

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

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

Pharmachemie BV, Haarlem, the Netherlands

citalopram hydrobromide

This assessment report is published by the MEB following Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected from the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH checked this report for the absence of any confidential information.

EU-procedure number: NL/H/692/01-03/MR
Registration number in the Netherlands: RVG 31125, 31126, 31127

20 June 2006

Pharmacotherapeutic group:	Antidepressant, Selective serotonin reuptake inhibitors
ATC code:	N06AB04
Route of administration:	oral
Therapeutic indication:	treatment of major depressive episodes.
Prescription status:	prescription only
Date of first authorisation (national):	27 October 2004
Application type/legal basis:	Directive 2001/83/EC, article 10.1 and 10.3

For product information for health care professionals and users, including information on pack sizes and presentations, see modules 2, 3 and 4.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MEB has granted a marketing authorisation for Citalopram 10 PCH, film-coated tablets 10 mg, Citalopram 20 PCH, film-coated tablets 20 mg and Citalopram 40 PCH, film-coated tablets 40 mg, from Pharmachemie BV. The product is indicated for the treatment of major depressive episodes.

A comprehensive description of the indications and posology is given in the SPC (see module 3).

This concerns a generic application claiming essential similarity with the innovator products Cipramil 20 and Cipramil 40, which have been registered in the Netherlands since 1997. The marketing authorisation holder is Lundbeck BV. Additionally, reference is also made to Cipramil applications in the individual Member States (reference product).

Citalopram 20 PCH and Citalopram 40 PCH, film-coated tablets, have been registered in accordance with Directive 2001/83/EC, article 10.1 (formerly the first paragraph of article 10.1 (a)(iii)).

Citalopram 10 PCH, film-coated tablets 10 mg, has been registered in accordance with Directive 2001/83/EC, article 10.3 (formerly the last paragraph of article 10.1 (a)(iii)).

This type of application refers to information that is contained in the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed if the data protection time of the dossier of the reference product has expired. For this kind of application, it is necessary to demonstrate that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Seropram® 20 mg film-coated tablets, registered in Spain (Seropram is the trade name for Lundbeck's citalopram-containing products in Spain). The trade name of these products in the Netherlands is Cipramil). A bioequivalence study is the widely-accepted means of demonstrating that a difference in use of excipients and methods of manufacture has no influence on efficacy and safety. A generic product can be used instead of its innovator product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for the manufacture and assembly of this product prior to granting its national authorisation.

Active substance and excipients

The active substance is citalopram hydrobromide, an established active substance. Citalopram hydrobromide is not described in a pharmacopoeia. The active substance specification is considered adequate for quality control.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder

(MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent authorities/EMA thus have access to the complete information necessary to evaluate the suitability of the active substance use in the medicinal product.

The active substance specification is considered adequate to guarantee consistent and sufficient quality.

In accordance with applicable European guidelines, stability data on the active substance have been provided for 3 batches, demonstrating the stability of the active substance for 36 months at 25°C, 60% R.H. and for 6 months at 40°C, 75% R.H.

All excipients comply with their Ph.Eur monographs. The substance Sepifilm 752 white complies with in-house specifications, but the individual excipients comply with their Ph.Eur monographs. The quantitative composition has been submitted.

Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition

The medicinal product is a film-coated tablet with immediate release. The 20 and 40 mg tablets have a score-line.

The tablets contain 10, 20 or 40 mg of citalopram as citalopram hydrobromide. The excipients are:

Core: Lactose Monohydrate, Microcrystalline Cellulose PH 101, Croscarmellose Sodium, Maize Starch, Glycerol, Copovidone, Magnesium Stearate.

Coating: Sepifilm ® 752 (Hydroxypropyl Methylcellulose, Microcrystalline Cellulose, Polyoxyethylene Stearate 40, Titanium Dioxide (E-171).

Citalopram 10, 20 and 40 mg film-coated tablets are packed in transparent and opaque blisters (PVC-PVDC / Alu), and in cartons.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The purpose was to develop tablets which are bioequivalent to the reference product Cipramil. The composition and characteristics have been analysed. The *in vitro* dissolution profile and purity parameters were targets for development to achieve essential similarity. The 20 mg and 40 mg tablets have a score-line that complies with the current requirements.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of granulate in accordance with the relevant European guidelines. These batches are around 10% of full-scale production batches. Since the active substance content in the granulate is 20%, the manufacturing process can be considered to be a standard manufacturing process, and since the results submitted originate from batches equivalent to 10% of full-scale batches it is acceptable for validation data on production batches to be submitted after registration. These validation data should include the content uniformity of the blend and tablet cores.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the *Monograph for Tablets* in the Ph.Eur. and includes tests for identity, purity, uniformity of weight, hardness, dissolution, related substances, and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the product have been provided from 3 production-scale batches in accordance with applicable European guidelines, demonstrating the stability of the product for 3 years. No specific storage conditions need to be included in the SPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies:

There are no substances of ruminant animal origin present or used in the manufacture of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Cipramil on the European market. No new preclinical data have been submitted and therefore the application has not been subjected to a pre-clinical assessment. This is acceptable for this type of application.

