Public Assessment Report
Scientific Discussion

Cipralex, tablets, 5, 10, 15 and 20 mg
(escitalopram oxalate)

SE/H/278/01-04/E03

This module reflects the scientific discussion for the approval of Cipralex tablets, 5, 10, 15 & 20 mg. The procedure was finalised at 20070717. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

H Lundbeck A/S has applied for a marketing authorisation for Cipralex, tablets, 5, 10, 15, and 20 mg. The active substance is escitalopram oxalate, the active enantiomer of the racemate citalopram (CIT). Escitalopram (ESC) acts as a selective serotonin reuptake inhibitor (SSRI). For approved indications, see the Summary of Product Characteristics (SPC).

II. QUALITY ASPECTS

II.1 Introduction

Cipralex is presented in the form of tablets containing 6.39 mg, 12.77 mg, 19.16 mg, and 25.54 mg of escitalopram oxalate which corresponds to 5 mg, 10 mg, 15 mg, and 20 mg of escitalopram base. The excipients are microcrystalline cellulose, colloidal anhydrous silica, talc, croscarmellose sodium, magnesium stearate, hypromellose, macrogl 400, and titanium dioxide (E 171). The tablets are packed in transparent PVC/PE/PVdC/aluminium blister.

II.2 Drug Substance

Escitalopram oxalate does not have a monograph in the Ph Eur.

Escitalopram oxalate is a white to slightly yellow crystalline powder, which is soluble in water, sparingly soluble in ethanol, freely soluble in methanol, and insoluble in heptane. The structure of escitalopram oxalate has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents, and solvents.

The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Cipralex, film-coated tablets are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin.

The manufacturing process has been sufficiently described and critical steps have been identified. Results from the process validation studies confirm that the process is under control and ensure both batch-to-batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.
Stability studies under ICH conditions have been performed and the data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Bridging studies on general toxicity and reproductive function were performed in the rat. Based on comparisons of metabolic patterns of CIT in rats and humans, the rat is considered a relevant species for human safety assessment.

ESC is present as the oxalate salt. The maximum recommended daily dose of ESC corresponds to 5 mg oxalate, which does not raise toxicological concerns.

III.2 Pharmacology

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake with high high affinity for the primary binding site. In vitro studies in human HEK 293 cells showed that ESC and CIT had a 30-fold higher affinity for the 5-HT transporter (Ki 1.1 - 1.6 nM) than R-CIT. In the same system, the IC<sub>50</sub> value for 5-HT reuptake inhibition for ESC (2.5 nM) was 4 and 27 times lower than for CIT and R-CIT, respectively. ESC has shown effects in animal models of anxiolytic and antidepressant activity.

Based on the primary pharmacological data, it cannot be excluded that the R-form (including its metabolites) could exert some pharmacological action. However, there is no indication that the racemate is more potent that ESC, and thus that removing the R-form would markedly alter the pharmacological effect of the racemate compared with ESC.

III.3 Pharmacokinetics

In rats, the pharmacokinetic information on ESC originates from the toxicokinetic data in the bridging repeat dose toxicity studies. These data indicated that dose-adjusted Cmax and AUC of S-CIT were approximately 2-3 times higher after administration of CIT than after administration of ESC.

No data on distribution, protein binding, elimination or metabolism, beyond toxicokinetic data on S-DCT and S-DDCT, have been obtained with ESC. The lack of data on distribution and metabolism is acceptable.

III.4 Toxicology

Briefly, the toxicity profile of CIT in rats is characterised by clinical signs, hepatic effects, phospholipidosis, and testicular atrophy. For bridging purposes, single dose (p.o. and i.v.) and oral repeat dose toxicity studies of up to 13 weeks duration were performed in rats with ESC and CIT. The bridging studies showed comparable toxicity profiles for CIT and ESC, which, with the exception of cardiotoxicity, were in accordance with previous data on CIT. On a dose basis, the effects appeared more pronounced with CIT. This could be explained by the higher systemic exposure to S-CIT achieved in the racemate groups than with ESC, and/or that R-CIT and/or its metabolites may be involved in the CIT induced toxicity.
In the original application for CIT, cardiotoxicity was not identified in rodents. However, similar findings have been reported with fluoxetine in mice. Furthermore, there is a body of literature on myocardial necrosis induced by biogenic amines in experimental animals, including rats (review, see Greaves 2000).

In 2002, the applicant also provided a 4-week repeat dose toxicity study in dogs with CIT (8 mg/kg/d) and ESC (1, 2, 4 mg/kg/d), focusing on potential cardiotoxic effects. There were no signs of cardiotoxicity. Toxicokinetic data revealed that exposure to S-CIT and both metabolites were comparable after administration of CIT 8 mg/kg/d or ESC 4 mg/kg/d, which were 8 (Cmax) or 5 (AUC) times above the clinical exposure. Thus, this study provides reassurance that ESC does not cause cardiotoxic effects in the dog at the doses tested. Furthermore, the study indicated a comparable toxicity profile of ESC and CIT, and thus supports the bridging concept.

