CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rualalit 20 mg/ml, oral drops, solution
Chanelle Medical, Ireland

escitalopram (as oxalate)

This assessment report is published by the MEB pursuant 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 of 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 has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2514/001/DC
Registration number in the Netherlands: RVG 111201

30 July 2013

Pharmacotherapeutic group:	selective serotonin reuptake inhibitors
ATC code:	N06AB10
Route of administration:	oral
Therapeutic indication:	major depressive episodes; panic disorder with or without agoraphobia; social anxiety disorder (social phobia); generalised anxiety disorder; obsessive-compulsive disorder
Prescription status:	prescription only
Date of authorisation in NL:	18 July 2013
Concerned Member States:	Decentralised procedure with DE, IT, PL, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Rualalit 20 mg/ml, oral drops, solution from Chanelle Medical. The date of authorisation was on 18 July 2013 in the Netherlands.

The product is indicated for:

- treatment of major depressive episodes.
- treatment of panic disorder with or without agoraphobia.
- treatment of social anxiety disorder (social phobia).
- treatment of generalised anxiety disorder.
- treatment of obsessive-compulsive disorder.

A comprehensive description of the indications and posology is given in the SPC.

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000 fold lower affinity.
Escitalopram has no or low affinity for a number of receptors including 5-HT1A, 5-HT2, DA D1 and D2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors.
The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

This decentralised procedure concerns a generic application with reference to the innovator product Cipralex 20 mg film-coated tablets, which has been registered in Sweden by H. Lundbeck A/S since 7 December 2001. Essential similarity is claimed with the oral drops formulation, named Lexapro 20 mg/ml (NL License RVG 35339), which was authorised in the Netherlands on 25 October 2007 by means of an MRP (SE/H/0279/006). In addition, reference is made to Cipralex/Lexapro authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of 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 once the data protection time of the dossier of the reference product has expired. The 20 mg/ml escitalopram oral solution is a watery solution with the same qualitative composition as Cipralex oral solution. In accordance with the *NfG on The Investigation of Bioavailability and Bioequivalence* no bioequivalence studies are deemed necessary. This generic product can be used instead of its reference product.

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

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted as this is not required for a generic 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 this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is escitalopram oxalate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*). It is a white to off-white, crystalline powder, which is sparingly soluble in water. Escitalopram contains one asymmetric carbon; hence, two enantiomers are possible. The (S)-enantiomer is the only isomer manufactured. The undesired (R)-enantiomer is adequately limited.

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, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Escitalopram oxalate is synthesized in a five step process. The related substances have been adequately specified and limited. No class 1 residual solvents are used in the manufacturing process. The limits for the used solvents are in accordance with the ICH.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with the specification have been provided for three production-scale batches.

Stability of drug substance
Stability data have been provided for 9 batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). At both long term and accelerated conditions no trends or out of specification results were observed. Therefore, the claimed retest period of 5 years was granted.

** 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
Rualalit 20 mg/ml is a clear solution with a bitter taste.
Each ml of solution contains 20 mg escitalopram (as 25.56 mg escitalopram oxalate). Each drop contains 1 mg of escitalopram.

The solution is packed in amber glass bottles (Type III) with dropper applicator (PE) and child resistant screw cap (PP/HDPE) with a fill volume of 15 ml.

The excipients are: propyl gallate (E310), anhydrous citric acid (E330), ethanol 96% (E1510), sodium hydroxide (E524), purified water.

The pH of the drug product is 3.77.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Escitalopram oxalate can be considered highly soluble. The objective was to develop a product having pharmaceutical quantities as close as possible to the innovator product, Cipralex (Lundbeck UK). Since the product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required. It is not expected that the excipients contained will affect gastrointestinal transit, absorption or *in vivo* stability of the active substance. Therefore no bioequivalence study is required.

The container closure system is considered to be suitable for the drug product. The dropper applicator was demonstrated to be comparable with the innovator product with respect to uniformity of drop weight. No overages are used in the formulation. In conclusion, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing consists of a standard mixing process followed by filtration in the final packaging. The process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale batches and two manufacturing-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with the Ph.Eur. monographs. These specifications are acceptable.

Microbiological attributes

Microbial purity testing and the test for efficacy of microbial preservation was conducted on two batches. Both batches complied with the Ph. Eur. requirements. In addition microbial purity testing is included in the control of drug specification.

Quality control of drug product

The product specification includes tests for appearance, condition of packaging, pH, density, assay of escitalopram oxalate, identification, antioxidant assay, dose, uniformity of dose and microbiological quality. Concerns are identified for antioxidant assay, fill volume, dose and uniformity of dose of the oral drops.

Control of the packaging is only included in the shelf-life specification. All other tests and acceptance criteria are identical for release and shelf-life testing. The analytical methods are adequately described. Where relevant, the stability indicating nature of analytical procedures was demonstrated. Batch analytical data from the proposed production sites have been provided on two production-scale batches and two pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product were provided for two pilot-scale and two production-scale batches in the proposed commercial packaging, manufactured at both production sites. The batches were stored at 25°C/60% RH (production-scaled - 24 months; pilot scaled - 9 months) and 40°C/75% RH (production scaled - 6 months; pilot scaled - 6 months) and 30°C/65% RH (pilot scaled - 9 months) .

The data obtained during accelerated and long-term conditions show some trends, but all parameters tested stayed within the specifications.

Based on the stability data, a shelf life of 2 years is acceptable, when stored below 25°C. The bottle should be kept tightly closed.

Based on in-use stability data from one batch an in-use shelf life of 8 weeks is acceptable, when stored below 25°C. The bottle should be kept tightly closed.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing 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 Cipralex, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

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

II.3 Clinical aspects

Escitalopram is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Escitalopram is a well-known active substance with established efficacy and tolerability. No new clinical data have been provided or are required, in accordance with the *NfG on The Investigation of Bioavailability and Bioequivalence*, as the 20 mg/ml escitalopram oral solution is an aqueous solution with the same qualitative composition as Cipralex 20 mg/ml oral drops, solution. Therefore bioequivalence studies can be waived. The pharmacology, pharmacokinetics and toxicology of the active substance are well known. This generic product can be used instead of its reference product.

Risk management plan
Escitalopram was first approved in 2001, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of escitalopram 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 MAH 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 European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Cipralex.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
Both rounds of testing showed that, for each question, 100% of participants were able to find the correct information, and 100% of participants were able to answer the questions correctly. During the whole test no changes to either the leaflet or the questionnaire were deemed necessary.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rualalit 20 mg/ml, oral drops, solution has a proven chemical-pharmaceutical quality and is a generic form of Cipralex oral drops. Cipralex is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are oral drops is a watery solution, no bioequivalence study is deemed necessary.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other escitalopram containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Rualalit 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 November 2012. Rualalit 20 mg/ml oral drops, solution was authorised in the Netherlands on 18 July 2013.

The date for the first renewal will be: 12 November 2017.

There were no post-approval commitments made during the procedure.

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
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
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached