5 mg tablet vs. levonorgestrel 0.75 mg tablet**

<table>
<thead>
<tr>
<th>Ratio $^1$</th>
<th>AUC$_{0-t}$</th>
<th>AUC$_{0-\infty}$</th>
<th>$C_{\text{max}}$</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: $e^{\frac{\text{levonorgestrel 1.5 mg tablet}}{\text{levonorgestrel 0.75 mg tablet}}} \times 100$
2. 90% geometric confidence interval using ln-transformed data
Levonorgestrel administered in two doses of 0.75mg at 12 hour intervals (First dose: one tablet of 0.75mg levonorgestrel, one tablet of a levonorgestrel placebo and two tablets of mifepristone placebo. Second dose: one tablet of 0.75mg levonorgestrel).

The study participants comprised of 4136 women with a mean age of 27 years who requested emergency contraception following unprotected sexual intercourse. Subjects were allocated randomly to one of the three treatment groups. The treatment was administered orally with the first dose being taken within 120 hours after unprotected sexual intercourse. There was a 12-hour interval between the two doses.

The primary outcome measurement was pregnancy. The 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 ad 100 X [1-(number of observed pregnancies/number of expected pregnancies)]

Three populations were studied:
- Full Intention-To-Treat (ITT) data set – All patients who completed the study
- Restricted ITT data set – The subpopulation of the ITT data set who presented no protocol violations
- Per-Protocol data set – The subpopulation of the ITT data set who were fully compliant with the study treatment and had no prohibited concomitant medication.

### Results

#### Table 3: 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>#</td>
<td>Rate</td>
<td>95% L</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>1282</td>
<td>10</td>
<td>0.7800</td>
<td>0.3747</td>
</tr>
<tr>
<td>Lng 1ds</td>
<td>1275</td>
<td>18</td>
<td>1.3921</td>
<td>0.8271</td>
</tr>
<tr>
<td>Lng 2ds</td>
<td>1274</td>
<td>20</td>
<td>1.5666</td>
<td>0.9607</td>
</tr>
<tr>
<td>All groups</td>
<td>3850</td>
<td>48</td>
<td>1.2468</td>
<td>0.9206</td>
</tr>
</tbody>
</table>

*Triangular method

#### Table 4: Efficacy results of the restricted 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>#</td>
<td>Rate</td>
<td>95% L</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>1272</td>
<td>9</td>
<td>0.7075</td>
<td>0.3240</td>
</tr>
<tr>
<td>Lng 1ds</td>
<td>1276</td>
<td>18</td>
<td>1.4107</td>
<td>0.8381</td>
</tr>
<tr>
<td>Lng 2ds</td>
<td>1258</td>
<td>20</td>
<td>1.5898</td>
<td>0.9737</td>
</tr>
<tr>
<td>All groups</td>
<td>3808</td>
<td>47</td>
<td>1.2349</td>
<td>0.9087</td>
</tr>
</tbody>
</table>

*Triangular method

Lng=levonorgestrel
Pregnancy rate
4071 women were included in the full ITT set, 65 were found to be pregnant; 1.5% in the mifepristone group, 1.5% in the levonorgestrel 1.5mg group and 1.8% in the levonorgestrel 0.75mg x 2 group. There were 48 pregnancies after excluding major protocol violators, 0.8% in the mifepristone group, 1.4% in the levonorgestrel 1.5mg X 1 group and 1.6% in the levonorgestrel 0.75mg x 2 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 levonorgestrel group 1.5mg group and 106 in the levonorgestrel 0.75mg X 2 group.

Among women receiving mifepristone, 80.6% of the pregnancies were prevented (CI: 70.3 to 88%)
Levonorgestrel 1.5mg: 81.9% (CI: 72.1 to 88.9%)
Levonorgestrel 0.75mg 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 1.5mg: 82.9% (CI: 73.0 to 89.9%)
Levonorgestrel 0.75mg X 2: 80.1% (CI: 69.3 to 87.8%).

The PP population demonstrated similar results.

Secondary efficacy analysis

<table>
<thead>
<tr>
<th>Table 6: Efficacy results of the full ITT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups Compared</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lng 1ds vs Lng 2ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 2ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1+2ds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7: Efficacy results of the restricted ITT Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups Compared</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lng 1ds vs Lng 2ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 2ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1+2ds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8: Efficacy results of the PP Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups Compared</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Lng 1ds vs Lng 2ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 1ds</td>
</tr>
<tr>
<td>Mifepristone vs Lng 2ds</td>
</tr>
</tbody>
</table>
The crude relative risk (RR)
Full ITT set
Levonorgestrel 1.5mg x 1 compared with levonorgestrel 0.75mg x 2: 0.83 (CI: 0.46 to 1.50)

Restricted ITT and PP set
Levonorgestrel 1.5mg x 1 compared with levonorgestrel 0.75mg 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 for levonorgestrel 1.5mg compared with levonorgestrel 0.75mg 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 compared with the levonorgestrel regimen

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 between pregnancy rates in case of women who were treated on the third or the fourth day after the unprotected act of 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. The results were similar for the two-dose levonorgestrel regimen. 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 2,651 women reported not having had any, while 61 women reported at least one.

