Public Assessment Report

Decentralised Procedure

Emoloza 250/35 micrograms film-coated tablets

(Norgestimate and ethinylestradiol)

Procedure No: UK/H/6593/001/DC

UK Licence Number: PL 35507/0193

Lupin (Europe) Limited
LAY SUMMARY
Emoloza 250/35 micrograms film-coated tablets
(Norgestimate and ethinylestradiol)

This is a summary of the Public Assessment Report (PAR) for Emoloza 250/35 micrograms film-coated tablets (PL 35507/0193; UK/H/6593/001/DC). It explains how Emoloza 250/35 micrograms film-coated tablets 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 Emoloza 250/35 micrograms film-coated tablets.

The product will be referred to as Emoloza Tablets throughout this lay summary for ease of reading.

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

What is Emoloza Tablets and what are they used for?
Emoloza Tablets is a ‘generic medicine’. This means that Emoloza Tablets is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Cilest 35/ 250 micrograms film-coated tablet (Janssen Cilag Limited).

Emoloza Tablets is a combined hormonal contraceptive tablet ('the Pill'). It prevents an egg being released from the ovaries and stops pregnancy. Emoloza also makes the fluid (mucus) in the cervix thicker which makes it more difficult for sperm to enter the womb.

How do Emoloza Tablets work?
Emoloza Tablets contain two types of female sex hormones, norgestimate and ethinylestradiol. These hormones work by preventing the release of an egg during menstrual cycle.

How are Emoloza Tablets used?
The pharmaceutical form of this medicine is a film-coated tablet, and the route of administration is oral (by mouth). The whole tablet must be swallowed with water, if necessary, at the same time everyday. The tablets must not be chewed.

The patient must always take this medicine exactly as their doctor has told them. The patient should check with their doctor or pharmacist if they are not sure.

The recommended dose is one tablet each day. Emoloza comes in a strip of 21 tablets, each marked with a day of the week. Women must start by taking a tablet marked with the correct day of the week and they must follow the direction of the arrows on the strip.

For further information on how Emoloza Tablets are used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Emoloza Tablets have been shown in studies?
Because Emoloza Tablets is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Cilest 35/ 250 micrograms film-coated Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.
What are the possible side effects of Emoloza Tablets?
Because Emoloza Tablets is a generic medicine and is bioequivalent to the reference medicine Cilest 35/250 micrograms film-coated Tablets, its benefits and possible side effects are taken as being the same as the reference medicine.

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

For the full list of all side effects reported with Emoloza Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Emoloza Tablets approved?
It was concluded that, in accordance with EU requirements, Emoloza Tablets has been shown to have comparable quality and to be bioequivalent to Cilest 35/250 micrograms film-coated Tablets. Therefore, the MHRA decided that, as for Cilest 35/250 micrograms film-coated Tablets; the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Emoloza Tablets?
A risk management plan (RMP) has been developed to ensure that Emoloza Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Emoloza Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Emoloza Tablets
The concerned member state, Luxembourg, was withdrawn from the procedure. The UK agreed to grant a Marketing Authorisation for Emoloza Tablets on 22 August 2017. A Marketing Authorisation was granted in the UK on 20 September 2017.

The full PAR for Emoloza Tablets follows this summary.

This summary was last updated in November 2017.
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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (Europe) Limited, a marketing authorisation for the medicinal product Emoloza 250/35 micrograms film-coated tablets (PL 35507/0193; UK/H/6593/001/DC). The product is a prescription-only medicine (POM), indicated as a contraceptive with the recognised indications for such oestrogen/progestogen combinations.

The decision to prescribe Emoloza should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Emoloza compares with other Combined Hormonal Contraceptives (CHCs).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). The concerned member state, Luxembourg, was withdrawn from the procedure. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Cilest 35/250 micrograms film-coated tablets, which was first authorised to Cilag Limited (PL 00076/0134) on 19 February 1991. This licence underwent a change of ownership procedure to the current Marketing Authorisation holder, Janssen-Cilag Limited (PL 00242/0209) on 01 July 1995.

Emoloza acts through the mechanism of gonadotrophin suppression by the oestrogenic and progesterational actions of ethinylestradiol and norgestimate. The primary mechanism of action is inhibition of ovulation, but alterations to the cervical mucus, the fallopian tube motility and to the endometrium may also contribute to the efficacy of the product.