Environmental risk

The product is intended as a substitute for identical products on the market. The approval of this product will not result in an increase in the total quantity of citalopram hydrobromide released into the environment. It does not contain any component which would result in additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Citalopram is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC accepted for the reference product Cipramil marketed by Lundbeck BV. The SPC is also in agreement with SPCs approved during other mutual recognition procedures for citalopram.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Citalopram 20 PCH is compared with the pharmacokinetic profile of the reference product Seropram 20 mg tablets (Seropram is the trade name for Lundbeck's citalopram-containing products in Spain).

A randomised, two-period, cross-over bioequivalence study was carried out. Citalopram 20 PCH, 20 mg film-coated tablets, from Pharmachemie BV was compared to the reference product Seropram, 20 mg film-coated tablets, from Lundbeck, Spain.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} median, range)

Treatment	AUC _{0-t} ng/ml/h	AUC _{0-∞} ng/ml/h	C _{max} ng/ml	t _{max} h	T _{1/2} h
Test	823 \pm 242	905 \pm 290	18.6 \pm 3.6	5.0 (2.0-7.0)	44.0 \pm 6.7
Reference	835 \pm 275	892 \pm 292	18.8 \pm 4.6	5.0 (3.5-6.0)	46.8 \pm 5.0
*Ratio (90% CI)	0.99 (0.95-1.04)	1.01 (0.98-1.04)	1.00 (0.97-1.04)	-	-
CV (%)	9.1	5.9	7.2	-	-
AUC_{0-∞} 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 T_{max} time for maximum concentration T_{1/2} half-life					

**In-transformed values*

Based on the pharmacokinetic parameters of citalopram in the reference tablet, Seropram (Lundbeck BV), marketed in Spain, and the test tablet are bioequivalent with respect to the extent and rate of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The 90% confidence intervals calculated for AUC_(0-inf), AUC_(0-t) and C_{max} are in agreement with those calculated by the applicant and are within the acceptance range of 0.80 – 1.25.

The 10 mg film-coated tablets and the 40 mg film-coated tablets are dose-proportional to the 20 mg film-coated tablets. The pharmacokinetics of the active substance is linear in the therapeutic range. The results of the bioequivalence study performed with the 20 mg film-coated tablets therefore apply to the other strengths.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of Seropram (Lundbeck, Spain) and Cipramil (Lundbeck, the Netherlands).

The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

The MEB has been assured that the bioequivalence study was conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk Management Plan

Citalopram was approved in the Netherlands for the first time in 1997, and therefore there is more than ten years post-authorisation experience with this active substance. The safety profile of citalopram can be considered to be well-established and no product-specific pharmacovigilance issues were identified pre- or post-authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed Risk Management Plan is not necessary for this product.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Citalopram 10, 20 and 40 PCH, film-coated tablets, have a proven chemical-pharmaceutical quality and are generic forms of Cipramil. Cipramil is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the reference product.

Satisfactory chemical-pharmaceutical documentation has been provided, assuring consistent and sufficient quality of the product.

The MAH has provided written confirmation that the systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, Patient Information Leaflet (PIL) and packaging are in the agreed template. Braille conditions are met by the applicant.

The Board followed the advice of the assessors. No discussion in a Board meeting was deemed necessary. The MEB, on the basis of the data submitted, considered that Pharmachemie BV has demonstrated bioequivalence for Citalopram 10, 20 and 40 PCH with the reference product, and has therefore granted a marketing authorisation.

The Member States mutually recognised the Dutch evaluation of the marketing authorisation. There was no discussion in the CMD(h). Agreement between Member States was reached through a written procedure.

The PSUR cycle is as follows: One PSUR should be submitted every six months during the first two years after End of Procedure, followed by a PSUR three years after End of Procedure. Thereupon, a PSUR should be submitted every three years.

The date for the first renewal will be 23 February 2011.

The following post-approval commitments were made during the procedure:

Quality

- Validation data on the first three production scale batches of the products;
- Batch analysis data on the same batches;
- Stability data on the same batches;
- Further stability data on the products (ongoing studies).

Patient information leaflet

- For each strength, a separate leaflet will be provided;
- Consultation with target patients groups will be performed.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products, CMD(h),
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States