Public Assessment Report

Emerres 1.5 mg Tablet

(levonorgestrel)

PL 20117/0138

Morningside Healthcare Ltd

LAY SUMMARY
Emerres 1.5 mg Tablet
(levonorgestrel)

This is a summary of the Public Assessment Report (PAR) for Emerres 1.5 mg Tablet (PL 20117/0138). It explains how Emerres 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 Emerres 1.5 mg Tablet.

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

What is Emerres 1.5 mg Tablet and what is it used for?
Emerres 1.5 mg Tablet is a generic medicine. This means that Emerres 1.5 mg Tablet is similar to a reference medicine already authorised in the UK called Levonelle-2^{TM} 750 microgram tablet (Medimpex UK Limited; PL 05276/0016).

Emerres 1.5 mg Tablet is commonly known as 'the morning after pill'. It is used to reduce the chances of becoming pregnant after unprotected sex or failure of a contraceptive method.

How is Emerres 1.5 mg Tablet used?
Emerres 1.5 mg Tablet should be taken as soon as possible, preferably within 12 hours, and no later than 72 hours (3 days) after having unprotected sex. Emerres 1.5 mg Tablet 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 Emerres 1.5 mg Tablet (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 not recommended for use in children and adolescents.

Emerres 1.5 mg Tablet can only be obtained on prescription from a doctor.

For further information on how Emerres 1.5 mg Tablet is used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How does Emerres 1.5 mg Tablet work?
Emerres 1.5 mg Tablet contains the active ingredient levonorgestrel, which is a synthetic derivative of the naturally occurring female sex hormone progesterone. Emerres 1.5 mg Tablet is thought to work by preventing ovulation, fertilisation and also by altering the lining of the womb, depending on which stage of the menstrual cycle the woman is at.

How has Emerres 1.5 mg Tablet been studied?
Because Emerres 1.5 mg Tablet is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Levonelle-2^{TM} 750 microgram tablet (Medimpex UK Limited; PL 05276/0016). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Emerres 1.5 mg Tablet?
As Emerres 1.5 mg Tablet is a generic medicine that is bioequivalent to Levonelle-2^{TM} 750 microgram tablet, its benefits and risks are taken as being the same as those for Levonelle-2^{TM} 750 microgram tablet (Medimpex UK Limited; PL 05276/0016).

Why is Emerres 1.5 mg Tablet approved?

It was concluded that, in accordance with EU requirements**,** Emerres 1.5 mg Tablet has been shown to have comparable quality to Levonelle-2^{TM} 750 microgram tablet (Medimpex UK Limited; PL 05276/0016). Therefore, the view was that, as for Levonelle-2^{TM} 750 microgram tablet (Medimpex UK Limited; PL 05276/0016), the benefit outweighs the identified risk.

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

A Risk Management Plan has been developed to ensure that Emerres 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 Emerres 1.5 mg Tablet, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Emerres 1.5 mg Tablet

A Marketing Authorisation was granted in the UK on 10th November 2014.

The full PAR for Emerres 1.5 mg Tablet follows this summary. For more information about using Emerres 1.5 mg Tablet, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2014.

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PL 20117/0138

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I Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Morningside Healthcare Ltd for the medicinal product Emerres 1.5 mg tablet (PL 20117/0138) on 10th November 2014. This is a prescription-only medicine (POM) used as an emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

This application was submitted as a national abridged application under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Levonelle-2™ 750 microgram tablet, authorised to Medimpex UK Limited (PL 05276/0016) on 30th November 1999.

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 non-clinical or clinical studies were conducted, which is acceptable given that reference is made to a medicinal product which has been licensed for over 10 years. A satisfactory bioequivalence study was submitted by the applicant.

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

II Quality aspects

II.1 Introduction

This product is a tablet and contains 1.5 mg of levonorgestrel, as an active ingredient. The pharmaceutical excipients are lactose monohydrate, maize starch, povidone (E1201), silica, colloidal anhydrous (E551) and magnesium stearate (E572). Appropriate justification for the inclusion of each excipient has been provided.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

All excipients comply with their respective European Pharmacopoeia monographs.

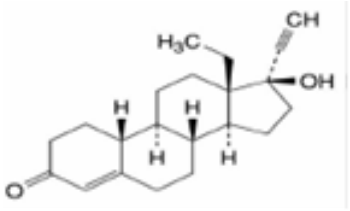
Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

The finished product is packaged in a blister composed of polyvinylchloride (PVC) film-coated with polyvinyledene dichloride (PVDC) and aluminium foil containing a pack size of 1 tablet.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with applicable European regulations.

