PAROXETINE 10 MG FILM-COATED TABLETS

PL 00142/0838

UKPAR

TABLE OF CONTENTS

Lay Summary ............................................. Page 2
Scientific discussion ............................... Page 3
Steps taken for assessment ................ Page 13
Steps taken after authorisation – summary Page 14
SmPC, PIL and Labelling ....................... Page 15
PAROXETINE 10 MG FILM-COATED TABLETS
PL 00142/0838

LAY SUMMARY

On 26th July 2012, the MHRA granted Actavis UK Limited a Marketing Authorisation (licence) for Paroxetine 10 mg Film-coated Tablets.

Paroxetine 10 mg Film-coated Tablets contain the active ingredient, paroxetine hydrochloride.

Paroxetine is one of a type of antidepressants known as Selective Serotonin Re-uptake Inhibitors (SSRIs). Low levels of the hormone serotonin are thought to be a cause of depression and other related conditions.

Paroxetine works by bringing the levels of serotonin back to normal.

Paroxetine is used in adults to treat:
- depression
- obsessive compulsive disorder
- panic disorder with or without agoraphobia (fear of open spaces or new situations)
- social anxiety disorders/social phobias
- post traumatic stress disorder
- anxiety disorders.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Paroxetine 10 mg Film-coated Tablets outweigh the risks; hence a Marketing Authorisation has been granted.
PAROXETINE 10 MG FILM-COATED TABLETS
PL 00142/0838

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 5
Non-clinical assessment Page 8
Clinical assessment Page 9
Overall conclusions and risk benefit assessment Page 12
INTRODUCTION

On 26th July 2012, the UK granted Actavis UK Limited a Marketing Authorisation for the medicinal product Paroxetine 10 mg Film-coated Tablets (PL 00142/0838).

Paroxetine 10 mg Film-coated Tablets is a prescription-only medicine (POM) for the treatment of:
- Major Depressive Episodes
- Obsessive Compulsive Disorder
- Panic Disorder with and without agoraphobia
- Social Anxiety Disorder/Social phobia
- Generalised Anxiety Disorder
- Post-traumatic Stress Disorder

This application for Paroxetine 10 mg Film-coated Tablets was submitted under Article 10 (1) of Directive 2001/83/EC, as amended, cross-referring to Seroxat 20 mg Film-coated Tablets, authorised in Sweden to SmithKline Beecham on 11th December 1990. The applicant is claiming that Paroxetine 10 mg Film-coated Tablets is a generic medicinal product of Seroxat 10 mg Film-coated Tablets first authorised to SmithKline Beecham Limited on 29th July 2005 (PL 10592/0218).

Paroxetine hydrochloride is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake and its antidepressant action and effectiveness in the treatment of obsessive compulsive disorder (OCD), social anxiety disorders/social phobia, generalised anxiety disorder, post-traumatic stress disorder and panic disorder is thought to be related to its specific inhibition of 5-HT uptake in brain neurons.

The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH 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.

A satisfactory justification has been provided for the absence of a Risk Management Plan.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN: Paroxetine hydrochloride anhydrous
Chemical name: \((3S,4R)-3-[(1,3\text{-} \text{benzodioxol-5\text{-}yloxy})\text{methyl}]\text{-}4\text{-}(4\text{-}fluorophenyl)\text{piperidine\ hydrochloride\ anhydrous}\)

Structure:

Physical form: A white or off-white powder
Molecular formula: \(\text{C}_{19}\text{H}_{20}\text{FNO}_{3}\text{HCl}\)
Molecular weight: 365.83

The paroxetine hydrochloride anhydrous used in the product complies with the European Pharmacopoeia monograph for paroxetine hydrochloride anhydrous.

Valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificates of Suitability have been provided. The quality of the substance is suitably controlled in line with the current edition of the relevant European Pharmacopoeia Monograph.

The manufacturing process, control of materials, control of critical steps, validation and process development for paroxetine hydrochloride anhydrous were assessed and approved by the EDQM in relation to the granting of the Certificates of Suitability and are therefore satisfactory.

An appropriate specification is provided for the drug substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Details have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

The container closure system and re-test period for paroxetine hydrochloride anhydrous complies with the container closure and re-test period specified on the Certificates of Suitability.

