Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Emerres Una 1.5mg tablet

(Levonorgestrel)

UK Licence No: PL 20117/0137

Morningside Healthcare Ltd

LAY SUMMARY

Emerres Una 1.5mg tablet
(Levonorgestrel)

This is a summary of the Public Assessment Report (PAR) for Emerres Una 1.5mg tablet (PL 20117/0137). It explains how Emerres Una 1.5mg 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 Una 1.5mg tablet.

The product will be referred to as Emerres Una throughout the remainder of this PAR.

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

What is Emerres Una and what is it used for?
Emerres Una is a generic medicine. This means that Emerres Una 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 Una 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 Una used?
Emerres Una should be taken as soon as possible, preferably within 12 hours, and no later than 72 hours (3 days) after having unprotected sex. Emerres Una 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. Do not delay taking the tablet; the tablet works better the sooner the person takes it after they have had unprotected sex. 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 Una (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 Una can be obtained without prescription.

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

How does Emerres Una work?
Emerres Una contains the active ingredient levonorgestrel, which is a synthetic derivative of the naturally occurring female sex hormone progesterone. Emerres Una 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.

It is estimated that 84 per cent (%) of pregnancies will be prevented if this morning-after pill is taken within 72 hours of unprotected sex. The tablet is more effective at preventing pregnancy the earlier it is taken, so it is important to take it as soon as possible after unprotected sex, rather than delay to the third day.

How has Emerres Una been studied?

Because Emerres Una is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited). 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 Una?
As Emerres Una is a generic medicine that is bioequivalent to Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited), its benefits and risks are taken as being the same as those for Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited).

Why is Emerres Una approved?
It was concluded that, in accordance with EU requirements**,** Emerres Una has been shown to have comparable quality to Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited). Therefore, the view was that, as for Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited), the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Emerres Una?
A Risk Management Plan has been developed to ensure that Emerres Una 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 Una, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Emerres Una
A Marketing Authorisation was granted in the UK on 30 March 2015.

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

This summary was last updated in December 2016.

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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 Una (PL 20117/0137) on 30 March 2015. This product is indicated as an emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method and is supplied through a pharmacy (P).

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 30 November 1999. The reference product used in the bioequivalence study was Levonelle® 1.5 mg Tablet (PL 05276/0019; Medimpex UK Limited). This is acceptable.

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.

One bioequivalence study was submitted to support this application comparing the applicant's test product Emerres Una (Morningside Healthcare Ltd) with the reference product Levonelle® 1.5 mg Tablet (Medimpex UK Limited) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with Good Clinical Practises (GCP) and Good Laboratory Practices (GLP) requirements.

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 a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Emerres Una outweigh the risks and a Marketing Authorisation was granted.

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.

No genetically modified organisms (GMO) have been used in the preparation of this product.

All excipients comply with their respective European Pharmacopoeia monographs.

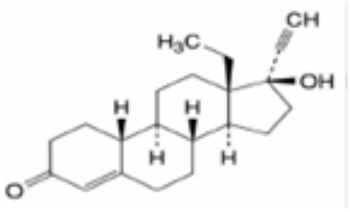
Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

The finished product is packaged in a blister composed of polyvinylchloride (PVC) film-coated with polyvinylidene chloride (PVDC) and aluminium foil. The pack size is 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, tablets containing levonorgestrel that could be considered as a generic medicinal product of Levonelle-2™ 750 microgram tablet (Medimpex UK Limited).

Comparative impurity and *in-vitro* dissolution profiles have been provided for the proposed and originator product.

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 at commercial-scale batch size and has shown satisfactory results.

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

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

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of levonorgestrel are well-known, no further non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Emerres Una 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.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the application was based on Emerres Una being a generic medicinal product of an originator product that has been licensed for over 10 years.

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

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of levonorgestrel is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of levonorgestrel.

Based on the data provided, Emerres Una can be considered bioequivalent to Levonelle® 1.5 mg Tablet (Medimpex UK Limited).

IV.2 Pharmacokinetics

In support of this application, the applicant submitted the following bioequivalence study:

STUDY

An open label, balanced, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Emerres Una (Morningside Healthcare Ltd) with the reference product Levonelle® 1.5 mg Tablet (Medimpex UK Limited) in healthy, adult, human female subjects under fasting conditions.