Among women without further acts of coitus the pregnancy rate in group 1 was 1.36% (95% CI 0.80% to 2.13%), while in group 2 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%) respectively. Pregnancy rates were lower if further acts of unprotected intercourse had not happened.

**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**
Mifepristone, levonorgestrel 1.5mg single dose and 0.75mg x 2 are effective for emergency contraception. A single daily dose of levonorgestrel 1.5mg is as effective as the levonorgestrel 2 x 0.75mg doses taken 12 hours apart. The relative risk of pregnancy of levonorgestrel 1.5mg x 1 compared to levonorgestrel 0.75mg 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. Thus, 1.5mg x 1 of levonorgestrel has been shown to have the same efficacy as the 0.75mg x 2 levonorgestrel regimen.

Levonorgestrel at a single dose of 1.5mg and 0.75mg given 12 hours apart was demonstrated to be both effective in preventing pregnancy and when taken within 72 hours of unprotected sexual intercourse and also when not followed by further acts of unprotected intercourse. The 1.5mg dose was shown to have similar efficacy to levonorgestrel 0.75mg given 12 hours apart.

**SUPPORTIVE STUDY**
The applicant has provided the following study to support this application:

A double-blind, comparative, randomised study carried out in Nigeria to find an acceptable levonorgestrel regimen for emergency contraception in the Nigerian community. The study compared the two-dose regimen 0.75mg levonorgestrel 12 hours apart (group A) with a single-dose 1.5 mg levonorgestrel (group B).

The participants were 1160 healthy women in the reproductive age group (mean age of group A was 27.4 years, mean age of group B was 26.6 years), who requested emergency contraception and did not take any contraceptives, and had been sexually exposed within 72 hours of presentation at the family planning clinic.

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 were 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>560</td>
<td>600</td>
</tr>
<tr>
<td>Population 2: Efficacy Population</td>
<td>545</td>
<td>573</td>
</tr>
<tr>
<td>Includes all women in Population 1 except:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False pregnancy status unknown (lost to follow-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 take minimum one tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results
Eleven intrauterine pregnancies (7 in group A and 4 in group B) were recorded. There was no ectopic pregnancy. Three women in group A and 1 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 it was 0.69% (0.02-1.38, 95% CI). There was no significant difference in the crude relative risk of pregnancy in 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 regimen A than for regimen 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 h delay in treatment to 0.82 (0.30-2.23, 95% CI) for 49-72 h delay in treatment. The relative risk of pregnancy for a delay between 24-48 hours 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% vs 1.1% in group A, and 1.1% vs. 0.5% in group B).

Overall conclusions on clinical efficacy
The results of the pivotal and supportive study demonstrate that levonorgestrel given as a 1.5mg dose and 0.750mg 12 hours apart are equally effective in the prevention of pregnancy after unprotected sexual intercourse. The results also demonstrated a reduction in efficacy if there was a delay beyond 72 hours for both treatment groups (1.5mg and 0.750mg 12 hours apart). There was also a reduction in efficacy with further acts of unprotected sexual intercourse.

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

IV CLINICAL SAFETY
All subjects who had received at least one dose of study medication were included in the safety analysis. Thus, the Safety Population was equal with the enrolled population and includes all women who took a minimum of one tablet when the first follow-up visit took place.

According to the summary of clinical safety, 1,359 women in the levonorgestrel 1-dose group and 1,361 women in the levonorgestrel 2-doses group were assessed. Twenty-two women in group 1 and 21 women in group 2 did not take the second dose of the study medication.

In the Nigerian study, 1,062 subjects (518 in 0.75mg levonorgestrel group and 544 in group of 1.5 mg levonorgestrel) were assessed.
The number of the total population analysed for safety was 3782, out of which 1,903 women were given a single dose of 1.5 mg of levonorgestrel, and 1879 women took two doses of 0.75 mg levonorgestrel, respectively.

