CITALOPRAM 40 MG/ML ORAL DROPS, SOLUTION.

(Citalopram hydrochloride)

PL 04416/0633

UKPAR

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 11
Steps taken after authorisation – summary Page 12
Summary of Product Characteristics Page 13
Patient Information Leaflet Page 14
Labelling Page 15
LAY SUMMARY

The MHRA granted Sandoz Ltd a Marketing Authorisation (licence) for the medicinal product Citalopram 40 mg/ml Oral Drops, Solution on 02 November 2012. This product is a prescription-only medicine (POM).

Citalopram 40 mg/ml Oral Drops, Solution contains the active ingredient citalopram which is a Selective Serotonin Reuptake Inhibitor (SSRI) and belongs to a group of medicines known as antidepressants. These medicines help to correct certain chemical imbalances in the brain that are causing the symptoms of your illness.

Citalopram 40 mg/ml Oral Drops, Solution is used for the treatment of depression and, when you feel better, to help prevent these symptoms recurring.

This medicine is also used for long-term treatment to prevent the occurrence of new episodes of depression or if you have recurrent depression.

Citalopram 40 mg/ml Oral Drops, Solution is also beneficial in relieving symptoms if you tend to suffer from panic attacks.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Citalopram 40 mg/ml Oral Drops, Solution outweigh the risks and a Marketing Authorisation was granted.
CITALOPRAM 40MG/ML ORAL DROPS, SOLUTION.

PL 04416/0633

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 10
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Sandoz Ltd a Marketing Authorisation (licence) for the medicinal product Citalopram 40 mg/ml Oral Drops, Solution (PL 04416/0633) on 02 November 2012. This product is a prescription-only medicine (POM).

Citalopram 40 mg/ml Oral Drops, Solution is used for the following indications:
- treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.
- treatment of panic disorder with or without agoraphobia

This is an abridged application submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Cipramil Drops 40mg/ml which was first authorised to Lundbeck Limited on 04 August 1998.

Citalopram hydrochloride is a selective serotonin reuptake inhibitor (SSRI). The therapeutic mechanism of action of SSRIs involves the potentiation of serotonin [5-hydroxytryptamine (5-HT)] by the inhibition of its neuronal uptake. Serotonin is a neurotransmitter with neurons located in the raphe nuclei. Serotonergic neurons are known to play a part in sleep-wakefulness cycles, thermoregulation, mood, emotional and food behaviours.

No new non-clinical data have been 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.

No new clinical studies were performed, 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. A bioequivalence study was not necessary to support an application of this type.

No new or unexpected safety concerns were raised during the assessment of this application and it was therefore judged that the benefits of taking Citalopram 40 mg/ml Oral Drops, Solution outweigh the risks and a Marketing Authorisation was granted.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE
INN: Citalopram hydrochloride
Chemical name: (1RS)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrochloride

Structure:

![Structure of Citalopram Hydrochloride]

Molecular formula: C_{20}H_{22}CIFN_{2}O
Molecular weight: 360.9
Appearance: white or almost white, crystalline powder
Solubility: very soluble in water and freely soluble in anhydrous ethanol

Citalopram hydrochloride is the subject of a European Pharmacopoeia monograph.

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

MEDICINAL PRODUCT
Other ingredients
Other ingredients consist of the pharmaceutical excipients, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), hydroxyethylcellulose, ethanol 96% and purified water

Appropriate justification for the inclusion of each excipient has been provided.

All of the excipients comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development
The aim of the development programme was to formulate a safe, efficacious, stable oral solution that could be considered a generic medicinal product of Cipramil Drops 40mg/ml (Lundbeck Limited).

Suitable pharmaceutical development data have been provided for this application.

Comparable impurity profiles have been provided for the proposed and originator products.
Manufacture
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have 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 and has shown satisfactory results.

Finished product specification
The finished product specifications are satisfactory. Test methods have been described and have been 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 finished product is packaged in amber type III glass bottles containing 15ml of oral drops, solution with tamper evident high density polyethylene (HDPE) child-resistant screw cap with low density polyethylene (LDPE) plastic vertical dropper.

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
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 3 years for the unopened product. Once the product has been opened it should be used within 16 weeks. The storage conditions are ‘Do not store above 25°C’.

Bioequivalence/Bioavailability
A bioequivalence study is not required to support an application of this type as per European guidance.

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

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.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.
Conclusion
It is recommended that a marketing authorisation is granted for this application.
NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY
No new non-clinical data were submitted, which is acceptable given that the proposed product is a generic medicinal product of an originator product that has been licensed for over 10 years.

NON-CLINICAL EXPERT REPORT
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.

ENVIRONMENTAL RISK ASSESSMENT
Since Citalopram 40 mg/ml Oral Drops, Solution is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

CONCLUSION
It is recommended that a marketing authorisation is granted for this application.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
Pharmacokinetics
In accordance with the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), a bioequivalence study is not required if the product is to be administered as an aqueous oral solution at the time of administration and contains the same active substance in the same concentration as the currently licensed product and the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the active substance. No bioequivalence study has been submitted or is required for this application.

EFFICACY
No new efficacy data have been submitted and none are required for an application of this type.

SAFETY
No new safety data have been submitted and none are required for this application.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are acceptable. The SmPC is consistent with that for the respective originator product. The PIL is consistent with the SmPC and is in line with current guidance. The labelling is in line with current guidance.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PHARMACOVIGILANCE SYSTEM MASTER FILE AND RISK MANAGEMENT PLAN
In line with Directive 2010/84/EU, the Marketing Authorisation Holder has committed to submit a Summary of Pharmacovigilance Master File (PSMF) and Risk Management Plan (RMP) by variation by the end of January 2013.

CONCLUSION
There are no objections to the approval of this product from a clinical viewpoint.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Citalopram 40 mg/ml Oral Drops, Solution 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 have been submitted and none are required for an application of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

SAFETY
No new or unexpected safety concerns arose from this application.

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

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 citalopram hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is therefore considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 31 January 2005.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 18 February 2005.

3 Following assessment of the application the MHRA requested further information on 13 January 2006, 18 April 2008, 05 August 2010 and 30 March 2012.

4 The applicant responded to the MHRA’s requests, providing further information on 12 September 2007, 24 November 2009, 11 March 2011 and 02 May 2012.

5 The application was determined on 02 November 2012.
CITALOPRAM 40MG/ML ORAL DROPS, SOLUTION.

PL 04416/0633

**STEPS TAKEN AFTER ASSESSMENT**

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

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.
Module 3
PATIENT INFORMATION LEAFLET

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.
Oral use. Use as directed by your doctor. Read the package leaflet before use. Do not store above 25°C. Do not use after 16 weeks of first opening. Keep out of the reach and sight of children. These oral drops contain 40 mg/ml of citalopram (as hydrochloride). One ml of solution is equivalent to 20 drops in total. Also contains ethanol 96%, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

Sandoz Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7FR.
Citalopram 40 mg/ml
Oral Drops, Solution

Citalopram hydrochloride

Note: 4 drops (8 mg) is equivalent in therapeutic effect to one 10 mg tablet.

1 drop = 2 mg citalopram

15 ml oral drops

SANDOZ

Oral use. Use as directed by your doctor.

Read the package leaflet before use. Do not store above 25°C. Do not use after 16 weeks of first opening. Keep out of the reach and sight of children. These oral drops contain 40 mg/ml of citalopram (as hydrochloride). One ml of solution is equivalent to 20 drops in total. Also contains ethanol 96%, methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate (E216).

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