The subjects were administered a single dose (1.5mg) of either the test or the reference product with 240 ml of water, after an overnight fast.

Blood samples were collected before and up to 72.0 hours post-dose. The washout period between treatment phases was 30 days. The pharmacokinetic results are presented below:

Geometric Least Square Mean, Ratios and 90% Confidence Interval for Levonorgestrel:

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%

AUC_{0-72} area under the plasma concentration-time curve from zero to t hours
C_{max} maximum plasma concentration

The 90% confidence intervals of the test/reference ratio for AUC, and C_{max} values for levonorgestrel lie within the acceptable limits of 80.00% to 125.00%, in line with the 'Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant's test product is bioequivalent to the reference product Levonelle® 1.5 mg Tablet (Medimpex UK Limited).

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 marketing authorisation holder (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 Una.

A summary table of safety concerns and risk minimisation measures as approved in RMP is listed as follows:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Ectopic pregnancy	The risk of ectopic pregnancy associated with the use of the drug product is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com. Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com
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.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com. Also, these documents will be provided on request or in response to queries and hard copies of the patient

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com
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 this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com
Contraceptive failure	The risk of contraceptive failure associated with the use of the drug product is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com
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 this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com
Contraceptive failure	The risk of contraceptive failure associated with the use of the drug product is described in the SPC Section 4.4, and appropriate advice is provided to the prescriber to minimise this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		contraceptives website: www.morningsidecontraceptives.com. Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.
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.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.
Drug exposure during pregnancy	The risk of drug exposure during pregnancy is described in the SPC Sections 4.6, 5.3 and appropriate advice is provided to the prescriber to minimise this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.
Drug exposure via breast milk (infant exposure in nursing mothers)	The risk of drug exposure via breast milk (infant exposure in nursing mothers) is described in the SPC Sections 4.6, 5.2, and appropriate advice is provided to the prescriber to minimise this risk.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.
Use beyond 72 hours of	The risk associated with the use of	To facilitate authorisation application

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
unprotected sex.	drug product beyond 72 hours of unprotected sex is described in the SPC Sections 4.1, 4.2, 4.4 and appropriate advice is provided to the prescriber to minimise this risk.	under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.
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.	To facilitate authorisation application under pharmacy license, educational materials / programmes are available in the form of: • Patient Questionnaire for access and use by pharmacy staff and healthcare professionals • Patient Advice Leaflet for users (Note: These documents will be available for download from Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com . Also, these documents will be provided on request or in response to queries and hard copies of the patient questionnaire will contain a covering page and also the Prescribing Information.) • E-learning module link will be

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		available at Morningside Healthcare's dedicated contraceptives website: www.morningsidecontraceptives.com.

IV.7 Discussion on the clinical aspects

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

Bioequivalence has been demonstrated between the applicant's product Emerres Una and the reference product Levonelle® 1.5 mg Tablet (Medimpex UK Limited), under fasting conditions.

The grant of a marketing authorisation is recommended for this application.