After approval, a 26-week repeated-dose toxicity study with dietary administration in rats, was submitted. The toxicity profile of ESC and CIT was comparable; there were no new findings and no signs of cardiotoxicity.

**Reproductive Toxicity**
Two main reproductive/developmental toxicity studies were undertaken. In the segment II study, embryotoxicity was observed, but the malformation incidence was not affected. In the developmental and peri-post natal study, F1 body weight gain and survival were reduced. ESC and CIT caused maternal toxicity in both studies. Overall, ESC and CIT showed comparable effects in the reproductive toxicity studies.

**Genotoxicity and Carcinogenicity**
No genotoxicity or carcinogenicity studies have been performed with ESC. This is acceptable, since the genotoxic potential of CIT has been extensively studied, and based on these studies, CIT is not considered to pose a genotoxic hazard for humans.

**III.5 Discussion on the Non-clinical Aspects**

Overall, the available data for ESC are considered sufficient for bridging purposes, and are in general accordance with the recommendations in the NfG on ‘Clinical investigation of chiral active substances’ (Vol III: EUDRA/91/038).

**IV. CLINICAL ASPECTS**

**IV.1 Pharmacokinetics**

The pharmacokinetic profile of the S-enantiomer of CIT when administered alone as ESC is comparable to that of the S-enantiomer of CIT when administered as a part of the racemate.

ESC exhibits linear pharmacokinetics. Steady state plasma levels are achieved in approximately 1 week. After oral dosing, the peak concentration is achieved after 4 hours. The elimination half-life after multiple dosing is approximately 30 hours and the oral clearance is approximately 0.6 L/min.
The pharmacokinetic documentation in special populations and regarding interactions includes one study of ESC in subjects with hepatic impairment and two studies that investigated the potential drug-drug interaction of ESC with drugs known to inhibit CYP2C19. In subjects with mild to moderate hepatic impairment, the half-life of ESC was approximately twice as long and the exposure was approximately 60% higher than in subjects with normal liver function. In subjects known as poor metabolisers with respect to CYP2C19, doubled plasma concentrations have been observed. A lower initial and maintenance dose is recommended. In elderly, an increased exposure of approximately 50% have been observed, why half the initial and lower maintenance dose is recommended.

Co-administration of ESC with omeprazole or cimetidine resulted in a moderate increase in ESC plasma concentrations (50 and 70% increased concentrations); caution should therefore be exercised when ESC is used concomitantly with CYP2C19 inhibitors or cimetidine. ESC is an inhibitor of CYP2D6. Caution is therefore advised when ESC is administered with CYP2D6 substrates that also have a narrow therapeutic index (e.g. metoprolol, risperidone, haloperidol).

**IV.2 Pharmacodynamics**

ESC is the S-enantiomer of the racemate CIT. According to the applicant, *in vitro* and *in vivo* pharmacological studies have demonstrated that the pharmacological activity of CIT resides in the S-enantiomer. ESC has high affinity for the primary binding site; it also binds to an allosteric site on the serotonin transporter, with a 1000-fold lower affinity. The inhibition of 5-HT reuptake is the only likely mechanism of action explaining the pharmacological and clinical effects of ESC.

**IV.3 Clinical Efficacy**

The efficacy and safety of ESC in the treatment of depression has been evaluated in four fixed- or flexible-dose, short-term studies, of which two were conducted in the United States (MD-01 and MD-02) and two were conducted in Europe and Canada (99003 and 99001). All four studies were randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. Three studies included CIT as an active reference. The primary efficacy parameter was the change from baseline to Week 8 in the Montgomery Åsberg Depression Rating Scale (MADRS) total score.

In all four studies, the same diagnostic criteria for a current episode of Major Depressive Disorder (MDD) according to DSM-IV were employed. The populations studied were outpatients. The total intent-to-treat (ITT) number was 1698.

Statistically significant superiority to placebo was seen already from Week 1 onwards for some secondary endpoints (for example, the Clinical Global Impression – Global Improvement [CGI-I]) and from Week 2 onwards for other secondary endpoints (MADRS intermittent values, Hamilton Depression Rating Scale [HAMD] scores) in the three studies where ESC showed efficacy in depression. CIT was only statistically significant at Week 8.

In a long-term relapse-prevention study, 274 patients who had responded to 8 weeks of open-label treatment with ESC and who were randomised to continue with ESC for another 36 weeks had a significantly longer time to relapse than patients randomised to placebo.

