Public Assessment Report

Ezinelle 1.5 mg tablet

(levonorgestrel)

PL 04569/1486

Generics (UK) Ltd t/a Mylan

Lay Summary
Ezinelle 1.5 mg tablet
(levonorgestrel)

This is a summary of the Public Assessment Report (PAR) for Ezinelle 1.5 mg tablet (PL 04569/1486). It explains how Ezinelle 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 this product.

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

What is Ezinelle 1.5 mg tablet and what is it used for?
This medicine is the same as Levonorgestrel 1.5 mg tablet (PL 04569/1374), which is already authorised. The company (Generics (UK) t/a Mylan) referred to its own data provided for the grant of the licence for Levonorgestrel 1.5 mg tablet (PL 04569/1374) as a basis for the grant of the identical licence for Ezinelle 1.5 mg tablet (PL 04569/1486).

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

How does Ezinelle 1.5 mg tablet work?
Ezinelle 1.5 mg tablet contains a synthetic hormone-like substance called levonorgestrel.

Ezinelle 1.5 mg tablet is thought to work by:
- stopping the ovaries from releasing an egg;
- preventing sperm from fertilising any egg that may have already released; or
- stopping a fertilised egg from attaching itself to the womb lining.

How is Ezinelle 1.5 mg tablet used?
Ezinelle 1.5 mg tablet is taken by mouth. The single tablet should be swallowed with water without chewing. Do not delay taking the tablet as it works better the sooner it is taken after having unprotected sex. This medicine can only be obtained on prescription from a doctor.

The recommended dose is one tablet as soon as possible, preferably within 12 hours, and no later than 72 hours (3 days) after having unprotected sex.

Ezinelle 1.5 mg tablet is indicated in adults and adolescents over 16 years of age. It is not indicated for use before the first menstrual bleeding (menarche).

For further information on how Ezinelle 1.5 mg tablet is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Ezinelle 1.5 mg tablet have been shown in studies?
As Ezinelle 1.5 mg tablet is considered to be identical to Levonorgestrel 1.5 mg tablet, its benefits and risks are taken as being the same as those for Levonorgestrel 1.5 mg tablet (PL 04569/1374).

What are the possible side effects from Ezinelle 1.5 mg tablet?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects with Ezinelle 1.5 mg tablet (which may affect more than 1 in 10 people) are feeling sick (nausea), lower abdominal pain, tiredness (fatigue), headache and irregular bleeding until the next period.

The most common side effects with Ezinelle 1.5 mg tablet (which may affect up to 1 in 10 people) are being sick (vomiting), diarrhoea, dizziness, tender breasts or irregular period.

For the full list of all side effects reported with Ezinelle 1.5 mg tablet, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why is Ezinelle 1.5 mg tablet approved?
No new or unexpected safety concerns arose from this application. It was, therefore, considered that the benefits of Ezinelle 1.5 mg tablet outweigh the risks, and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Ezinelle 1.5 mg tablet?
A Risk Management Plan (RMP) has been developed to ensure that Ezinelle 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 Ezinelle 1.5 mg tablet, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Ezinelle 1.5 mg tablet
A Marketing Authorisation was granted in the UK on 13 May 2015.

For more information about taking Ezinelle 1.5 mg tablet, read the Patient Information Leaflet (PIL), or contact your doctor or pharmacist.

The full PAR for Ezinelle 1.5 mg tablet follows this summary.

This summary was last updated in February 2017.

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I Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Generics (UK) Ltd t/a Mylan a Marketing Authorisation for the medicinal product Ezinelle 1.5 mg tablet (PL 04569/1486) on 13 May 2015.

This prescription only medicine (POM) is indicated for emergency contraception within 72 hours of unprotected sexual intercourse or failure of a contraceptive method.

This application was submitted as an abridged simple national application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Levonorgestrel 1.5 mg tablet, which was first authorised to Generics (UK) Ltd t/a Mylan (PL 04569/1374) on 8th April 2014.

The precise mode of action of Ezinelle 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. It may also cause endometrial changes that discourage implantation. Ezinelle is not effective once the process of implantation has begun.

