National Institute of Pharmacy

Public Assessment Report

Mutual Recognition Procedure

DALSAN 10 mg / 20 mg / 40 mg film-coated tablets (citalopram)

HU/H/0109/001-003

Applicant: EGIS PHARMACEUTICALS LTD.

Date: 27. 09. 2005

Administrative information

Product (name in the Reference Member State)	Marketing Authorisation no.	MRP-no.
Dalsan 10 mg	OGYI-T-09985	HU/H/0109/001
Dalsan 20 mg	OGYI-T-09986	HU/H/0109/002
Dalsan 40 mg	OGYI-T-09987	HU/H/0109/003

Name of the active substance:	Citalopram
Pharmaceutical form and strength	Film-coated tablets, 10/20/40 mg
Type of application:	Mutual recognition, Initial application, Abridged, Generic [Article 10.1.(a)(iii), first paragraph]
Reference Member State:	HU
Concerned Member State(s):	CZ, LT, LV, PL, SK
ATC code:	N06AB04
Authorwasation holder`s name and address:	EGIS Pharmaceuticals Ltd. H-1106 Budapest, Keresztúri út 30-38.
Name and address of manufacturer of the dosage form:	EGIS Pharmaceuticals Ltd. H-1106 Budapest, Keresztúri út 30-38.
Name and address of manufacturer responsible for batch release in the EEA:	EGIS Pharmaceuticals Ltd. H-1106 Budapest, Keresztúri út 30-38.
Date of first authorwasation:	07.01.2005.
Date of Assessment Report:	27.09.2005.

OVERVIEW

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I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Dalsan® 10, 20, and 40 mg tablets, in the treatment of depression and panic disorder, could be approved. A national marketing authorisation was granted on 7 January 2005.

II. EXECUTIVE SUMMARY

II.1 PROBLEM STATEMENT

The object was to develop pharmaceutical products that were essentially similar to the innovator's (H. Lundbeck A/S's) citalopram hydrobromide tablet preparations (Cipramil®). Citalopram was a well-known antidepressant (a selective serotonin reuptake inhibitor of the second generation).

II.2 ABOUT THE PRODUCT

Therapeutic indications: treatment of depressive disorders and panic disorders with or without agarophobia. The dosage should be set individually depending on the nature and severity of the disease, as well as the patient's condition and age. Citalopram was a Selective Serotonin Reuptake Inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram, the most selective serotonin reuptake inhibitor, like other second generation antidepressant agents enhances serotoninerg neurotransmission through selective and potent inhibition of serotonin reuptake. It has a very low affinity for a range of receptors including muscarinic acethylcholine receptors as well as 5-HT1A, 5-HT1b, 5-HT2, dopamine1 and dopamine2, α1-, α2-, β1- and β2- adreno, histamine1, benzodiazepine, gamma aminobutyric, opioid and monoamine oxidase inhibitor receptors.

II.3 THE DEVELOPMENT PROGRAMME

Citalopram hydrobromide containing products have been available both in Europe and in the USA for years. Citalopram has been marketed in EU since 1989 (Denmark), it has a well establwashed medicinal use, with recognized efficacy and acceptable level of safety. The originator's (H. Lundbeck's) citalopram product has been authorised and marketed under different brand names in different member states of EU and in Hungary. Cipramil® was the brand name of the innovator's citalopram product in the UK, Germany, Poland, Czech Republic, Slovakia and Russia while Seropram in France and Hungary. The company Bayer has Citalopram containing tablets on the market in Germany under the name Sepram, and the company Forest markets such product under the name Celexa in the USA. EGIS Pharmaceuticals Ltd. has developed a citalopram containing generic product line (film-coated tablets containing citalopram hydrobromide, under the trade name Dalsan®) in the strengths of 10 mg, 20 mg and 40 mg. The application was based on Article 10.1 (a) (iii) first paragraph of Directive 2001/83/EC, claiming essential similarity to tablets Seropram® (Lundbeck), identical to Lundbeck's Cipramil® that have been authorised in Hungary. No new pre-clinical and clinical studies (except the bioequivalence ones) were conducted, which was acceptable for this type of application. No scientific advice has been given to the applicant with respect to these products. No paediatric development was available in the submitted dossier.

