Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

Citalopram 10 mg film-coated tablets
Citalopram 20 mg film-coated tablets
Citalopram 40 mg film-coated tablets

(Citalopram hydrobromide)

UK Licence No: PL 20532/0041-0043

Aurobindo Pharma Ltd

LAY SUMMARY

Citalopram 10 mg film-coated tablets
Citalopram 20 mg film-coated tablets
Citalopram 40 mg film-coated tablets

The products may be referred to as 'Citalopram tablets' in this report.

This is a summary of the Public Assessment Report (PAR) for Citalopram 10 mg, 20 mg and 40 mg film-coated tablets (PL 20532/0041-0043). It explains how the applications for Citalopram tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Citalopram tablets.

For practical information about using Citalopram tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Citalopram tablets and what are they used for?
Citalopram tablets are 'generic' medicines. This means that Citalopram 10 mg, 20 mg and 40 mg film-coated tablets are similar to 'reference medicines' already authorised in the UK called Cipramil 10 mg, 20 mg and 40 mg film-coated tablets (Lundbeck Limited, UK), which were first authorised in the UK in March 1995. Cipramil 10 mg, 20 mg and 40 mg film-coated tablets may be referred to as 'Cipramil tablets' in this report.

Citalopram tablets are used to treat the symptoms of depression and, when a patient is feeling better, to help prevent these symptoms recurring. Citalopram tablets are also beneficial in relieving symptoms in patients prone to panic attacks.

Treatment for depression is usually continued for at least six months, and for panic disorder for at least three months.

How do Citalopram tablets work?
The active substance, citalopram belongs to the group of medicines known as antidepressants which work by relieving the symptoms of depressed mood.

How are Citalopram tablets used?
Citalopram tablets are taken by mouth (orally).

The patient should always take Citalopram tablets exactly as his/her doctor has advised. The patient should check with his/her doctor or pharmacist if he/she is not sure.

The capsules should be swallowed with a drink of water and should not be chewed.

Usually the patient's doctor will prescribe between 20 mg and 40 mg per day, taken as a single dose either in the morning or in the evening.

The recommended dose in adults is:

Depression
The usual dose is 20 mg per day. This may be increased by the patient's doctor to a maximum of 40 mg per day.

Panic disorder
The starting dose is 10 mg per day for the first week before increasing the dose to 20 mg-30 mg per day. The dose may be increased by the patient's doctor to a maximum of 40 mg per day.

Elderly patients (above 65 years of age)
The starting dose should be decreased to half of the recommended dose, e.g. 10 mg-20 mg per day.

Elderly patients should not usually receive more than 20 mg per day.

Citalopram tablets should not be used in the treatment of children and adolescents under the age of 18 years

Patients with special risks
Patients with liver complaints should not receive more than 20 mg per day.

It may take several days before the patient feels any benefit from these tablets. This is normal for this type of medicine. The patient should continue to take the tablets for as long as his/her doctor recommends.

The patient should not stop taking the tablets even if he/she begins to feel better, unless he/she is told to do so by his/her doctor.

The patient should never change the dose of his/her medicine without talking to his/her doctor first.

Please read section 3 of the package leaflets for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Citalopram tablets can only be obtained with a prescription.

What benefits of Citalopram tablets have been shown in studies?
As Citalopram tablets are generic medicine, studies in patients have been limited to tests to determine that Citalopram tablets are bioequivalent to the reference medicines Cipramil tablets (Lundbeck Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (MAH) has presented data from the scientific literature to support the applications.

What are the possible side effects of Citalopram tablets?
Like all medicines, Citalopram tablets can cause side effects, although not everybody gets them.

If any of the following happens, the patient should stop taking Citalopram tablets and tell his/her doctor immediately or go to the casualty department at your nearest hospital:

Serotonin syndrome has been reported in patients treated with these types of antidepressants (SSRIs). The patient should tell his/her doctor if he/she experiences high fever, trembling, muscle twitches and anxiety, because these symptoms may indicate the development of this condition. Treatment with citalopram should be discontinued immediately.

