

**LEVONORGESTREL 1.5 MG TABLETS
PL 35507/0126**

UKPAR

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LAY SUMMARY

Levonorgestrel 1.5 mg Tablets (levonorgestrel)

This is a summary of the public assessment report (PAR) for Levonorgestrel 1.5 mg Tablets (PL 35507/0126). It explains how Levonorgestrel 1.5 mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Levonorgestrel 1.5 mg Tablets.

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

What are Levonorgestrel 1.5 mg Tablets and what are they used for?

Levonorgestrel 1.5 mg Tablets are a 'generic medicine'. This means that Levonorgestrel 1.5 mg Tablets are similar to a 'reference medicine' already authorised in the European Union (EU) called Levonelle-2 750 microgram tablets.

Levonorgestrel 1.5 mg Tablets are an emergency contraceptive that can be used within 72 hours (3 days) of unprotected sex or if the usual contraceptive method has failed.

How are Levonorgestrel 1.5 mg Tablets used?

Levonorgestrel 1.5 mg Tablets should be taken as soon as possible, preferably within 12 hours, and no later than 72 hours (3 days) after having unprotected sex. Levonorgestrel 1.5 mg tablets can be taken at any time in the menstrual cycle assuming the person is not already pregnant. The tablet should not be chewed but should be swallowed whole with water. If a regular method of contraception, such as the contraceptive pill, is already being used, this can be continued at the regular times. If unprotected intercourse takes place again after the use of Levonorgestrel 1.5 mg 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.

This medicine is available in a pharmacy, without a prescription.

How do Levonorgestrel 1.5 mg Tablets work?

Levonorgestrel 1.5 mg tablets contain a synthetic hormone-like active ingredient called levonorgestrel. Levonorgestrel 1.5 mg tablets are thought to prevent pregnancy by stopping the ovaries from releasing an egg; preventing sperm from fertilising any egg that may have already been released; or by stopping a fertilised egg from attaching itself to the womb lining.

How have Levonorgestrel 1.5 mg Tablets been studied?

Because Levonorgestrel 1.5 mg Tablets are a generic medicine, studies in patients have been limited to tests to determine that the product is bioequivalent to a higher strength of the reference medicine, called Levonelle 1500 microgram tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body. It was deduced from these tests that Levonorgestrel 1.5 mg Tablets are comparable to Levonelle 1500 microgram tablets.

What are the benefits and risks of Levonorgestrel 1.5 mg Tablets?

Because Levonorgestrel 1.5 mg Tablets are a generic medicine that is comparable to the reference medicine, their benefits and risks are taken as being the same as the reference medicine.

Why are Levonorgestrel 1.5 mg Tablets approved?

It was concluded that, in accordance with EU requirements Levonorgestrel 1.5 mg Tablets have been shown to have comparable quality and to be comparable to the reference medicine Levonelle-2 750 microgram tablets. Therefore, the view was that, as for Levonelle-2 750 microgram tablets, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Levonorgestrel 1.5 mg Tablets?

A risk management plan has been developed to ensure that Levonorgestrel 1.5 mg Tablets are 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 Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Levonorgestrel 1.5 mg Tablets

The UK agreed to grant a Marketing Authorisation for Levonorgestrel 1.5 mg Tablets on 02 June 2014.

The full PAR for Levonorgestrel 1.5 mg Tablets follows this summary. For more information about treatment with Levonorgestrel 1.5 mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2014.

**LEVONORGESTREL 1.5 MG TABLETS
PL 35507/0126**

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Lupin (Europe) Limited a Marketing Authorisation (licence) for the medicinal product Levonorgestrel 1.5 mg Tablets (PL 35507/0126) on 02 June 2014.

This product is not subject to medical prescription, but will be supplied through pharmacies only (legal status P).

It is indicated for use as emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method. Levonorgestrel 1.5 mg tablets are not recommended for use by young women under 16 years of age without medical supervision.