During development of the products the following guidance documents were followed by the applicant: CPMP/EWP/QWP/1401/98 and CPMP/QWP/155/96,CPMP/QWP/486/95 and CPMP/QWP/848/96,CPMP/ICH/381/95 and 3AQ11a.

II.4 GENERAL COMMENTS ON COMPLIANCE WITH GMP, GLP, GCP AND AGREED ETHICAL PRINCIPLES

The products have been developed, manufactured and the bioequivalence study conducted in compliance with GMP, GLP and GCP rules, respectively, as well as agreed ethical principles.

II.5 GENERAL COMMENTS ON THE SUBMITTED DOSSIER

The dossier was submitted in CTD format. The legal basis for the products proposed for marketing was Directive 2001/83/EC Article 10.1 (a) (iii) first paragraph. The products were considered essentially similar to the original products, which was placed more than 10 years on the EU market. The applicant demonstrated bioequivalence to the reference medicinal product. The proposed SmPC text of the Dalsan® tablets was similar to that already approved for branded products of the innovator in Hungary. The SmPC was also adequate from the clinical, pre-clinical and pharmaceutical points of view.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

Drug substance

The active substance was manufactured by EGIS, i.e. the manufacturer of the finished product. Copy of the Applicants and Restricted Part of the Drug Master File (DMF) was provided. Reference was made to the Applicants Part of DMF dated August, 2004. The referred DMF was included as appendix to Module 3. Appropriate Letters of Access have been provided. Drug Product satisfactory chemical and pharmaceutical data have been submitted for marketing authorization. There were no significant deviations from EU and ICH quality guidelines. The granted shelf-life was 2 years with no special storage condition. Assessors of quality recommended granting a marketing authorwasation for Dalsan 10 mg, 20 mg and 40 mg tablets.

III.2 NON CLINICAL ASPECTS

The assessors find it acceptable that specific studies have not been performed, for the application was submitted in accordance with article 10.1 a (iii) of Directive 2001/83/EEC.

III.3 CLINICAL ASPECTS

Efficacy/Safety

No formal clinical assessment was performed since citalopram-containing medicinal products have been marketed in many countries for many years and no new data were submitted. The indications requested by the application have also been approved for the innovator's product in Hungary. The application contains an adequate review of published clinical data. The applicant has demonstrated bio-equivalence with the Brand Leader authorised in the European Community.

IV. SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg, 20 mg, 40 mg citalopram (as 12.495 mg, 24.99 mg 49.98 mg citalopram hydrobromide) in each film-coated tablet.

Excipients are listed in section 6.1.

3. PHARMACEUTICAL FORM

10 mg film-coated tablets: white or off-white, odourless or nearly odourless, round, biconvex film-coated tablets with imprinted stylistic "E" on one side and imprinted "771" on the other side. The fracture surface is off-white.

20 mg film-coated tablets: white or off-white, odourless or nearly odourless, round, biconvex, scored film-coated tablets with halving line on one side and imprinted "E 772" on the other side. The fracture surface is off-white.

40 mg film-coated tablets: white or off-white, odourless or nearly odourless, round, biconvex, scored film-coated tablets with halving line on one side and imprinted "E 773" on the other side. The fracture surface is off-white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of depressive disorders of different aetiology and with different symptoms (including depression in the elderly), prevention of their recurrences and the development of new episodes;
- Depression associated with dementia;
- Panic disorder with or without agoraphobia (episodes of anxiety attack).

4.2 Posology and method of administration

The dosage should be set individually depending on nature and severity of the disease, as well as on the patient's condition and age.

