AMISULPRIDE 50 MG, 100 MG AND 200MG TABLETS
PL 39891/0004-6

AMISULPRIDE 400MG FILM-COATED TABLETS
PL 39891/0007

UKPAR

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LAY SUMMARY

On 15 February 2013, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Double-E Pharma Limited Marketing Authorisations for the medicinal products Amisulpride 50 mg, 100 mg and 200 mg tablets, and Amisulpride 400 mg film-coated tablets (PL 39891/0004-7). These are prescription-only medicines (POM) used to treat schizophrenia.

The active ingredient is amisulpride, which belong to a group of medicines called ‘anti-psychotics’. Amisulpride is used to treat an illness called schizophrenia. Schizophrenia can make you feel, see or hear things which do not exist, have strange and frightening thoughts, change how you act and make you feel alone. Sometimes people with these symptoms may also feel tense, anxious or depressed. Amisulpride works by improving disturbed thoughts, feelings and behaviour. It is used to treat schizophrenia when it starts and also over the longer term.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Amisulpride 50 mg, 100 mg and 200 mg tablets, and Amisulpride 400mg film-coated tablets outweigh the risks and Marketing Authorisations have been granted.
AMISULPRIDE 50 MG, 100 MG AND 200 MG TABLETS
PL 39891/004-6
AMISULPRIDE 400MG FILM-COATED TABLETS
PL 39891/0007

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Double-E Pharma Limited, Marketing Authorisations for the medicinal products Amisulpride 50 mg, 100 mg and 200 mg tablets, and Amisulpride 400mg film-coated tablets (PL 39891/0004-7) on 15 February 2013. The products are prescription-only medicines (POM) and are indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

The applications were submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Solian 50 mg, 100 mg, 200 mg and 400 mg tablets (Sanofi-Aventis France, France) first approved in France in January 1986. The corresponding reference products in the UK are Solian 50 mg, 100 mg, 200 mg and 400 mg tablets (PL 04425/0650-53; Aventis Pharma Limited), first authorised in the UK in August 1997.

No new non-clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed for over 10 years.

Two single-dose, fasting, bioequivalence studies were submitted to support the applications, one with the 200mg tablet and the other with the 400 mg film-coated tablet. The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence studies, no new clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed 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 Amisulpride 50 mg, 100 mg and 200 mg tablets, and Amisulpride 400mg film-coated tablets outweigh the risks, hence Marketing Authorisations have been granted.
ACTIVE SUBSTANCE

INN: Amisulpride
Chemical Name: 4-amino-N-[(2RS)-1-ethylpyrrolidin-2-yl]methyl]-5-(ethylsulphonyl)-2-methoxybenzamide 4-amino-N-[ethyl-2-pyrrolidinyl]methyl]-5-(ethylsulfonyl)-o-anisamide
Molecular Formula: C_{17}H_{27}N_{3}O_{4}S

Amisulpride is the subject of a European Pharmacopoeia monograph.

Manufacture

All aspects of the manufacture and control of the active substance amisulpride are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

MEDICINAL PRODUCT

Other ingredients

The 50 mg, 100 mg and 200 mg tablets contain the pharmaceutical excipients lactose monohydrate, methylcellulose, sodium starch glycollate (Type A), microcrystalline cellulose and magnesium stearate.

The 400 mg tablets contain the pharmaceutical excipients lactose monohydrate, methylcellulose, sodium starch glycollate (Type A), microcrystalline cellulose, magnesium stearate, Eudragit (E100), titanium dioxide (E171), talc and Macrogol 6000.

Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph. 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 products.
Pharmaceutical Development
The objective of the development programme was to produce safe, efficacious products containing 50 mg, 100 mg, 200 mg and 400 mg amisulpride, that could be considered generic medicinal products of Solian 50 mg, 100 mg, 200 mg and 400 mg Tablets (Sanofi-Synthelabo, France, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative physicochemical data and in vitro dissolution profiles have been provided for the test and reference products.

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 with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container Closure System
All strengths of the tablets are packaged in polyvinylchloride/aluminium blister strips in a pack size of 60 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

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. Based on the results, a shelf-life of 36 months has been proposed, with no special storage precautions for the product.

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

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence studies.
Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, 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 Forms
The MAA forms are satisfactory.

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 Marketing Authorisations is recommended.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of originator products that have been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
The non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT
An environmental Risk Assessment was not submitted and none is required for these applications. This is acceptable given that the applications are for generic medicinal products of originator products that have been licensed for over 10 years.

CONCLUSION
The grant of Marketing Authorisations is recommended.
CLINICAL ASSESSMENT

PHARMACOKINETICS
In support of these applications, the Marketing Authorisation holder has submitted the following bioequivalence studies:

Study 1
A randomised, open-label, single-dose, two-period, crossover study comparing the test product Amisulpride 200 mg tablets (Double-E Pharma Limited) and the reference product Solian 200 mg tablets (Sanofi-Synthelabo, France) in healthy male subjects under fasting conditions.