**Adverse events**

**Pivotal study**

Table of most common adverse events in pivotal study:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Group</th>
<th>No. of Volunteers/Total</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Mifepristone</td>
<td>196 / 1380</td>
<td>14.20</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>189 / 1379</td>
<td>13.71</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>199 / 1377</td>
<td>14.45</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Mifepristone</td>
<td>12 / 1380</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>19 / 1379</td>
<td>1.38</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>19 / 1377</td>
<td>1.38</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Mifepristone</td>
<td>61 / 1380</td>
<td>4.42</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>53 / 1379</td>
<td>3.84</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>44 / 1377</td>
<td>3.20</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Mifepristone</td>
<td>208 / 1380</td>
<td>15.07</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>184 / 1379</td>
<td>13.34</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>182 / 1377</td>
<td>13.22</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Mifepristone</td>
<td>123 / 1380</td>
<td>8.91</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>132 / 1379</td>
<td>9.57</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>126 / 1377</td>
<td>9.15</td>
</tr>
<tr>
<td>Headache</td>
<td>Mifepristone</td>
<td>140 / 1380</td>
<td>10.14</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>142 / 1379</td>
<td>10.30</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>130 / 1377</td>
<td>9.44</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>Mifepristone</td>
<td>114 / 1380</td>
<td>8.26</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>113 / 1379</td>
<td>8.19</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>115 / 1377</td>
<td>8.35</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>Mifepristone</td>
<td>191 / 1380</td>
<td>13.84</td>
</tr>
<tr>
<td></td>
<td>LNG One Dose</td>
<td>183 / 1379</td>
<td>13.27</td>
</tr>
<tr>
<td></td>
<td>LNG Two Doses</td>
<td>198 / 1377</td>
<td>14.38</td>
</tr>
</tbody>
</table>

LNG=levonorgestrel

There were a total number of 6,261 adverse events (2,035 in the mifepristone group, 2,120 in the levonorgestrel single 1dose group, and 2,106 in the levonorgestrel x 2 dose group) observed during the study. A total of 2,012 women reported at least one adverse event (624 in the mifepristone group, 695 in the levonorgestrel single dose group, and 693 in the levonorgestrel x 2 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 reporting it on average.

While bleeding disturbances were reported by 31% of subjects, delay of menses occurred in 4.5% of them 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 difference in the delay of menses between mifepristone and levonorgestrel groups. This effect was significantly more common in the mifepristone group than in the LNG 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 Nigerian 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 the table below:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group A % (n=518)</th>
<th>Group B % (n=544)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>22.9</td>
<td>24.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8.4</td>
<td>7.8</td>
</tr>
<tr>
<td>Dizziness</td>
<td>13.9</td>
<td>12.6</td>
</tr>
<tr>
<td>Headache</td>
<td>14.5</td>
<td>21.3</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>8.8</td>
<td>12.9</td>
</tr>
<tr>
<td>Lower abdominal pains</td>
<td>18.3</td>
<td>15.6</td>
</tr>
<tr>
<td>Heavy menses</td>
<td>10.5</td>
<td>15.5</td>
</tr>
</tbody>
</table>

Some users reported more than one side effect

There were no deaths. 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 was hospitalised for pyelonephritis. One subject in the mifepristone group had two tender nodules in the right breast.

One subject had ectopic pregnancy in the levonorgestrel two doses group. No serious adverse events were reported in the supportive Nigerian study.

Use in pregnancy and lactation
20 pregnancies occurred in the levonorgestrel one dose group and 24 in the two doses group during the pivotal study. In the Nigerian study out of 11 pregnancies, 3 women in the
levonorgestrel two doses group and 1 in the levonorgestrel one dose group continued with their pregnancies and delivered live healthy babies, while the others were lost to follow-up.

There was one ectopic pregnancy, which developed in the levonorgestrel two doses group in the pivotal study. In the Nigerian study all the pregnancies occurred were reported as intrauterine.

Overall conclusions on clinical safety
Levonorgestrel has been widely used as an emergency contraceptive and no new safety concerns have been identified.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are acceptable. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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.

A suitable Risk Management Plan has been submitted for this product.

Conclusion
There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The quality characteristics of Ramonna 1500 microgram tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of levonorgestrel are well-known.

EFFICACY
The results of the pivotal and supportive study demonstrate that levonorgestrel given as a 1.5mg dose and two 0.750mg doses 12 hours apart are equally effective in the prevention of pregnancy after unprotected intercourse. The results also demonstrated a reduction in efficacy if there was a delay beyond 72 hours for both treatment groups (1.5mg and 2 x 0.750mg 12 hours apart). There was also a reduction in efficacy with further acts of unprotected intercourse.
SAFETY
Levonorgestrel has been widely used as an emergency contraceptive and no new safety concerns have been identified in the new studies that have been submitted.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified.

Overall, levonorgestrel 1.5mg has been demonstrated to be effective when used as an emergency contraceptive. The pharmacokinetics of levonorgestrel given at a dose of 1.5mg has also been demonstrated to be similar to a dose of 2 x 0.750mg given 12 hours apart.

Extensive clinical experience with levonorgestrel is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
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