The tablets should be taken as a whole, without chewing them, with a small volume of water once daily. Concomitant food intake does not influence the efficacy.

Treatment of depression
The recommended daily dose is 20 mg. If necessary, this dose can be increased with maximum increments of 20 mg weekly to a maximum of 60 mg daily. Following remission a treatment period of at least 6 months is usually necessary to provide adequate maintenance against the potential for relapse. In recurrent (unipolar) depression it may be necessary to continue treatment for several years.

Treating panic disorder
A low starting dose - 10 mg daily - is advised on the first week, since these patients are more susceptible to the paradoxical initial anxiogenic side effect. The majority of the patients respond well to the maintenance dose of 20 mg daily. Here, too, the maximum daily dose of 60 mg should never be exceeded. Maximum effectiveness of citalopram in treating panic disorder is reached after about 3 months. Dependent on individual patient response it may be necessary to continue treatment for several months.
Elderly patients (above the age of 65 years)
Lower doses, usually 20 mg daily are recommended depending on individual patient response. The maximum daily dose is 40 mg.
Children and adolescents under 18 years of age
Not recommended, as the safety and efficacy of citalopram have not been established in this population.
Reduced hepatic function
Dosage should be restricted to the lower end of the dose range (10-20 mg). The maximal dose is 30 mg daily
Reduced renal function
Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20 mL/min).

4.3 Contraindications

- Hypersensitivity to any component of the preparation.
- Pregnancy (see section 4.6)
- Lactation (see section 4.6)
- Similarly to other SSRIs, concomitant administration of citalopram with MAO-inhibitors is contraindicated. The only exception of this rule is selegiline (a selective MAO-inhibitor) if administered in lower than 10 mg doses (see section 4.5).

4.4 Special warnings and precautions for use

Activation of panic disease
In certain patients treated for panic attacks increased anxiety may occur at the beginning of the treatment, therefore, in order to avoid this paradoxical anxiogenic effect lower starting doses should be applied (see section 4.2).
Activation of mania
In patients with bipolar (maniac/depression) disorder, activation of mania/hypomania may occur. In patients manifesting mania citalopram administration should be suspended and an appropriate antimania therapy should be started.
Suicide
The possibility of a suicide thoughts and attempts is inherent in depression and may persist until significant remission occurs. Consequently, early phases of drug therapy patients require close supervision until optimum clinical effect is attained.
Use in children and adolescents under 18 years of age
Dalsan should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempt and suicide thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.
Withdrawal symptoms
Sudden discontinuation of a long-term administration may provoke withdrawal symptoms, such as tremor, anxiety, dizziness, paraesthesia, nausea and palpitation. Withdrawal symptoms may

be avoided if the preparation is withdrawn during the period of 1-2 weeks by gradually decreasing the dose.

Serotonin syndrome

The occurrence of serotonin syndrome has been reported in some patients receiving SSRIs. A combination of symptoms, including hyperthermia, myoclonus, muscular rigidity, mental confusion (irritability, agitation, delirium, confusion, coma) and rapid fluctuation of vital functions may indicate the development of this condition.

Epilepsy

Although citalopram was not shown to be epileptogenic in pre-clinical studies, the treatment should be discontinued if the number of seizures increases during the therapy.

Electroconvulsive therapy (ECT)

There is little clinical experience of concurrent administration of citalopram and ECT, therefore, caution is advisable.

Hepatic and renal impairment

Special caution is needed if citalopram is administered to patients with severe hepatic and/or renal impairment (see section 4.2).

Potential arrhythmogenic effect

Consideration should be given to factors which may affect the disposition of a minor metabolite of citalopram (didemethylcitalopram) since increased levels of this metabolite could theoretically prolong the QTc interval in susceptible individuals. However, in clinical trials in large patient populations, no clinically significant changes were noted.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely. Especially elderly patients appear to be at risk.***Diabetes mellitus***

In patients with diabetes, treatment with an SSRI may alter glycaemic control, possibly due to improvement of depressive symptoms. Insulin and or oral hypoglycaemic dosage may need to be adjusted.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura, as well as haemorrhagic manifestations, e .g. gastrointestinal haemorrhage with SSRIs. The risk of gastrointestinal haemorrhage may be increased in elderly people during treatment with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) as well as in patients with a history of bleeding disorders.

