Quichelle 0.02 mg / 3mg Film-Coated Tablets
(ethinylestradiol and drospirenone)

PL 35507/0090

UKPAR

TABLE OF CONTENTS

Lay Summary .............................................. Page 2
Scientific discussion .................................. Page 3
Steps taken for assessment ......................... Page 13
Steps taken after authorisation – summary ....
Summary of Product Characteristics .............. Page 14
Patient Information Leaflet ......................... Page 15
Labelling .................................................. Page 16
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Lupin (Europe) Limited a Marketing Authorisation for the medicinal product Quichelle 0.02 mg / 3mg Film-Coated Tablets (PL 35507/0090) on 22 February 2013. This medicine is only available on prescription from your doctor.

Quichelle 0.02 mg / 3mg Film-Coated Tablets are a combined contraceptive pill and are used to prevent pregnancy. Each of the 24 pink tablets contains two different hormones called ethinylestradiol and drospirenone. The white tablets contain no hormones and are called placebo (inert) tablets. Contraceptive pills that contain two hormones are called ‘combination’ pills.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Quichelle 0.02 mg / 3mg Film-Coated Tablets outweigh the risks and a Marketing Authorisation was granted.
Quichelle 0.02mg / 3mg Film-Coated Tablets (ethinylestradiol and drospirenone)

PL 35507/0090

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 9
Clinical assessment Page 10
Overall conclusions and risk assessment Page 12
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Lupin (Europe) Limited a Marketing Authorisation for the medicinal product Quichelle 0.02 mg / 3mg Film-coated Tablets (PL 35507/0090) on 22 February 2013. This product is a prescription-only medicine (POM) used for oral contraception.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, cross-referring to Yasmin, Omhulde tabletten 0.03/3 mg (Bayer BV, Netherlands), which was authorised in the Netherlands on 07 April 2000. The corresponding reference product in the UK is Yasminelle 0.02 mg / 3mg film-coated Tablets (PL 00010/0573; Bayer plc, UK), which first authorised in the UK on 31 August 2006.

Quichelle 0.02 mg / 3mg Film-coated Tablets are a combined oral contraceptive, which contain the active ingredients ethinylestradiol and drospirenone. Combination oral contraceptives (COCs) act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. The contraceptive effect of drospirenone and ethinylestradiol tablets is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.

One bioequivalence study was submitted to support this application, comparing the applicant’s test product Drospirenone and Ethinyl Estradiol Tablets 3 mg/0.02 mg with the reference product Jasminelle Tablets (Schering SAS, 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 the 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 review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Quichelle 0.02 mg / 3mg Film-Coated Tablets outweigh the risks and a Marketing Authorisation was granted.
**PHARMACEUTICAL ASSESSMENT**

**ACTIVE SUBSTANCE – ETHINYLESTRADIOL**

INN: Ethinylestradiol  
Chemical name: 19-Nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol;  
(17α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol;  
17α-ethynyl-1,3,5(10)-estra-triene-3,17β-diol;.

Structure:

![Structure of Ethinylestradiol](image)

Molecular formula: $C_{20}H_{24}O_2$  
Molecular weight: 296.4  
Appearance: White or slightly yellowish-white crystalline powder. Practically insoluble in water, soluble in chloroform and in ether, freely soluble in alcohol.

Ethinylestradiol 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 specifications. 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 supporting a suitable retest period when stored in the proposed packaging.

**ACTIVE SUBSTANCE - DROSPIRENONE**

INN: Drospirenone  
Chemical Name: (2′,S, 6R, 7R, 8R, 9S, 10R, 13S, 14S, 15S, 16S) - 1, 3′, 4′, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,16, 20, 21-Hexadecahydro -10, 13-dimethylspirol [17H-dicyclopropa [6,7:15,16]cyclopenta [a] phenanthrene-17, 2′, (5′H)-furan] -3, 5′ (2H) dione;  
3-Oxo-6α,7α,15α,16α-tetrahydro-3′H,3″H-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone.

Molecular Formula: $C_{24}H_{30}O_3$
Structure

Molecular weight: 366.49
Appearance: A white or almost white powder.
Solubility Practically insoluble in water, soluble in methylene chloride and methanol and sparingly soluble in ethanol (96%).

Drospirenone 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 specifications. 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 supporting a suitable retest period when stored in the proposed packaging.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients in the tablet core and coating namely lactose monohydrate, corn starch, pregelatinised starch, magnesium stearate, hypromellose (E464), titanium dioxide (E171), talc (E553b; active tablet only) iron oxide red (E172; active tablet only) and macrogol/PEG (placebo tablet only). Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of, hypromellose, titanium dioxide (E171), talc (E553b) and iron oxide red and macrogol/PEG which are controlled to suitable in-house specifications. Satisfactory 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:

- safe efficacious, stable tablets containing ethinylestradiol and drospirenone, that were comparable in performance to the originator products Jasminelle 0.02/3 mg (Schering SAS, France) and Yasminelle 0.02/3 mg (Schering Germany),
- robust, stable inert tablets that were comparable in performance to the inert tablets in the US version of the reference product (Yaz tablets, Bayer Healthcare).

Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution and impurity profiles have been provided for this product and the reference product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing processes. The manufacturing processes have been validated with pilot-scale batches and have shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production 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 packaged in transparent polyvinyl chloride/aluminium or polyvinyl chloride/Aclar/aluminium blisters. Each blister contains 24 active tablets and 4 placebo tablets. The blisters are packed in either a carton or carton wallet, with a Patient Information Leaflet, in pack sizes of 28, 3x28 and 6x28 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
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 the storage conditions ‘Store below 25°C.’

Bioequivalence
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory 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 the patients/users are able to act upon the information that it contains.

**MAA (Marketing Authorisation Application) Form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Expert Report (Quality Overall Summary)**
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
As the pharmacodynamic, pharmacokinetic and toxicological properties of ethinylestradiol and drospirenone are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT (NON-CLINICAL OVERVIEW)
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.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
The clinical pharmacology of ethinylestradiol and drospirenone is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

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

A randomised, open label, two-treatment, two-sequence, two-period, crossover single-dose study to compare the pharmacokinetics of the test product Drospirenone and Ethinyl Estradiol Tablets 3mg/0.02 mg (Lupin Limited) versus the reference product Jasminelle Tablets (Schering SAS, France) in healthy postmenopausal female subjects under fasting conditions.

The subjects were administered either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood samples were collected before 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:

### Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI]) for drospirenone

<table>
<thead>
<tr>
<th></th>
<th>Geometric least square means</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (Test)</td>
<td>R (Reference)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>41.992</td>
<td>45.382</td>
<td>92.53</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ng*hr/mL)</td>
<td>714.769</td>
<td>705.969</td>
<td>101.25</td>
</tr>
</tbody>
</table>

C<sub>max</sub> maximum plasma concentration
AUC<sub>0-72</sub> area under the plasma concentration-time curve from time zero to 72 hours
Ratios and 90% CI calculated from ln-transformed data
T- Test product (Drospirenone and Ethinyl Estradiol Tablets 3mg/0.02 mg)
R-Reference product (Jasminelle Tablets [Drospirenone and Ethinyl Estradiol Tablets 3mg/0.02 mg])

### Pharmacokinetic parameters (geometric least square means, ratios and confidence intervals [CI]) for ethinylestradiol

<table>
<thead>
<tr>
<th></th>
<th>Geometric least square mean</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T (Test)</td>
<td>R (Reference)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>58.228</td>
<td>62.282</td>
<td>93.49</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (pg*hr/mL)</td>
<td>776.429</td>
<td>774.288</td>
<td>100.28</td>
</tr>
</tbody>
</table>

C<sub>max</sub> maximum plasma concentration
AUC<sub>0-72</sub> area under the plasma concentration-time curve from time zero to 72 hours
T- Test product (Drospirenone and Ethinyl Estradiol Tablets 3mg/0.02 mg)
R-Reference product (Jasminelle Tablets [Drospirenone and Ethinyl Estradiol Tablets 3mg/0.02 mg])

The Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits as 80.00 to 125.00 % for AUC and C<sub>max</sub> values. Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Jasminelle Tablets (Schering SAS, France) under fasting conditions.
Efficacy
The efficacy of ethinylestradiol and drospirenone are well-known. No new efficacy data have been submitted and none are required for this type of application.

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

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), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory 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 in line with the current guidance. The labelling is in line with current guidance.

Clinical Expert Report (Clinical Overview)
The clinical overview is 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.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Quichelle 0.02 mg / 3mg Film-coated Tablets 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. As the pharmacokinetics, pharmacodynamics and toxicology of ethinylestradiol and drospirenone are well-known, no additional data were required.

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 Jasminelle Tablets (Schering SAS, France) under fasting conditions.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profiles of ethinylestradiol and drospirenone are well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and in line with the current guidance. The labelling is in line with current guidance.

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 ethinylestradiol and drospirenone is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk balance is, therefore, considered to be positive.
Quichelle 0.02 mg / 3 mg Film-Coated Tablets
(ethinylestradiol and drospirenone)

PL 35507/0090

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Marketing Authorisation application on 31 December 2010.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 17 February 2011.
3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 12 January 2012, and on the quality dossier on 12 January 2012, 11 May 2012 and 12 June 2012.
5. The application was granted on 22 February 2013.
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.
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.
UKPAR Quichelle 0.02 mg / 3 mg Film-Coated Tablets

LABELLING