II.2 Drug Substance

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



Molecular formula: $C_{21}H_{28}O_2$
Molecular weight: 312.5 g/mol
Appearance: White or almost white crystalline powder.
Solubility: Practically insoluble in water, sparingly soluble in methylene chloride, 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 and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate robust, stable, tablet containing levonorgestrel that could be considered as a generic medicinal product of Levonelle-2™ 750 microgram tablet (Medimpex UK Limited).

Comparable dissolution and impurity profiles are provided for this product versus the originator products.

Manufacturing Process
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. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and 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
Finished 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 24 months, with no special storage conditions. This is satisfactory.

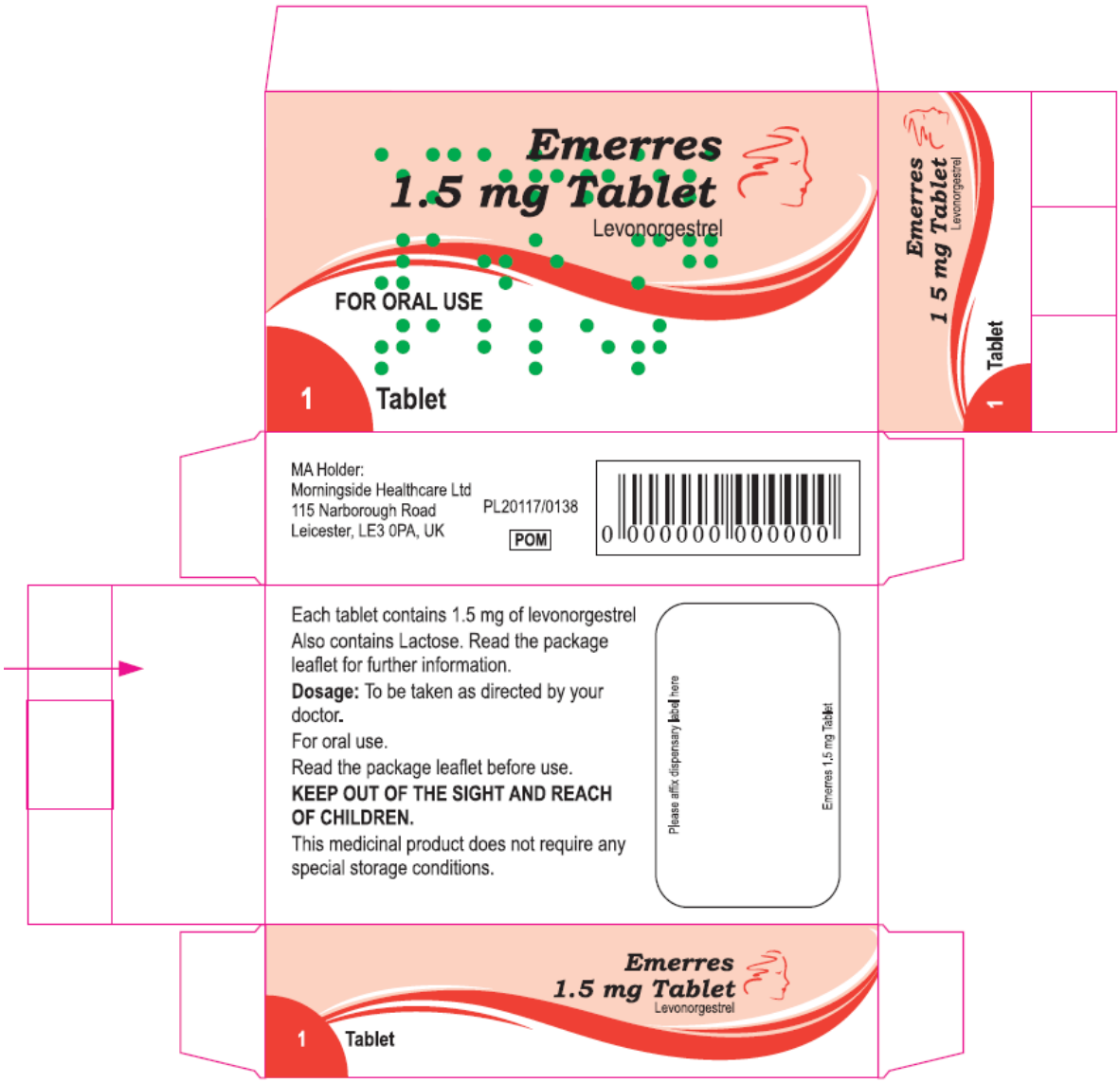
Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a Marketing Authorisation is recommended.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.