Since Dalsan contains lactose monohydrate patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicaments and other forms of interaction

The metabolism of citalopram is only partly dependent on the hepatic cytochrome P450 isozyme CYP2D6 and, unlike some other SSRIs, citalopram is only a weak inhibitor of this important enzyme system which is involved in the metabolism of many drugs (including antiarrhythmics, neuroleptics, beta-blockers, tricyclic antidepressants and some SSRIs). In addition, protein-binding is relatively low (<80 %). These properties give citalopram a low potential for clinically significant drug interactions.

MAO-inhibitors

Owing to the risk of severe, sometimes fatal interaction, citalopram must not be used in combination with a MAO-inhibitors, except with selegiline, the selective MAO-B inhibitor if the daily dose of the latter does not exceed 10 mg.

Patients receiving selective serotonin reuptake inhibitors (SSRIs) in combination with a monoamine oxidase inhibitor may be presented with serotonin syndrome, including the signs of

hyperthermia, rigidity, myoclonus, rapid fluctuations of vital signs, and mental status changes, like confusion, irritability and occasionally extreme agitation progressing to delirium and coma.

Citalopram treatment should not be started sooner than after a minimum of 14 days following the withdrawal of any irreversible MAO-inhibitor.

At least one day should also be allowed if citalopram treatment is started after the therapy with a reversible MAO-inhibitor (RIMA, e.g. moclobemide) is discontinued.

The administration of reversible (RIMA), or irreversible MAO-inhibitors should not be started sooner than after a minimum of 7 days after citalopram therapy is discontinued.

Alcohol

The concomitant use of alcohol and citalopram should be avoided, although, in contrast to other psychotropic agents, the interaction studies did not show citalopram to potentiate the cognitive and psychomotor effects of alcohol.

Cimetidine

Increased maximum plasma levels (Cmax) and area under the plasma concentration time curves (AUC) were reported in cases, where citalopram and cimetidine were used concomitantly. The clinical significance of these changes has not been clarified as yet.

Digoxin

Coadministration of citalopram and digoxin did not affect the pharmacokinetics of either digoxin or citalopram.

Lithium

Coadministration of citalopram and lithium did not affect the pharmacokinetics of either drug to any significant extent. However, since lithium may increase serotonergic neurotransmission and as such may potentiate the effects of citalopram, patients require a more close medical supervision if concomitant treatment with these two drugs is applied.

Sumatriptan

According to certain postmarketing reports, in very rare cases weakness, hyperreflexia and incoordination occurred, following the concomitant administration of citalopram and sumatriptan, a selective 5-HT1 agonist. The patients should carefully be observed if an SSRI is to be used in combination with sumatriptan.

Warfarin

On the basis of the interaction studies, coadministration of citalopram did not affect the pharmacokinetics of warfarin, but prolonged the prothrombin time by 5 %. The clinical relevance of the alteration is unclear.

Carbamazepine

Coadministration of citalopram and carbamazepine did not affect the pharmacokinetics of either drug to any significant extent. However, since carbamazepine is a microsomal enzyme inducer, the possibility that carbamazepine may increase the clearance of citalopram should be considered if the two drugs are given concomitantly.

CYP3A4 and CYP2C19 inhibitors (e.g. ketoconazole, itraconazole, fluconazole or erythromycin)

Using *in vitro* studies, the biotransformation of citalopram was shown to depend on both CYP2C19 and CYP3A4. Although, in principle, the coadministration of citalopram and ketoconazole may inhibit CYP3A4, yet the combination does not affect the pharmacokinetics of citalopram. This phenomenon is explained by the fact that citalopram is metabolised by other isoenzymes, too, and the inhibition of a single isoenzyme does not cause any discernible changes in the clearance of citalopram.

