Public Assessment Report

Decentralised Procedure

Feanolla 75 microgram film coated tablet (desogestrel)

Procedure No: UK/H/4185/DC

UK Licence No: PL 35507/0040

Lupin (Europe) Limited
LAY SUMMARY

On 11 December 2012, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Lupin (Europe) Limited for the medicinal product Feanolla 75 microgram film coated tablet (PL 35507/0040; UK/H/4185/001/DC). This medicine is only available on prescription from your doctor and is used to prevent pregnancy. Feanolla 75 microgram film coated tablet may be referred to as ‘Feanolla’ in this report.

There are 2 main kinds of hormone contraceptive:
- the combined pill, - “The Pill”, which contains 2 types of female sex hormone, an oestrogen and a progestogen
- the progestogen-only pill, POP or mini-pill, which does not contain an oestrogen.

Feanolla is a progestogen-only pill (POP), or a mini-pill. Feanolla contains a small amount of one type of female sex hormone, the progestogen desogestrel.

Most POPs or minipills work primarily by preventing the sperm cells from entering the womb but they do not always prevent the egg cell from ripening, which is the main way that combined pills work. Feanolla is different from other mini-pills in having a dose that in most cases prevents the egg cell from ripening. As a result, Feanolla is a highly effective contraceptive. In contrast to the combined pill, Feanolla can be used by women who do not tolerate oestrogens and by women who are breast feeding. A disadvantage is that vaginal bleeding may occur at irregular intervals during the use of Feanolla. On the other hand the patient may not have any bleeding at all.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Feanolla 75 microgram film coated tablet outweigh the risks and a Marketing Authorisation was granted.
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Module 1
Information about the initial procedure

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<th>Product Name</th>
<th>Feanolla 75 microgram film coated tablet</th>
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<tr>
<td>Type of Application</td>
<td>Directive 2001/83/EEC (as amended) Generic, Article 10(1)</td>
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<td>Active Substance</td>
<td>Desogestrel</td>
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<td>Form</td>
<td>Film-coated tablets</td>
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<td>Strength</td>
<td>75 micrograms</td>
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<td>MA Holder</td>
<td>Lupin (Europe) Limited, Victoria Court, Bexton Road, Knutsford, Cheshire, WA16 0PF, United Kingdom</td>
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<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Germany, Spain and Italy</td>
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<td>Procedure Number</td>
<td>UK/H/4185/001/DC</td>
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<tr>
<td>Timetable</td>
<td>Day 210 – 31 October 2012</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Carton:
Module 5

Scientific discussion during initial procedure

1 INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Feanolla 75 microgram film coated tablet (PL 35507/0040; UK/H/4185/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for oral contraception.

Desogestrel is the active ingredient in Feanolla 75 microgram film coated tablet. The contraceptive effect of desogestrel is primarily by inhibition of ovulation and also by increasing the viscosity of the cervical mucus.

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS), and Germany, Spain and Italy as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Cerazette 75 microgram film-coated tablet (Organon Laboratories, UK), first authorised in the UK on 09 November 1998.

A single-dose, bioequivalence study was submitted to support this application, comparing the applicant’s test product Desogestrel tablets 75 microgram and the reference product Cerazette tablets 75 microgram (Organon, France). The bioequivalence study was carried out in accordance with 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 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 31 October 2012. After a subsequent national phase, a licence was granted in the UK on 11 December 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Feanolla 75 microgram film coated tablet |
| Name of the active substance(s) (INN) | Desogestrel |
| Pharmacotherapeutic classification (ATC code) | Hormonal contraceptives for systemic use, (G03AC09) |
| Pharmaceutical form and strength(s) | Film-coated tablets; 75 micrograms |
| Reference number for the Mutual Recognition Procedure | UK/H/4185/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Germany, Spain and Italy |
| Marketing Authorisation Number | PL 35507/0040 |
| Name and address of the authorisation holder | Lupin (Europe) Limited, Victoria Court, Bexton Road, Knutsford, Cheshire, WA16 0PF, United Kingdom |

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Desogestrel
Chemical name(s): 13-ethyl-11-methylidene-18, 19-dinor-17a-pregn-4-en-20-yn-17-ol

Structure:

![Structure of Desogestrel]

Molecular formula: C22H30O
Molecular mass: 310.5
Appearance: White or almost white crystalline powder.
Solubility: Practically insoluble in water, very soluble in methanol, freely soluble in anhydrous ethanol and in methylene chloride.

Desogestrel is the subject of a European Pharmacopoeia monograph.

Synthesis of the active 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. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards. Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.
Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.

**Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in the tablet core and film-coating, namely lactose monohydrate, All rac α Tocopherol (E307), povidone K30, silica colloidal anhydrous, talc (E553b), maize starch, stearic acid, magnesium stearate (E470b), hypromellose (HPMC2910, E464), titanium dioxide (E171) and Macrogol 400 (PEG 400). Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that intended for human consumption. In addition, the supplier has confirmed that no ruminant material other than calf rennet is used during the production of lactose monohydrate.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

**Pharmaceutical Development**

The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the reference product, Cerazette 75 microgram film coated tablets (Organon, France).

Suitable pharmaceutical development data have been provided for this application. Comparative in-vitro dissolution profiles have been provided for this product and the reference 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. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation holder has committed to performing process validation on future production-scale batches.

**Control of Finished Product**

The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**

The tablets are packed in blister packs, using clear transparent PVC film as forming (base) material and hard tampered plain aluminium foil as lidding material. Each blister is packed in an aluminium laminated pouch, which are further packed in cartons with Patient Information Leaflets. Each blister contains 28 tablets.
Feanolla is available in packs of 28 (1x28), 84 (3x28) and 168 (6x28) film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.

**Stability of the product**

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years. This medicinal product does not require any special storage precautions.

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

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

The SmPC, PIL and labelling are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. 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 patients/users are able to act upon the information that it contains.

**MAA (Marketing Authorisation Application) form**

The MAA form is 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**

The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of desogestrel are well-known, no new non-clinical data have been submitted and none are required.

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.

Although the proposed product will be used to substitute for the originator product, the Marketing Authorisation Holder (MAH) has provided an Environmental Risk Assessment as the active substance (or its active metabolite, 3-keto desogestrel [etonorgestrel]) is likely to act as an endocrine disruptor. The Predicted Environmental concentration/Predicted No-Effect Concentration (PEC/PNEC) ratios for surface water and groundwater were estimated to be less than one (the threshold value), which suggest that desogestrel should not pose a risk to aquatic organisms. 3-keto desogestrel (etonorgestrel) is not readily biodegradable and are likely to demonstrate significant shifting to the sediment. However, upon extrapolation of toxicity data generated with ethinylestradiol, the MAH considers that etonorgestrel should not pose a risk to sediment-dwelling organisms, which is acceptable.

The grant of a Marketing Authorisation is recommended.
III.3 CLINICAL ASPECTS

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

Pharmacokinetics

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

An open label randomised, two-period, two-treatment, two-sequence, single-dose crossover study comparing the pharmacokinetics of the test product Desogestrel tablets 75 microgram (Lupin Limited) and the reference product Cerazette tablets 75 microgram (Organon, France) in healthy, adult female subjects under fasting conditions.

The subjects were given a single dose (4x75 micrograms) of either the test or reference product with 240 ml of water, after at least an 8 hour overnight fast. Blood samples were collected before and up to 72 hours after each administration. The washout period between the treatment arms was 16 days. As it has been demonstrated that desogestrel is virtually undetectable in plasma and 3-keto desogestrel is responsible for the pharmacodynamic action of desogestrel, the plasma concentrations of 3-keto desogestrel (etonorgestrel) were determined. The pharmacokinetic results are presented below.

Pharmacokinetic parameters (geometric least squares mean, ratios and 90% confidence intervals [CI] of 3-keto desogestrel (etonorgestrel))

<table>
<thead>
<tr>
<th>Parameters (units)</th>
<th>Desogestrel 4x75 mcg (Test)</th>
<th>Cerazette 4x75 mcg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
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<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>3450.651</td>
<td>3129.561</td>
<td>110.26</td>
<td>99.43-122.27</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>31798.830</td>
<td>30893.401</td>
<td>102.93</td>
<td>97.69-108.45</td>
</tr>
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</table>

AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours
C<sub>max</sub> maximum plasma concentration

Ratios and 90% CI calculated from ln-transformed data

The 90% confidence intervals of the test/reference ratio for AUC<sub>0-t</sub>, AUC<sub>0-inf</sub> and C<sub>max</sub> lie within the acceptable limits of 80% to 125%, in line with the Note for Guidance 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 Desogestrel tablets 75 microgram is bioequivalent to the reference product Cerazette tablets 75 microgram (Organon, France).

Efficacy

The efficacy of desogrestrel is well-known. No new efficacy data have been submitted and none are required for this type of application.

Safety

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

Pharmacovigilance System and Risk Management Plan

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.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

**Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL), Labels**
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and is in line with the current guidelines. The labelling is in line with the current guidelines.

**Clinical Expert Report (Clinical Overview)**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Feanolla 75 microgram film coated 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 an application of this type.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application.

Bioequivalence has been demonstrated between the applicant’s product and the reference product Cerazette tablets 75 microgram (Organon, France).

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of desogestrel is well-known, no additional data were required.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with desogestrel is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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