Very common side effects (≥1/10):
• sleepiness
• difficulty sleeping
• feeling sick
• dry mouth
• increased sweating

For the full list of all side effects reported with Citalopram tablets, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet available on the MHRA website.

Why were Citalopram tablets approved?
The view was that the benefits of Citalopram tablets outweighed the identified risks and it was recommended that these products be approved for use.

What measures are being taken to ensure the safe and effective use of Citalopram tablets?
Safety information has been included in the Summaries of Product Characteristics and the package leaflet for Citalopram tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Citalopram tablets
Marketing Authorisations were granted in the UK to Aurobindo Pharma Limited on 05 August 2008.

The full PAR for Citalopram tablets follows this summary.

For more information about use of Citalopram tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2016.

SCIENTIFIC DISCUSSION

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Scientific Discussion

I INTRODUCTION Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Citalopram 10mg, 20mg and 40mg Tablets (PL 20532/0041-0043) on 05/08/2008. The products are Prescription Only Medicines and are indicated for the treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence. Citalopram tablets are also indicated in the treatment of panic disorder with or without agoraphobia.

The three strengths of Citalopram were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC claiming to be generic medical products of the original products Cipramil 10 mg, 20 mg and 40 mg film-coated tablets (Lundbeck Limited, Denmark), which were authorised in Denmark in October 1989. The reference products in the UK are Cipramil 10 mg, 20 mg and 40 mg film-coated tablets (Lundbeck Limited; PL 0458/0057-0059), which were authorised on 17 March 1995.

The products contain the active ingredient, citalopram, a potent inhibitor of serotonin (5-HT)-uptake.

One bioequivalence study was submitted to support these applications, comparing the applicant's test product Citalopram 40 mg tablets (x 2) with the reference product Cipramil 40 mg Tablets (x 2; H Lundbeck Limited A/S, Denmark) under fasting conditions

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that the applications were based on the products being generic medicinal products of an originator products that have 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 Citalopram tablets outweigh the risks and Marketing Authorisations were granted.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Each film-coated tablet contains 10 mg, 20 mg or 40 mg of the active substance, citalopram (as citalopram hydrobromide). The other ingredients in the drug products are listed below:

Core tablets:
Lactose monohydrate
Maize starch
Copovidone
Croscarmellose sodium
Cellulose microcrystalline
Magnesium stearate.

Film-coating:
Hypromellose
Macrogol 400
Titanium dioxide (E 171).

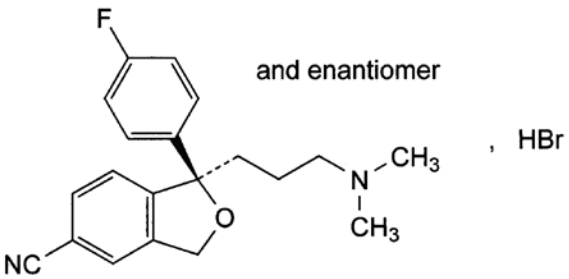
Appropriate justification for the inclusion of each excipient has been provided.

The tablets are packaged in polyvinylidene chloride/polyvinylchloride/aluminium blisters, in pack sizes of 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 film-coated tablets.
Not all pack sizes may be marketed.

All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

NOMENCLATURE

INN:	Citalopram hydrobromide
BAN/USAN	Citalopram hydrobromide
Chemical Name:	1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, monohydrobromide
Structure	
Molecular Formula:	$C_{20}H_{21}N_2OF.HBr$
Molecular Weight:	405.30

General properties

Appearance:	White or almost white crystalline powder
Solubility:	Freely soluble in methanol, sparingly soluble in water, slightly soluble in acetone.
Melting range:	184-188˚C
Specific optical rotation:	+0.2 to -0.2˚

An appropriate specification has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active citalopram is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active

substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, with no specific storage instructions.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, tablets that were considered to be bioequivalent to the reference medicinal products, Cipramil 10 mg, 20 mg and 40 mg tablets (Lundbeck Limited).Suitable pharmaceutical development data have been provided for these applications.

All excipients apart from purified water and Opadry comply and are tested to their respective Ph.Eur monograph. Lactose monohydrate (Pharmatose 200M) includes additional controls for particle size. The specification for Opadry white 03B58902 consists of controls on description, identification for titanium dioxide, colour difference, dispersion and ash and is considered satisfactory.Purified water is tested to in-house specification that complies with Ph.Eur requirements with additional controls on pH, and specified pathogens. The retesting period and tests performed for each excipient (apart from purified water) is given. The manufacturer's declarations regarding residual solvents are also provided and are satisfactory. Typical Certificates of Analysis from the dosage form manufacturer and suppliers are provided and are satisfactory.

Lactose monohydrate is the only material of animal or human origin contained in or used in the manufacturing process for the proposed products and that it is not susceptible to TSE. A signed declaration has been provided for lactose monohydrate from the supplier stating that the milk used in manufacture of this excipient is sourced from healthy animals in the same conditions as milk collected for human consumption (EMEA 410/01 rev 1) and that calf rennet used in production of whey is in accordance with EMEA/CPMP/571/02.

Dissolution and impurity profiles

Dissolution and impurity profiles for both strengths of drug product were found to be similar to those for the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. There are no special storage conditions.

Conclusion

It is recommended that Marketing Authorisations are granted for these applications.

III NON-CLINICAL ASPECTS

No new non-clinical data were submitted and none were required for these applications.

IV. CLINICAL ASPECTS

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.

Citalopram is indicated for the treatment of both the initial phase of depressive illness and as maintenance therapy against relapse or recurrence, as well as the treatment of panic disorder with or without agoraphobia. The relatively long half life allows once daily dosing.

The proposed indications and other details in the SPC are broadly in line with those of the reference product but various sections of the SPC will require updating to incorporate the latest warnings on the SSRI class of drugs including those relating to use in children/adolescents, suicidal thoughts, withdrawal reactions and akathisia / psychomotor restlessness.

Bioequivalence

An open label randomised, cross-over bioequivalence study to compare the bioavailability of two 40mg citalopram tablets under fasting conditions

Objective: To compare the rate and extent of absorption of Citalopram Hydrobromide tablets (test) of Aurobindo Pharma Limited with that of the reference tablets , Cipramil 40 mg tablets of H Lundbeck A/S, Denmark when given in equal doses of a single dose of Citalopram Hydrobromide in 24 healthy adult male subjects under fasting conditions.

Subjects: 24 healthy male [+4 standby], aged 18-50 years.

Test: Citalopram Hydrobromide 40mg tablets. Batch number – CP4003002 manufactured by Aurobindo Pharma Limited India.

Reference: Cipramil 40mg tablets manufactured by H Lundbeck A/S, Denmark. Batch number – C122B.

Duration of treatment: A single oral dose was administered with 240ml of water after a supervised overnight fast of 10hrs 44mins according to the randomisation scheme.

Blood sampling: Prior to drug administration and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 hrs post dose in each period.

Parameters: $AUC_{0\text{-}t,}$ $AUC_{0\text{-}inf}$, C_{max}. Descriptive safety data were recorded.

Statistical analyses: The test product was compared to the reference product with respect to the variables $C_{max,}$ $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ after logarithmic transformation of the data. Bioequivalence of the test and reference product was assessed on the basis of the confidence intervals (Cis) for the above variables for citalopram in relation to the conventional bioequivalence range of 80% to 125%.

Results:

Comparative pharmacokinetics:

	Citalopram test	**Cipramil reference**	**Point Estimate**	**Test/Ref (90% CI)**
AUC_{0-t} (ng/ml h)	2667 (591)	2671 (574)	99.68 %	96.40 to 103.08
AUC_{0-inf} (ng/ml h)	2871 (690)	2889 (666)	99.16%	95.73 to 102.72
C_{max} (ng/ml)	52.58 (10.3)	54.93 (13.1)	98.3%	93.47 to 103.48
T_{max} (hrs)	4.0 (1.76)	5.0 (1.9)		

For T_{max} median used instead of median

Withdrawals: The quality assessor pointed out a number of issues with withdrawals which have been responded to by the applicant. Subjects 13, 21 and 26 were withdrawn for reasons of vomiting, DNA for period 2, and absence for last 4 blood assays respectively.