Nevertheless, the possibility that the clearance of citalopram will be decreased when citalopram is administered with an inhibitor of CYP3A4 or CYP2C19 (e.g., ketoconazole, itraconazole, fluconazole or erythromycin) should be considered.

Metoprolol

Coadministration of citalopram and metoprolol resulted in a two-fold increase in the plasma levels of metoprolol with a secondary decrease of its cardioselectivity. However, blood pressure and heart rate was not affected to any clinically significant extent with the use of the two drugs in combination.

Imipramine and other tricyclic antidepressants

Coadministnation of citalopram and imipramine did not affect the pharmacokinetics of either drug, however, in the presence of citalopram, the concentration of desipramine, a metabolite of imipramine, increased by approximately 50 %. The clinical relevance of the finding has not been clarified as yet.

Serotonergic agents

The length of the wash-out period required for switching the patients from one to another serotonin reuptake inhibitor has not been established, therefore, special caution is recommended in these cases.

Coadministration of citalopram with other serotonergic drugs (e.g. triptophane, phenfluramine) requires special caution and should be avoided if possible.

Hypericum perforatum

Dynamic interactions between citalopram and herbal remedy St John's Wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects.

According to pre-clinical data citalopram potentiates the effects of amphetamine, morphine and the related compounds.

Citalopram does not affect the pharmacokinetics of benzodiazepines, neuroleptics, analgetics, anthypertensives, ß-blockers and other cardiovascular agents.

4.6 Pregnancy and lactation

Pregnancy

In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In the absence of controlled clinical study data citalopram administration is contraindicated in pregnancy. Women of fertile age should apply appropriate contraceptive method during the therapy (see section 4.3).

Lactation

Citalopram is known to be excreted in breast milk. In the absence of controlled clinical study data citalopram administration is contraindicated during the period of nursing (see section 4.3).

4.7 Effects on ability to drive and use machines

Although citalopram has no sedative effects it may affect one's ability to drive a car and operate machinery. Accordingly, in the first period of the therapy – for a period to be determined individually – driving and operating machinery should be prohibited. Later on the extent of prohibition should be determined on a case by case basis considering the patient's psychomotor performance.

4.8 Undesirable effects

Adverse effects observed with citalopram are in general mild and transient. They are most prominent during the first one or two weeks of treatment and usually attenuate as the depressive state improves.

The most commonly observed adverse events associated with the use of citalopram and not seen at an equal incidence among placebo-treated patients were: nausea, diarrhoea, somnolence, dry mouth, hyperhydrosis, tremor and ejaculation failure. The incidence of each in excess over placebo is low (<10%).

Comparative clinical trials with tricyclic antidepressants showed more favourable adverse event profile for citalopram. The incidence of dry mouth, hyperhydrosis, constipation, tremor,

postural hypotension, palpitation, dizziness, somnolence, accommodation problems and dysgeusia appeared to be lower, whereas two adverse reactions – nausea and ejaculation problems – were more frequent in the citalopram-treated group of patients.

Withdrawal reactions have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Similar observations were made also with citalopram. Sudden withdrawal may result in dizziness, paraesthesia, headache, anxiety and nausea, therefore, it is recommended that the treatment is discontinued gradually. The majority of symptoms experienced on withdrawal of SSRIs are non-serious and self-limiting.