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The originator product is Levonelle-2 750 microgram tablets (PL 05276/0016; MedimpexUK Limited), which was granted a licence in the UK on 30 November 1999. The reference product used in the bioequivalence study is Levonelle 1500 microgram tablets (PL 05276/0019; MedimpexUK Limited), which was granted a licence in the UK on 14 June 2004.

Levonorgestrel 1.5 mg tablets contain the active ingredient levonorgestrel. The precise mode of action of levonorgestrel as an emergency contraceptive is not known. It 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.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence studies were performed, which compared the pharmacokinetics of the applicant's Levonorgestrel 1.5 mg tablets (PL 35507/0126) with those of Levonelle 1500 microgram tablets (MedimpexUK Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.

PHARMACEUTICAL ASSESSMENT

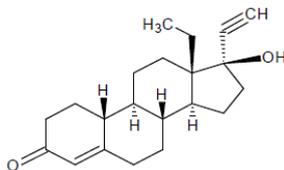
DRUG SUBSTANCE

Levonorgestrel

INN: Levonorgestrel

Chemical name: 13-Ethyl-17-hydroxy- 18,19-dinor-17 α -pregn-4-en-20-yn-3-one

Structure:



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

Molecular weight: 312.45

Physical form: White or almost white, crystalline powder

Solubility: Practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol (96 %)

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance levonorgestrel.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

Appropriate specifications are provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specifications.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of the pharmaceutical excipients, namely lactose monohydrate, maize starch, povidone K30, colloidal anhydrous silica and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monographs.

With the exception of the lactose monohydrate, none of the excipients used contain material of animal or human origin. The magnesium stearate is of vegetable origin.

The milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical development

The objective of the pharmaceutical development programme was to produce safe, tolerable tablets that could be considered a generic medicinal product of Levonelle-2 750 microgram tablets (Medimpex UK Limited). The applicant has provided a suitable product development rationale and data.

Comparative *in vitro* dissolution profiles have been provided for the applicant's product versus the reference product used in the bioequivalence study.

Manufacture

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on three batches of finished product. The results are satisfactory.

Finished product specification

The finished product specifications are satisfactory. Test methods have been described and 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.

Container Closure System

The finished product is packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters in a pack size of 1 tablet per blister, which is further packed into a carton.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided.

Stability

Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years, with the special storage conditions of "Store below 25°C" and "Store in the original package in order to protect from light".

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels

The SmPC, PIL and text version of the labels are pharmaceutically acceptable.

The results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet was provided. 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.

MAA forms

The MAA form is pharmaceutically satisfactory.

Expert report (Quality Overall Summary)

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of levonorgestrel are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study to compare the pharmacokinetics of Levonorgestrel 1.5 mg tablets (PL 35507/0126) with those of Levonelle 1500 microgram tablets (MedimpexUK Limited) in healthy, adult, female subjects, under fasting conditions.

Volunteers were given each treatment after an overnight fast of 8 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 72 hours post dose. Each regimen was separated by a washout period of 14 days.

A summary of the main pharmacokinetic results is presented in the tables below:

Descriptive statistics of pharmacokinetic parameters of test formulation for levonorgestrel

PK parameter (Units)	Mean	SD	Min	Median	Max	CV%	Geometric Mean
t _{max} (hr)	2.050	0.813	1.00	2.00	4.00	39.67	1.919
C _{max} (pg/mL)	21478.1635	8791.3047	7314.117	19370.509	49855.241	40.93	19857.1704
AUC ₀₋₇₂ (pg*hr/mL)	321788.4886	184272.6444	85534.880	267271.802	894041.745	57.27	279683.8396

Descriptive statistics of pharmacokinetic parameters of reference formulation for levonorgestrel