No new data were submitted nor were they necessary for this simple application, as the data are identical to those of the previously granted cross-reference product.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

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 Ezinelle 1.5 mg tablet outweigh the risks and a Marketing Authorisation was granted.

Following the grant of this Marketing Authorisation an application to reclassify the legal category of the product from a prescription-only medicine (legal status POM) to a pharmacy medicine (legal status P) was granted on 01 September 2015.

II Quality aspects

II.1 Introduction

This is a simple informed consent application for Ezinelle 1.5 mg tablet, submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Levonorgestrel 1.5 mg tablet, which was first authorised to Generics (UK) Ltd t/a Mylan (PL 04569/1374) on 08 April 2014. The current application is considered valid.

Each tablet contains 1.5 mg of levonorgestrel as active ingredient. The excipients present are povidone K-25, lactose monohydrate, maize starch, silica, colloidal anhydrous and magnesium stearate. The qualitative and quantitative composition of these excipients is identical to that of the reference product.

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 used for human consumption. Confirmation has also been given that the magnesium stearate used in the tablet is of vegetable origin.

The finished product is packed in blisters composed of polyvinylchloride (PVC) film coated with polyvinylidenechloride (PVdC) and aluminium foil with a pack size of 1 tablet.

Specifications and Certificates of Analysis for all packaging components used have been provided that are satisfactory. The packaging and pack size are the same as those for the cross-reference product.

II.2 Drug Substance

Levonorgestrel

The drug substance specification is identical to that of the reference product and is acceptable.

II.3 Medicinal Product

Pharmaceutical development

A quality expert statement was provided by an appropriately qualified person, confirming that the chemical and pharmaceutical data supporting the application are identical to those of the respective reference product.

Manufacture of the product

The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

The proposed composition and manufacturing process are identical to those of the reference product and are acceptable.

Finished Product Specification

The proposed finished product specification, at release and shelf-life, is in line with the details registered for the cross-reference product.

Stability of the product
The proposed shelf-life is 2 years with no special storage condition. This is acceptable.

The shelf-life is identical to that of the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The quality data for this application are consistent with those previously assessed for the Marketing Authorisation for Levonorgestrel 1.5 mg tablet (PL 04569/1374) and, as such, have been judged to be satisfactory. The grant of a Marketing Authorisation is recommended.

III Non-clinical aspects
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data has been supplied and none are required.

The grant of a Marketing Authorisation is recommended.

The MAH submitted an ERA following the grant of this Marketing Authorisation; please refer to annex 2 on page 7.

IV Clinical aspects
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The grant of a Marketing Authorisation is recommended.

Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ezinelle 1.5 mg tablet.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, is listed below:

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Pregnancy after post coital contraception (contraceptive failure)	• Section 4.4 of SPC contains warnings on this risk. • Section 1 of PIL contains warning on the risk of contraceptive failure and advises patients to consult with the prescriber in case of pre-existing malabsorbtion syndromes. • Product is POM only	None
Drug use in conditions which can affect the efficacy of levonorgestrel (malabsorption, vomiting)	• Section 4.4 of SPC contains warnings on this risk. • Sections 2 and 3 of PIL contain warning on this risk and advise patients to consult with the prescriber in case of delayed menstrual periods. • Product is POM only	None
Off label use (use more than 72 hours after the sexual intercourse)	• Section 4.4 of SPC contains warnings on this risk. • Section 2 of PIL contains warning on the risk of off label use. • Product is POM only	None
Ectopic pregnancy	• Section 4.4 of SPC contains warnings on this risk. • Section 2 of PIL contains warning on the risk of ectopic pregnancy. • Product is POM only	None