Conclusions: Both formulations were well tolerated with no relevant safety differences. The test product was accepted as bioequivalent in terms of rate and extent of absorption to the reference product.

The formulation of the 10 mg and 20 mg strengths of these generic citalopram tablets are in scale with the 40mg tablet and the ratio between the amount of active substance and excipients is the same. The same manufacturing process was used and the pharmacokinetics for citalopram are linear over the therapeutic range [10-60 mg].

The results for the 40 mg tablet can be considered applicable to the 10 and 20 mg tablets as they have similar dissolution profiles.

Efficacy
Efficacy is reviewed in the Clinical Expert Report (clinical overview). The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Safety
Safety is reviewed in the Clinical Expert Report. The reference product is established and the application depends upon the ability to show bioequivalence with the reference product.

Expert Report
The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

Summary of Product Characteristics
These are satisfactory.

Patient Information Leaflet
This is satisfactory.

Conclusions
The applicant has demonstrated bioequivalence. Marketing Authorisations should be granted for these products.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Paroxetine 20 mg and 30 mg film-coated tablets (PL 20532/0095-0096; DK/H/1135/001-02/DC). The bridging report submitted by the applicant has been found acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Quality

The important quality characteristics of Citalopram 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 applications of this type.

Clinical

Bioequivalence has been demonstrated between the applicant's Citalopram Tablets and the reference product Cipramil.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for Cipramil tablets.

Risk/Benefit Analysis

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The risk benefit is, therefore, considered to be positive.

STEPS TAKEN AFTER THE INITIAL PROCEDURE – SUMMARY

The following table lists non-safety updates to the Marketing Authorisations for Citalopram 10mg, 20mg and 40mg Tablets (PL 20532/0041-0043) that have been approved by the MHRA since the products were first licensed. This is not a complete list of the post-authorisation changes that have been made to the Marketing Authorisations.

Date submitted	**Application type**	**Scope**	**Outcome**
17 March 2009	Type IB	To change the shelf life of the finished product from 3 years to 4 years based on the available stability data.	Approved on 02 June 2009
18 March 2016	Type IB	To update sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.6 (Fertility, pregnancy and lactation), 4.8 (Undesirable effects), and 7 (Marketing Authorisation Holder) of the Summaries of Product Characteristics (SmPCs) and consequentially the Patient information Leaflet (PIL) in line with the Quality Review of Documents (QRD) template.	Approved on 14 April 2016 (see Annex 1)

ANNEX 1

Our Reference:	PL 20532/0041, Application 27 PL 20532/0042, Application 28 PL 20532/0042, Application 28
Product:	Citalopram tablets 10mg
Marketing Authorisation Holder:	Aurobindo Pharma Limited
Active Ingredient(s):	Citalopram Hydrobromide.
Type of Procedure:	National
Submission Type:	Variation
Submission Category:	Type IB
Submission Complexity:	Standard
EU Procedure Number (if applicable):	

Reason:
To update sections 2 (Qualitative and quantitative composition), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.6 (Fertility, pregnancy and lactation), 4.8 (Undesirable effects), and 7 (Marketing Authorisation Holder) of the Summaries of Product Characteristics (SmPCs) and consequentially the Patient information Leaflet (PIL) in line with the Quality Review of Documents (QRD) template.

Supporting Evidence
1. Revised SmPCs
2. Revised Patient Information Leaflet

Evaluation
The proposed changes to the SmPCs and PIL are satisfactory.

Conclusion
The proposed changes to the SmPCs and PIL are considered acceptable and there are no objections to approval.

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

Decision – Approved on 14 April 2016.