DRUG PRODUCT
Other ingredients
Other ingredients in the tablet core are pharmaceutical excipients magnesium stearate, sodium starch glycollate, mannitol and microcrystalline cellulose.
The tablet is coated with Opadry AMB blue coating. The ingredients in this coating are polyvinyl alcohol-part hydrolysed, titanium dioxide (E171), talc, indigo carmine lake (E132), lecithin soya (E322), xanthan gum (E415), sunset yellow FCF lake (E110), quinoline yellow lake (E104) and basic butylated methacrylate copolymer.

With the exception of indigo carmine lake (E132), lecithin soya, quinoline yellow lake (E104) and sunset yellow FCF lake (E110), all the ingredients comply with their relevant European Pharmacopoeia monographs. Indigo carmine lake (E132), quinoline yellow lake (E104) and sunset yellow FCF lake (E110) all comply with in-house specifications and EEC requirements for colouring agents. Lecithin soya complies with the United States Pharmacopoeia- National Formulary (USP-NF).

None of the excipients used contain material of animal or human origin. Confirmation has been provided to confirm that the magnesium stearate used in this product is of vegetable origin.

**Pharmaceutical Development**

The objective of the development programme was to produce a safe, efficacious product containing paroxetine that could be considered a generic medicinal product of Seroxat 10 mg Film-coated Tablets.

Paroxetine 10 mg Film-coated Tablets were developed as a line extension to the MAH’s existing licences for Paroxetine 20 mg and 30 mg Film-coated Tablets (PL 00142/0538-9). The composition of the tablet core of Paroxetine 10 mg Film-coated Tablets is identical and dose-proportional to the tablet cores of Paroxetine 20 mg and 30 mg Film-coated Tablets.

The applicant has provided suitable product development information. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution and impurity profiles were provided for the proposed and reference product, Seroxat 10 mg Film-coated Tablets. Comparative *in vitro* dissolution profiles were also provided for the proposed product and Paroxetine 20 mg and 30 mg Film-coated Tablets.

**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 and has shown satisfactory results. Process validation data on batches have been provided and are satisfactory. The applicant has committed to perform process validation on future full scale commercial batches.

**Finished Product Specification**

The finished product specification is acceptable. 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 product is packaged in blisters composed of aluminium and comes in pack sizes of 10, 14, 20, 28, 30, 50, 56, 60, 98, 100 and 500 tablets, or 1 x 50 unit dose. Not all pack sizes may be marketed.
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and legislation.

**Stability of the product**
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with no special storage instructions. This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically acceptable.

As the PIL is similar to already approved products Paroxetine 20 mg and 30 mg Film-coated Tablets (PL 00142/0538-9), user testing results for these licences have been submitted with a satisfactory bridging report.

The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and 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 Form**
This is pharmaceutically satisfactory.

**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**
From a quality point of view, it is recommended that a Marketing Authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

A satisfactory justification was provided for the absence of an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed, however, to support the application, the Marketing Authorisation Holder has included two studies:
- A single-dose bioavailability comparison study of the test and reference products at the 20 mg tablet strength and,
- A steady state comparison of the test and reference products at the 30 mg tablet strength.
These studies were used to support licence applications for Paroxetine 20 mg and 30 mg Film-coated Tablets (PL 00142/0538-9).
A satisfactory waiver for any additional study with the 10 mg strength has been provided.

Study 1
A comparative, randomised, two-way, two-period, single-dose, crossover study comparing the pharmacokinetics of Paroxetine 20 mg Film-coated Tablets (Test) versus Seroxat (paroxetine) 20 mg Film-coated Tablets (SmithKline Beecham Limited, UK) (Reference) in healthy volunteers under fasting conditions.

Blood sampling was performed pre-dose and at set time-points up to 96 hours post dose in each treatment period. There was a washout period of 14 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>geometric Least Mean Squares and 90% Confidence Interval for paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC_{0-t} (ng.hr/mL)</td>
</tr>
<tr>
<td>Test</td>
<td>158 (4.28)</td>
</tr>
<tr>
<td>Reference</td>
<td>146 (4.59)</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>108 (98.6 - 118 %)</td>
</tr>
</tbody>
</table>

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

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio for AUC_{0-t} and C_{max} for paroxetine lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products for the 20 mg tablet strength.