Safety Concern	Routine risk minimisation measures	Additional risk minimisation measures
Abortion spontaneous	• There is no reference in the SPC or package leaflet about the risk of abortion spontaneous. • Product is POM only	None
Drug exposure during pregnancy	• Sections 4.6 and 5.3 of SPC contain transparent warnings on this risk. • Sections 2 and 3 of PIL contain warning on this risk and advise patients to consult with the prescriber in case of delayed menstrual periods. • Product is POM only	None
Drug interactions	• Section 4.5 of SPC contains warnings on this risk. • Section 2 of PIL contains warning on the risk of drug interactions. • Product is POM only	None
Drug exposure via breast milk (infant exposure in nursing mothers)	• Section 4.6 of SPC contains warnings on this risk. • Section 2 of PIL contains warning on the risk of infant exposure in nursing mothers. • Product is POM only	None
Use in population under 16 years of age	• Section 4.3 of SPC contains warnings on this risk. • Section 3 of PIL contains warning on the risk of use in population under 16 years of age. • Product is POM only	None

V User consultation

The package leaflet is identical to the leaflet for the reference product.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant's product is identical to the reference product. The benefit-risk assessment is, therefore, considered to be positive.

Summary of Product Characteristics, Patient Information Leaflet & Labels

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The currently approved labelling is listed 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, 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)**
To reclassify the legal category POM to P based on an analogous product, Levonelle One Step 1500 mg Tablet	Pl 04596/1486 - 0002	SmPC and PIL	06/07/16	01/09/16	Approved	N (Annex 1 pending)
To update sections 4.2 and 5.1 of the SmPC in line with the recommendations in the Public Assessment Report for the European paediatric work-sharing procedure UK/W/0087/pdWS/001. Additionally the PIL has been updated.	PL 04569/1486 - 0005	SmPC and PIL	26/05/16	09/06/16	Approved	Y (Annex 2)
To submit an updated Environmental Risk Assessment.	PL 04569/1486 - 0011	ERA	09/12/2016	09/01/2017	Approved	Y (Annex 3)

Annex 2

Reference: PL 04569/1486 - 0005
Product: Ezinelle 1.5 mg tablet
Marketing Authorisation Holder: Generics (UK) Limited
Active Ingredient(s): Levonorgestrel

Reason:
To update sections 4.2 and 5.1 of the SmPC in line with the recommendations in the Public Assessment Report for the European paediatric work-sharing procedure UK/W/0087/pdWS/001. Additionally the PIL has been updated.

Background:
A European paediatric work-sharing procedure (UK/W/0083/pdWS/001) under Article 45 of the Regulation (EC) No 1901/2006, as amended, was conducted to assess the benefit-risk balance of levonorgestrel, when used in the paediatric population. The procedure concluded that the benefit-risk balance of levonorgestrel remains unchanged. Based on the review of the submitted paediatric data, updates were recommended to the PIL and SmPC.

This Type IB variation was to update the SmPC and PIL accordingly.

Supporting Evidence
Revised SmPC fragments 4.2 and 5.1 and a revised PIL have been provided.

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

The current approved UK version of the SmPC and PIL are available on the MHRA website.

Decision
Approved on 09 June 2016.

Annex 3

Reference: PL 04569/1486 - 0011
Product: Ezinelle 1.5 mg tablet
Marketing Authorisation Holder: Generics (UK) Limited
Active Ingredient(s): Levonorgestrel

Reason:
To submit an updated Environmental Risk Assessment.

Background:
During the submission of the BROMI Informed Consent Article 10(c) application, the applicant committed to submit a revised environmental risk (Phase II) assessment, as agreed for the reference application (UK/H/5342/01/DC).

At Day 210 for the reference application - Levonorgestrel 1.5 mg Tablet, the RMS Final Assessment Report included a commitment to conduct the following post-authorisation measure in accordance with Article 21a of Directive 2001/83:

A revised environmental risk (Phase II) assessment should be provided so that the content is in line with the Guideline on the Environmental risk assessment of medicinal products for Human use [EMEA/CHMP/SWP/4447/00].

Supporting Evidence
An updated module 1-6-1 - Non-GMO - Revised Environmental Risk Assessment

Evaluation
The applicant has provided an acceptable environmental risk assessment (ERA), in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP4447/00).

Conclusion
The updated Environmental Risk Assessment is acceptable.

Decision
Approved on 09 January 2017.