PK parameter (Units)	Mean	SD	Min	Median	Max	CV%	Geometric Mean
t _{max} (hr)	2.767	0.980	1.50	3.00	4.00	35.43	2.588
C _{max} (pg/mL)	18996.8981	7264.9010	8701.852	18111.895	44151.045	38.24	17894.7940
AUC ₀₋₇₂ (pg*hr/mL)	342663.8749	189128.6085	116671.504	290181.466	911519.623	55.19	303861.5918

Summary statistics of log transformed primary pharmacokinetic parameters for levonorgestrel

Parameter		Geometric Least Square Means		Ratio T/R (%)	90% CI	p-value		
		T	R			Formulation	Period	Sequence
C _{max} (pg/mL)		20071.8356	17896.7233	112.15	104.81 to 120.01	0.0076	0.0004	0.2119
AUC ₀₋₇₂ (pg*hr/mL)		283598.0438	304788.4695	93.05	86.50 to 100.09	0.1050	0.0007	0.1627
Parameter	ISCV %	Power	T- Test Product – Levonorgestrel Tablets 1.5 mg R – Reference Product- 'Levonelle [®] ' (Levonorgestrel) 1500 microgram Tablet N-Number of Observations					
C _{max}	15.42	0.9997						
AUC ₀₋₇₂	16.62	0.9992						

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for AUC and C_{max}. Levonorgestrel 1.5 mg tablets can, therefore, be considered to be bioequivalent with Levonelle 1500 microgram tablets.

EFFICACY

No new data on efficacy have been submitted and none are required for this type of application

SAFETY

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

PHARMACOVIGILANCE SYSTEM

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 provided for this product.

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.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

This is consistent with the SmPC for the reference product and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

This is consistent with that for the reference product and is satisfactory.

LABELLING

This is satisfactory

APPLICATION FORMS (MAA)

This is satisfactory.

CONCLUSION

The grant of a Marketing Authorisations is recommended for this application.

OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT**QUALITY**

The important quality characteristics of Levonorgestrel 1.5 mg 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.

CLINICAL

Bioequivalence has been demonstrated between Levonorgestrel 1.5 mg Tablets and the reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and text versions of labelling are satisfactory and consistent with that for the reference product.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's product and the reference product. 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.

LEVONORGESTREL 1.5 MG TABLETS
PL 35507/0126

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the Marketing Authorisation application on 07 March 2013.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15 March 2013.
3	Following assessment of the application the MHRA requested further information on 17 June 2013, 11 December 2013 and 06 February 2014.
4	The applicant responded to the MHRA's requests, providing further information on 13 September 2013, 22 January 2014 and 30 April 2014.
5	The application was approved on 02 June 2014.

LEVONORGESTREL 1.5 MG TABLETS
PL 35507/0126

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics and Patient Information Leaflet

In accordance with Directive 2010/84/EU, the current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.

Labelling

The following text is the approved label text for Levonorgestrel 1.5 mg Tablets (PL 35507/0126). No label mock-ups have been provided for this product. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON BLISTER STRIPS

BLISTER TEXT

1. NAME OF THE MEDICINAL PRODUCT

Levonorgestrel 1.5mg Tablets
Levonorgestrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

BN:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON TEXT****1. NAME OF THE MEDICINAL PRODUCT**

Levonorgestrel 1.5mg Tablets
Levonorgestrel

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains 1.5mg of levonorgestrel

3. LIST OF EXCIPIENTS

This medicine contains lactose. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablet

1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use. For oral use.

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

Expiry Date:

9. SPECIAL STORAGE CONDITIONS

Store below 25°C. 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

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Lupin (Europe) Limited
Victoria Court,
Bexton Road
Knutsford
Cheshire
WA16 0PF

12. MARKETING AUTHORISATION NUMBER(S)

MA xxxx/xxx

13. BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

Not subject to medical prescription. Supply through pharmacies only.

“P” in a box

15. INSTRUCTIONS FOR USE**16. INFORMATION IN BRAILLE**

Levonorgestrel 1.5mg Tablets