Subjects were administered one tablet of either the test or the reference product with 240 ml of water, after at least a 10-hour fast. Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. The washout period between the two treatment arms was 6 days. Pharmacokinetic parameters were measured from plasma and statistically analysed. The pharmacokinetic results (presented as ratios and 90% confidence intervals) are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic means ± SD, ratios and confidence intervals [CI]) of amisulpride)</th>
<th>Amisulpride 200 mg (Test)</th>
<th>Solian 200 mg (Reference)</th>
<th>Test/Ref Ratio (%)</th>
<th>90% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋₅ (ng.h/mL)</td>
<td>5215.27±1303.78</td>
<td>5432.87±1417.49</td>
<td>96.65%</td>
<td>90.76-102.92</td>
</tr>
<tr>
<td>AUC₀₋₅₀ (ng.h/mL)</td>
<td>5311.76±1298.50</td>
<td>5546.93±1409.85</td>
<td>96.36%</td>
<td>90.67-102.40</td>
</tr>
<tr>
<td>Cₘₐₓ (ng/mL)</td>
<td>687.05±353.28</td>
<td>730.52±423.33</td>
<td>96.61%</td>
<td>86.39-108.04</td>
</tr>
</tbody>
</table>

The 90% confidence interval of the test/reference ratio of geometric means for AUC₀₋₅, AUC₀₋₅₀ and Cₘₐₓ lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 50 mg, 100 mg and 200 mg strength products meet all the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions from the bioequivalence study with the 200 mg tablet strength can be extrapolated to the 50 mg and 100 mg tablet strengths.

Study 2
A randomised, open-label, single-dose, two period crossover study comparing the test product Amisulpride 400mg film-coated tablets (Double-E Pharma Limited) and the reference product Solian 400mg Film-Coated Tablets (Sanofi-Synthelabo, France) in healthy male subjects under fasting conditions.

Subjects were administered one tablet of either the test or the reference product with 240 ml of water, after at least a 10-hour fast. Blood sampling was performed, pre-dose and up to 60 hours post dose in each treatment period. The washout period between the two treatment arms was 7 days. Pharmacokinetic parameters were measured from the plasma.
and statistically analysed. Pharmacokinetic results (presented as ratios and 90% confidence intervals) from the study are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic mean ± SD, ratio and confidence intervals [CI]) of amisulpride</th>
<th>Amisulpride 400 mg (Test)</th>
<th>Solian 400 mg (Reference)</th>
<th>Test/Ref Ratio</th>
<th>(90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀-t (ng.h/mL)</td>
<td>8662±1962</td>
<td>8733±2074</td>
<td>99.4%</td>
<td>94.8-104</td>
</tr>
<tr>
<td>AUC₀-inf (ng.h/mL)</td>
<td>8808±1962</td>
<td>8891±2096</td>
<td>99.4%</td>
<td>94.7-104</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>1269±512</td>
<td>1391±602</td>
<td>92.0%</td>
<td>81.8-103</td>
</tr>
</tbody>
</table>

The 90% confidence interval of the test/reference ratio of geometric means for AUC₀-t, AUC₀-inf and C_max lie within the acceptable limits. Thus, the data support the claim that the test product is bioequivalent to the reference product.

**EFFICACY**
The efficacy of amisulpride is well-known. No new efficacy data have been submitted and none are required for applications of this type.

**SAFETY**
With the exception of the safety data generated during the bioequivalence studies, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence studies.

**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.

A suitable justification has been provided for not submitting a Risk management plan for these products.

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**
The SmPCs, PIL and labelling are acceptable from a medical perspective. The SPCs are consistent with those for the originator products.

**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 Marketing Authorisations is recommended.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Amisulpride 50 mg, 100 mg and 200 mg tablets, and Amisulpride 400 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. As the pharmacokinetics, pharmacodynamics and toxicology of amisulpride are well-known, no additional data were required.

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

Bioequivalence has been demonstrated between the applicant’s 200 mg and 400 mg strength tablets and the respective reference products. As the 50 mg, 100 mg and 200 mg strengths of the product meet the criteria specified in the Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study with the 200 mg tablet strength can be extrapolated to the 50 mg and 100 mg tablet strengths.

SAFETY
With the exception of the safety data from the bioequivalence studies, no new data were submitted and none are required for this type of application. As the safety profile of amisulpride is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence studies.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate and in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data provided support the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with amisulpride is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
AMISULPRIDE 50 MG, 100 MG AND 200 MG TABLETS  
PL 39891/004-6
AMISULPRIDE 400MG FILM-COATED TABLETS  
PL 39891/0007

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the Marketing Authorisation applications on 15 July 2011.

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 16 August 2011.


5 The applications were determined on 15 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.
Product 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.
Amisulpride 50 mg tablets
50 mg
ORAL USE

Each tablet contains: amisulpride 50 mg.

60 Tablets