Adverse events reported in clinical trials are classified in body systems and listed below as very common >1/10); common (<1/10 and >1/100); uncommon (<1/100 and >1/1000); rare (<1/1000); very rare (<1/10,000):

Immune system disorders - *Uncommon:* allergic reactions.
Metabolic and nutritional disorders - *Common:* weight decrease, weight increase.
Psychiatric disorders - *Very common:* somnolence, insomnia, asthenia; *Common:* nervousness, anxiety, impaired concentration, excitation, disturbing dreams, decreased libido, apathy, anorexia, malaise, depressed mood, confusion, yawning; *Uncommon:* euphoria, aggression.
Nervous system disorders - *Very common:* headache, tremor; *Common:* dizziness; *Uncommon:* convulsions.
Eye disorder - *Common:* abnormal vision.
Ear and labyrinth disorders - *Uncommon: tinnitus.*
Cardiac disorders - *Common:* palpitation, tachycardia; *Uncommon:* bradycardia.
Vascular disorders - *Common:* postural hypotension; *Uncommon: syncope.*
Respiratory, thoracic and mediastinal disorders - *Common:* rhinitis; *Uncommon:* coughing, dyspnoea.
Gastrointestinal disorders - *Very common:* dry mouth, nausea, constipation; *Common:* diarrhoea, abdominal pain, digestion problems, increased salivation, flatulence, taste abnormalities.
Hepato-biliary disorders - *Uncommon:* elevated enzyme levels.
Skin and subcutaneous tissue disorders - *Very common:* hyperhydrosis; *Common:* rash, pruritus; *Uncommon:* photosensitivity.
Musculo-skeletal, connective tissue and bone disorders - *Common:* myalgia.
Renal and urinary disorders - *Common:* micturition disorder.
Reproductive system and breast disorders - *Common:* ejaculation failure, impotence, dysmenorrhoea; *Uncommon:* female anorgasmia.

Post-marketing adverse event reports:
Immune system disorders: anaphylactoid reactions
Metabolism and nutrition disorders: hyponatraemia and insufficient ADH secretion – sporadically, mainly in elderly female patients
Psychiatric disorders: hallucinations, mania, depersonalisation, panic attack
Nervous system disorders: serotonin syndrome, withdrawal reactions (dizziness, nausea, paraesthesia)
Hepatobiliary disorders: elevated enzyme levels
Skin and subcutaneous tissue disorders: ecchymosis, photosensitivity reaction – very rarely
Musculoskeletal disorders: arthalgia*Reproductive system and breast disorders*: galactorrhoea.

4.9 Overdose

Symptoms
Overdose with lower than 600 mg: fatigue, weakness, sedation, vertigo, tremor of the hands, nausea, tachycardia were observed.

Overdose with higher than 600 mg: convulsions, somnolence, stupor and coma, respiratory insufficiency, ECG anomalies, rhabdomyolysis occurred.

Treatment

No specific antidote is known. Gastric lavage should be made as soon as possible. Supportive and symptomatic treatments are to be applied. It is important to ensure free airways to maintain oxygenation and ventilation. Diazepam is recommended to treat convulsions. In the case of an overdose with higher than 600 mg dose, monitoring is recommended.

Owing to the high apparent volume of distribution of citalopram, forced diuresis, dialysis, haemoperfusion cannot be expected to be of any benefit.

One adult patient survived intoxication with 5200 mg citalopram.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

ATC: N06A B04

Mechanism of action: Citalopram is a drug belonging to the group of selective serotonin reuptake inhibitors (SSRIs). Citalopram increases highly selectively the mediator (serotonin, 5-HT) level in serotonergic synapses of the central nervous system through the inhibition of presynaptic reuptake of 5-HT. Tolerance to the inhibition of 5-HT reuptake does not develop even during long-term treatment with citalopram.

Pharmacodynamic effects: Citalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, DAD_1 and D_2 receptors, α_1-, α_2-, β-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, gamma aminobutyric, and opioid receptors. This absence of effects on receptors explains the lack of antidopaminergic, antiserotonergic, anthistaminergic, anticholinergic effects of citalopram and/or its metabolites and the fewer traditional side-effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension associated with citalopram administration. Like tri- and tetracyclic antidepressants, other SSRIs and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep. (The suppression of the REM phase is a predictor of the antidepressant effect).