Study 2
A comparative, open-label, laboratory-blind, randomised, multiple-dose, two-period, crossover study comparing the pharmacokinetics of Paroxetine 30 mg Film-coated Tablets (Test) versus Seroxat (paroxetine) 30 mg Film-coated Tablets (SmithKline Beecham Limited, UK) (Reference) in healthy volunteers under fasting conditions.

The study consisted of two consecutive treatment phases with a run-in period of 10 days with serum drug levels being recorded for 24 hours through days 11 – 12. Pharmacokinetic parameters were calculated and statistically analysed.
Results from this study are presented below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC (ng.hr/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>2350 (1.53)</td>
<td>132 (1.53)</td>
</tr>
<tr>
<td>Reference</td>
<td>2223 (1.67)</td>
<td>125 (1.62)</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>105 (99.3 – 112 %)</td>
<td>106 (101 – 111 %)</td>
</tr>
</tbody>
</table>

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

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio for AUC and C_{\text{max}} for paroxetine lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products for the 30 mg tablet strength.

As the 10mg, 20 mg and 30 mg tablet strengths meet all the biowaiver criteria as specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results and conclusions of the studies on the 20 mg and 30 mg tablet strengths can be extrapolated to Paroxetine 10 mg Film-coated Tablets.

**Efficacy**
No new efficacy data were submitted with this generic application and none were required.

**Safety**
With the exception of the data submitted during the studies, no new safety data were submitted with this generic application and none were required. No new or unexpected safety concerns were raised during the studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product.

**MAA Form**
The MAA form is clinically satisfactory.

**Clinical Overview**
The clinical overview has been written by a suitably qualified person and is satisfactory.

**Conclusion**
The studies have shown that Paroxetine 20 mg and 30 mg Film-coated Tablets can be considered as generic medicinal products to the reference products Seroxat 20 mg and 30 mg Film-coated Tablets. A satisfactory waiver has been provided and therefore, no bioequivalence study for the 10 mg tablet strength is required. The bioequivalent outcome from the studies for the 20 mg and 30 mg tablet strengths can be extrapolated to Paroxetine 10 mg Film-coated Tablets.
From a clinical point of view, it is recommended that a Marketing Authorisation is granted for this application.
OVERALL CONCLUSIONS AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Paroxetine 10 mg 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 and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between previously approved Paroxetine 20 mg and 30 mg Film-coated Tablets and the reference product, Seroxat 20 mg and 30 mg Film-coated Tablets. As the 10mg, 20 mg and 30 mg tablet strengths meet all the biowaiver criteria as specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results and conclusions of the studies on the 20 mg and 30 mg tablet strengths can be extrapolated to Paroxetine 10 mg Film-coated Tablets.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The studies support the claim that the proposed product and the reference product are interchangeable. Clinical experience with paroxetine is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
PAROXETINE 10 MG FILM-COATED TABLETS  
PL 00142/0838

STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 22nd March 2011.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 6th April 2011.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the dossier on 15th June 2011, 18th October 2011, 12th January 2012 and 14th March 2012.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 19th July 2011, 12th January 2012, 21st February 2012 and 11th April 2012.</td>
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<td>5</td>
<td>The application was determined on 26th July 2012.</td>
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<tr>
<td>Date submitted</td>
<td>Application type</td>
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<td>07/08/2013</td>
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SUMMARY OF PRODUCT CHARACTERISTICS
The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.

PATIENT INFORMATION LEAFLET
The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.

LABELLING
<table>
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Annex 1

Reference: PL 00142/0838-0011
Product: Paroxetine 10 mg Film-Coated Tablets
Marketing Authorisation Holder: Actavis UK Limited
Active Ingredient(s): Paroxetine hydrochloride anhydrous

Reason:
To update section 5.1 (Pharmacodynamic properties) of the SmPC by including the text regarding the adult suicidal analysis, to bring it in line with the brand leader Seroxat (Smithkline Beecham Limited).

Supporting Evidence
A revised SmPC has been provided.

Evaluation
The amended text in section 5.1 of the SmPC is satisfactory.

The current approved UK version of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.

Decision
Approved on 29 August 2013.