III NON-CLINICAL ASPECTS

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 relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Since the proposed product is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV CLINICAL ASPECTS

IV.1 Introduction

In support of this application, the Marketing Authorisation Holder has submitted a bioequivalence study under fasting conditions.

With the exception of the bioavailability study, no new clinical data have been submitted and none are required for an application of this type. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

This is an open label, balanced, randomized, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Levonorgestrel 1.5 mg Tablet (Famy Care Ltd, India) with the reference product Levonelle® (levonorgestrel) 1.5 mg Tablet (Medimpex UK Limited) in 40 healthy, adult, human female subjects under fasting conditions.

Blood samples were collected at pre-dose and at 0.250, 0.500, 0.750, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 6.00, 8.00, 12.0, 16.0, 24.0, 48.0 and 72.0 hours post-dose. The washout period was 30 days.

Geometric Least Square Mean, Ratios and 90% Confidence Interval for Levonorgestrel (n=40)

Parameters (Units)	**(In-transformed) Geometric Least Squares Mean**			**90% Confidence Interval (Parametric)**
	Test (T)	Reference (R)	Ratio (T/R)%	
C_{max} (ng/ml)	18.039	17.783	101.4	94.74 – 108.61%
AUC_{0-72} (ng.h/ml)	294.211	281.461	104.5	99.30 – 110.04%

The 90% confidence intervals for C_{max} and AUC_{0-72} were within the pre-defined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr**). Bioequivalence has been shown for the test formulation (Levonorgestrel 1.5 mg Tablet) and the reference formulation (Levonelle® 1.5 mg Tablet) under fasting conditions.

IV.3 Pharmacodynamics

No new data have been submitted and none are required for applications of this type.

IV.4 Clinical efficacy

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

IV.5 Clinical safety

No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP)

The MAH has submitted a risk management plan, 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 Emerres 1.5 mg Tablet.

Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Ectopic pregnancy • Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting) • Drug interaction leading to loss of efficacy • Contraceptive failure
Important potential risks	• Spontaneous abortion • Drug exposure during pregnancy • Drug exposure via breast milk (infant exposure in nursing mothers) • Use beyond 72 hours of unprotected sex
Missing information	• Use in women less than 16 years of age

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Ectopic pregnancy	The risks of ectopic pregnancy associated with the use of the drug product are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting)	The risks associated with the use of the drug in conditions which can affect the efficacy of levonorgestrel (malabsorption syndrome and vomiting) are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Drug interaction leading to loss of efficacy	The risks of drug interaction leading to loss of efficacy are described in the SPC Section 4.5 and appropriate advice is provided to the prescriber to minimise these risks.	None
Contraceptive failure	The risks of contraceptive failure associated with the use of the drug product are described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Important potential risks		
Spontaneous abortion	The Market Authorization Holder (MAH) will monitor and evaluate post-marketing reports of spontaneous abortion with use of levonorgestrel and these reports will be assessed for any further action.	None
Drug exposure during pregnancy	The risk of drug exposure during pregnancy is described in the SPC Section 4.6, 5.3 and	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	appropriate advice is provided to the prescriber to minimise these risks.	
Drug exposure via breast milk (infant exposure in nursing mothers)	The risk of drug exposure via breast milk (infant exposure in nursing mothers) is is described in the SPC Section 4.6, 5.2, and appropriate advice is provided to the prescriber to minimise these risks.	None
Use beyond 72 hours of unprotected sex.	The risk associated with the use of drug product beyond 72 hours of unprotected sex is described in the SPC Section 4.1, 4.2, 4.4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Missing information		
Use in women less than 16 years of age	The SPC Section 4.2 states that limited information is available related to the use of the drug product in women less than 16 years of age.	Not applicable

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V USER CONSULTATION

The package leaflet 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 language used for the purpose of user testing the PIL was English.

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

QUALITY

The important quality characteristics of Emerres 1.5 mg Tablet 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 applications of this type.

CLINICAL

Bioequivalence has been demonstrated between the applicant's Levonorgestrel 1.5 mg Tablet and the reference product, Levonelle® (levonorgestrel) 1.5 mg Tablet under fasting conditions.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT/RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical 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.

VII Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)