The indication “panic disorder (PD), with or without agoraphobia” was applied for based on a pure extrapolation of CIT data. Independent placebo-controlled evidence of the efficacy of
ESC in the treatment of PD, with or without agoraphobia, has since substantiated the effectiveness and safety of ESC in this indication.

The efficacy and safety of ESC in the treatment of generalised anxiety disorder (GAD) has been established in four short-term (8 to 12 weeks) placebo-controlled studies and in three long-term studies. Two of the studies included paroxetine as an active comparator or active reference. The primary efficacy scale in all the studies was the Hamilton Anxiety Scale (HAMA).

All the studies included outpatients, aged between 18 and 80 years, with a primary diagnosis of GAD according to DSM-IV or DSM-IV-TR. The development programme in GAD included more than 1600 patients treated with ESC. The studies provided convincing data that ESC is efficacious and well tolerated in the acute and long-term treatment of GAD and the prevention of relapse of the disease.

The short-term (12 weeks) and long-term (24 and 36 weeks) efficacy and safety of ESC in the treatment of social anxiety disorder (SAD) has been established in three placebo-controlled studies. One study included paroxetine as an active reference. The primary efficacy scale in all the studies was the Liebowitz Social Anxiety Scale (LSAS).

All the studies included outpatients, aged between 18 and 80 years, with a primary diagnosis of SAD according to DSM-IV. The development programme in SAD included more than 1100 patients treated with ESC. The studies showed that ESC is efficacious and well tolerated in the acute and long-term treatment of SAD and the prevention of relapse of the disease.

Two long-term studies established the efficacy and safety of ESC in the acute and long-term treatment of obsessive-compulsive disorder (OCD) and the prevention of relapse of the disease. The studies included outpatients, aged between 18 and 65 years, with a primary diagnosis of OCD according to DSM-IV-TR. One of the studies included paroxetine as an active reference. The primary efficacy scale in both studies was the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). The development programme in OCD included nearly 700 patients treated with ESC.

**IV.4 Clinical Safety**

The cumulative exposure to ESC in the clinical development programme in MDD, PD, GAD, SAD, and OCD exceeds 2700 patient-years and more than 7600 patients have been exposed to ESC in clinical studies. As of 31 December 2005, it is estimated that in excess of 59 million patients have been exposed to ESC. So far, no clinically serious aggravations of adverse events or unexpected new adverse events were seen with ESC. The low rate of dropouts due to adverse events in the clinical studies (approximately 6%) also suggests a good tolerability.

Based on the toxicology studies, the main potential clinical safety issue is cardiac toxicity. The cardiac toxicity observed in the rat is assessed as being related to pharmacological effects of CIT/ESC causing haemodynamic alterations, leading to myocardial ischaemia and subsequent myocarditis, necrosis, and heart failure.

The available clinical data with ESC have been reviewed for corresponding effects on cardiovascular function. No signals of clinical importance have been observed. Data on blood pressure from about 600 patients were presented. Mean changes in blood pressure from screening to Day 56 in any of the treatment groups were negligible (PBO: 1.51; CIT: 1.77;
ESC: 2.11 mm/Hg). In line with other SSRIs, pulse rate showed a tendency to decrease, with mean decreases between groups that were comparable and judged as clinically irrelevant.

Analyses of ECG data and QT intervals did not indicate changes compared to placebo that were considered clinically relevant.

The clinical study experience with ESC do not indicate that the findings in the rat toxicity studies have any clinical correlate.

When comparing CIT and ESC, discontinuation reactions were without clinically important differences.

The MAH has submitted a Risk Management Plan (RMP) including a Pharmacovigilance Plan. The RMP is in line with current guidelines and focus on relevant safety issues and routine pharmacovigilance actions are outlined. The MAH concludes that the benefit/risk evaluation for ESC is positive with the presently labelled indications (MDD, PD, SAD, GAD). Extension of the labelled indications to include OCD does not change the benefit/risk, which continues to be favourable. This conclusion and the RMP are assessed as adequate.

IV.5 Discussion on the Clinical Aspects

Overall, the available efficacy and safety data supports the use of ESC for the indications major depressive disorder, panic disorder, social anxiety disorder, generalised anxiety disorder, and obsessive-compulsive disorder.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed.

The risk/benefit ratio is considered positive and Cipralex, tablets, 5, 10, 15 and 20 mg was recommended for approval.

The applicant committed to submit a type II variation to include requested changes to the SmPC and PIL.

VI. APPROVAL

The Mutual recognition procedure for Cipralex, tablets, 5, 10 15 and 20 mg was successfully finalised on 20070717.
Public Assessment Report – Update

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In the table above, the columns represent various aspects of the assessment report, including the scope, procedure number, product information affected, dates of start and end of the procedure, approval or non-approval status, and whether an assessment report is attached. The Y/N column indicates the version number of the report attached.