One bioequivalence study was submitted to support the application, comparing the applicant’s test product Emoloza 250/35 micrograms film-coated tablets with the reference product Cilest 35/250 micrograms film-coated tablets (Janssen Pharmaceuticals NV, Belgium) in healthy, adult, human female subjects under fasting conditions. The bioequivalence study was conducted in line with current Good Clinical Practice (GCP).

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

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

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

All involved Member States agreed to grant a Marketing Authorisation for the above product at the end of the procedure (Day 153 – 22 August 2017). After a subsequent national phase, the UK granted a Marketing Authorisation (PL 35507/0193) for this product on 20 September 2017.
II QUALITY ASPECTS

II.1 Introduction
The product is presented as film-coated tablets and each tablet contains 250 micrograms of norgestimate and 35 micrograms of ethinylestradiol as the active ingredients. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, croscarmellose sodium, lactose anhydrous, microcrystalline cellulose, magnesium stearate and povidone making up the tablet core and the film-coating is comprised of hypromellose (E464), titanium dioxide (E171), F.D. & C. blue No. 2 AL 3-5% (E132), polyethylene glycol (E1521) and F.D. & C. blue No. 2 aluminium lake (E132).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of F.D. & C. blue No. 2 AL 3-5% (E132) and F.D. & C. blue No. 2 aluminium lake (E132) which comply with the Japanese Standard for food Additives (JSFA). Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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.

The finished product is packaged in polyvinylchloride (PVC)/foil blister strips of 21 tablets. Each blister strip is further packed in an aluminium laminated pouch along with one desiccant (silica gel sachet). Each carton contains 1 (starter pack), 3 and 6 blister strips. Not all pack sizes may be marketed.

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

II.2 Drug Substances

1. Norgestimate
INN: Norgestimate
Chemical name: (17a)-17-(acetyloxy)13-ethyl-18,19-dinor-pregn-4-en-20-yn-3-one 3-oxime 17a-acetoxy-13-ethyl-17-ethynylgon-4-en-3-one oxime,
Structure:

![Structure of Norgestimate](image)

Molecular formula: C_{23}H_{31}NO_{3}
Molecular weight: 369.50 g/mol
Description: White or almost white powder.
Solubility: Practically insoluble in water, freely soluble in dichloromethane, soluble in acetone.

Norgestimate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, norgestimate, are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.
2. Ethinylestradiol

INN: Ethinylestradiol

Chemical name: (17α)-19-Norpregna-1,3,5(10)-trien-20-yn-3,17-diol

17α – ethynyl – 1,3,5 (10) – estra – triene – 3,17β – diol

19 – Nor - 17α – pregna - 1,3,5 (10) – trien -20 – yne – 3, 17 – diol

Structural formula:

![Structural formula](image)

Molecular formula: C_{20}H_{24}O_{2}

Molecular mass: 296.40 g/mol

Appearance: White or slightly yellowish-white crystalline powder.

Solubility: Practically insoluble in water, soluble in chloroform and in ether, freely soluble in alcohol.

Ethinylestradiol is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ethinylestradiol, are covered by the 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 safe, efficacious film-coated tablets containing 250 micrograms norgestimate and 35 micrograms ethinylestradiol per tablet, that are generic versions of the reference product Cilest 35/250 micrograms film-coated tablet (Janssen Cilag Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in-vitro dissolution profiles have been provided for the proposed and originator products.

Manufacture of the product

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 proposed finished product specification is acceptable. The test methods that have been described have been adequately validated. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with the storage condition ‘Store below 25°C’.
Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

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 norgestimate and ethinylestradiol are well-known, no new 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 expert report 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 Emoloza 250/35 micrograms film-coated tablets are intended for generic substitution, their use 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
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 norgestimate and ethinylestradiol 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 norgestimate and ethinylestradiol.

Based on the data provided, Emoloza 250/35 micrograms film-coated tablets can be considered bioequivalent to Cilest 35/250 micrograms film-coated tablet (Janssen Cilag Limited).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:
STUDY 1
An open label, balanced, randomised, single-dose, two-treatment, two-sequence, two-period
crossover oral bioequivalence study of the applicant’s test product Emoloza 250/35 micrograms
film-coated tablets versus the reference product Cilest 35/250 micrograms film-coated tablet
(Janssen Cilag Limited) in healthy, adult, subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose of the test or the reference product
with 240 mL of water.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after
each administration. The washout period between the treatment phases was 28 days. The
pharmacokinetic results are presented below:

Results
Summary of pharmacokinetic parameters, ratios and 90% Confidence Interval

| Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for 17-Desacetyl Norgestimate (n=34) |
|---|---|---|---|---|---|---|
| Obs. | Parameters | N  | Geometric mean | % Ratio T/R | Power | % Intra Subject CV | 90% Confidence Interval |
|     |     |     | Test (T) | Reference (R) |     |     | Lower Limit | Upper Limit |
| 1   | C_{max} (ng/mL) | 34 | 1.963 | 1.813 | 108.27 | 0.9999 | 15.844 | 101.49 | 115.51 |
| 2   | AUC_t (ng*h/mL) | 34 | 21.809 | 20.876 | 104.47 | 1.0000 | 7.972 | 101.11 | 107.94 |

Acceptance Limit for 90% Confidence Interval: 80.00% to 125.00%.

| Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for Ethinyl Estradiol (n=34) |
|---|---|---|---|---|---|---|
| Obs. | Parameters | N  | Geometric mean | % Ratio T/R | Power | % Intra Subject CV | 90% Confidence Interval |
|     |     |     | Test (T) | Reference (R) |     |     | Lower Limit | Upper Limit |
| 1   | C_{max} (pg/mL) | 34 | 98.146 | 90.838 | 108.05 | 1.0000 | 11.586 | 103.04 | 113.29 |
| 2   | AUC_t (pg*h/mL) | 34 | 1149.956 | 1109.503 | 103.65 | 1.0000 | 10.098 | 99.44 | 108.02 |
| 3   | AUC_{inf} (pg*h/mL) | 34 | 1232.928 | 1188.980 | 103.70 | 1.0000 | 9.878 | 99.58 | 107.98 |

Acceptance Limit for 90% Confidence Interval: 80.00% to 125.00%.

Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and C_{max} values for norgestimate and
ethinylestradiol 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 Emoloza 250/35 micrograms film-coated tablets is bioequivalent
to the reference product Cilest 35/250 micrograms film-coated tablet (Janssen Cilag Limited).

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for applications of this type.
IV.5 Clinical safety
No new safety data were submitted and none are required.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The marketing authorisation holder (MAH) has submitted a risk management plan (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 Emoloza 250/35 micrograms film-coated tablets.

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

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>Labeling: Sufficient information regarding risk of Venous thromboembolism is included in following sections of SmPC i.e. Section 4.3; Contraindications, Section 4.4; Special warnings and precautions for use and Section 4.8; Undesirable effects. PIL also includes sufficient information</td>
<td>None proposed</td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td>Labeling: Sufficient information regarding risk of Arterial thromboembolism is included in following sections of SmPC i.e. Section 4.3; Contraindications, Section 4.4; Special warnings and precautions for use and Section 4.8; Undesirable effects. PIL also includes sufficient information</td>
<td>None proposed</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Labeling: Sufficient information regarding risk of breast cancer is included in following sections of SmPC i.e. Section 4.3; Contraindications, Section 4.4; Special warnings and precautions for use and Section 4.8; Undesirable effects. PIL also includes sufficient information</td>
<td>None proposed</td>
</tr>
<tr>
<td>Hepatic adenomas</td>
<td>Labeling: Sufficient information regarding risk of hepatic adenomas is included in following sections of SmPC i.e. Section 4.3; Contraindications, Section 4.4; Special warnings and precautions for use and Section 4.8; Undesirable effects. PIL also includes sufficient information</td>
<td>None proposed</td>
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TABLE

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tr>
<td>Cervical cancer</td>
<td>Labeling: Sufficient information regarding risk of cervical cancer is included in following sections of SmPC i.e. Section 4.4; Special warnings and precautions for use and Section 4.8; Undesirable effects. PIL also includes sufficient information</td>
<td>None proposed</td>
</tr>
<tr>
<td>Drug interaction with hepatic enzyme inducers</td>
<td>Labeling: Sufficient information regarding risk of cervical cancer is included in following sections of SmPC i.e. Section 4.5; Interaction with other medicinal products and other forms of interaction. PIL also includes sufficient information</td>
<td>None proposed</td>
</tr>
</tbody>
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IV.7 Discussion on the clinical aspects
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. 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 concerns have been identified. Extensive clinical experience with norgestimate and ethinylestradiol is considered to have demonstrated the therapeutic value of the compounds. 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 this medicine is as follows:
PAR Emoloza 250/35 micrograms film-coated tablets

Norgestimate / Ethinylestradiol

Lupin (Europe) Limited

UK/H/6593/001/DC
Table of content of the PAR update for MRP and DCP

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

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