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.*

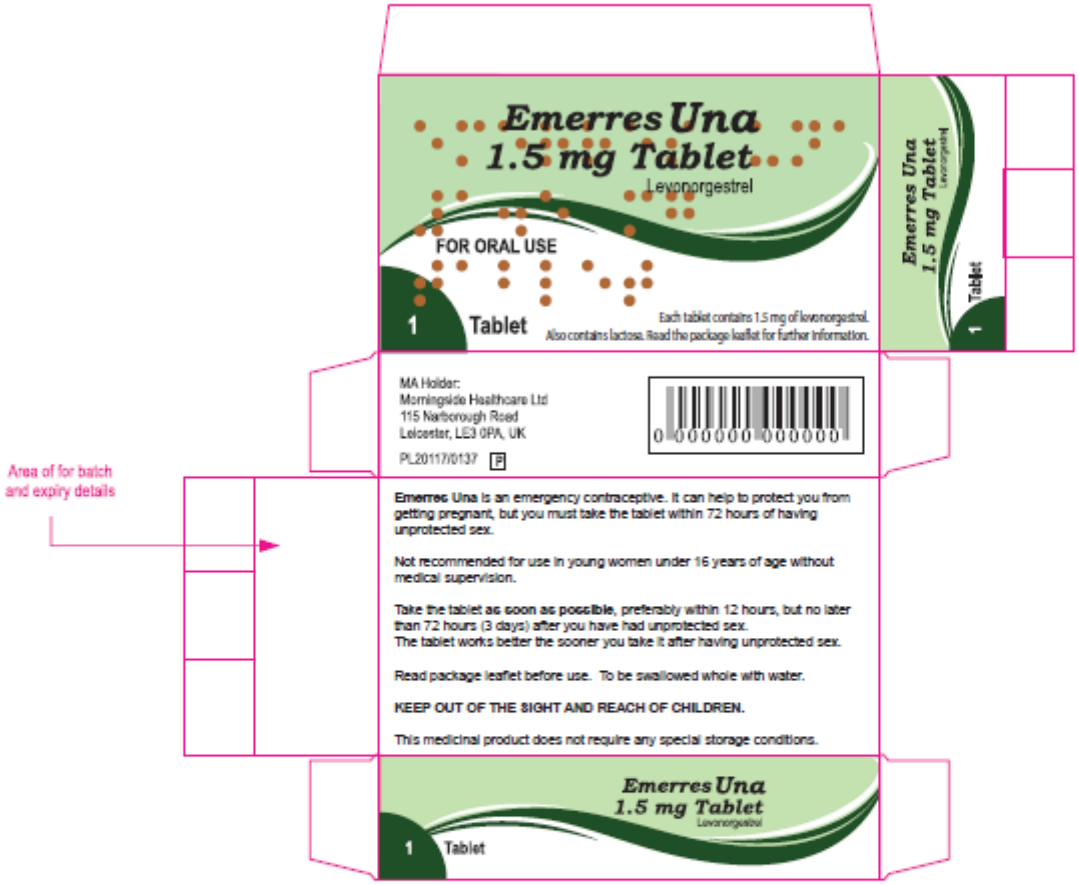
VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with levonorgestrel is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

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

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

The approved labelling for Emerres Una is presented below:



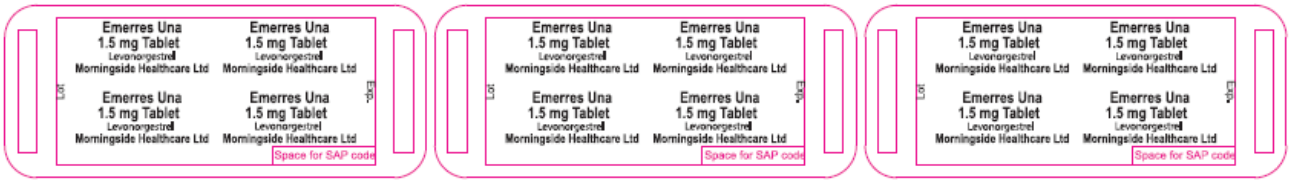


Table of content of the PAR update

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

Date submitted	Application type	Scope	Outcome
01/11/2016	Type IB	To update section 4.2 (Posology and method of administration) of the Summary of Product Characterisctics (SmPC) and consequentially the leaflet in line with EU Art 46 paediatric work-sharing (PdWS) procedure (UK/W/0087/pdWS/001).	Approved on 22/11/2016

Annex 1

Reference: **PL 20117/0137-0008**

Product: **Emerres Una 1.5mg tablet**

Marketing Authorisation Holder: **Morningside Healthcare Ltd**

Active Ingredient: **Levonorgestrel**

Reason:
To update section 4.2 (Posology and method of administration) of the Summary of Product Characterisctics (SmPC) and consequentially the leaflet in line with EU Art 46 paediatric work-sharing (PdWS) procedure (UK/W/0087/pdWS/001).

Supporting evidence
The applicant has submitted updated section of the SmPC and PIL.

Evaluation
The amended section of the SmPC and PIL are satisfactory.

Conclusion
The updated SmPC fragment and PIL have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

Decision: Grant
Date: 22 November 2016