The main metabolites of citalopram are desmethyl-citalopram, didesmethyl-citalopram, citalopram-N-oxide, desaminated propionic acid derivative. Except for the last one all metabolites are selective serotonin reuptake inhibitors although their potency is lower than that of citalopram, therefore, the metabolites do not contribute to the overall antidepressant effect. Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. In humans citalopram has no or minimal sedative properties, either alone or in combination with alcohol. Citalopram does not impair cognitive (intellectual function) and psychomotor performance. Citalopram does not induce body weight gain and does not potentiate the effects of alcohol. Citalopram has no effect on the serum levels of prolactin and growth hormone. Citalopram does not reduce saliva flow and in none of the clinical studies did citalopram have significant influence on cardiovascular parameters.

5.2 Pharmacokinetic properties

Absorption: Absorption is almost complete and independent of food intake. Maximum plasma concentration is attained within 3 hours, on the average, after drug intake. Oral bioavailability is about 80 %.
Distribution*:* The apparent volume of distribution varies between 12-16 L/kg with a mean of about 14 L/kg. The plasma protein binding is below 80 % for citalopram and its main metabolites.
Biotransformation: Citalopram is metabolized to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.
Elimination*:* The elimination half-life is about 36 hours, the systemic citalopram plasma clearance is about 0.33 L/min, and the oral plasma clearance is about 0.4 L/min.

Citalopram is excreted mainly via the liver (85 %) and the remainder (15 %) via the kidneys. About 12-23 % of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.33 L/min and renal clearance is about 0.05-0.08 L/min.

The kinetics is linear in the dose range of 10-60 mg. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 300 nmol/L (165-405 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects. Unchanged citalopram rather than the metabolites is the predominant compound in plasma. Enzyme inducers (e.g. barbiturates) do not affect the plasma concentration.

Longer half-lives (36-90 hours) and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients (>65 years); these may result in higher citalopram plasma concentrations.

The pharmacokinetics of citalopram changes to a small extent in patients with mild to moderate reduction of renal function and the alteration is not of clinical importance. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min). Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

5.3 Preclinical safety data

Citalopram has low acute toxicity. In chronic toxicity studies there were no findings of concern for the therapeutic use of citalopram.

According to the results of the preclinical studies citalopram has no mutagenic or carcinogenic potential.

Pregnancy
In preclinical studies in rats treated with 18-fold of the recommended maximum human dose (on mg/m^2 basis) during the period of organogenesis teratogenic effects (cardiovascular and bone development malformations) were observed. No similar alterations were observed with the 9-fold dose. No evidence of teratogenic effects was found in rabbits treated with 5-fold of the recommended maximum human dose (on mg/m^2 basis).

If administered to rats in 5 times higher doses than the recommended maximum human dose (mg/m^2) during the late phase of pregnancy, citalopram increased the perinatal mortality and retardation in the later development of the offsprings could be observed.

Fertility
If administered to rats in 5 times higher doses than the recommended maximum human dose (on mg/m^2 basis) citalopram decreased fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Core: anhydrous colloidal silicon dioxide, magnesium stearate, lactose monohydrate, microcrystalline cellulose

Coating: macrogol 6000, titan dioxide, hypromellose

6.2 Incompatibilities

None is known.

6.3 Shelf-life

2 years

6.4 Special precautions for storage

No special storage condition is required.

6.5 Nature and contents of container

28 film-coated tablets in PVC/PVDC/aluminium foil blister and carton box.

6.6 Instructions for use and handling

Note ✠ (single cross)
Legal category: Group II/1
To be dispensed only on prescription (V).

7. MARKETING AUTHORISATION HOLDER

EGIS Pharmaceuticals Ltd. 1106 Budapest, Keresztúri út 30-38. HUNGARY

8. MARKETING AUTHORISATION NUMBER(S)

*OGYI-T-9985/01	(Dalsan 10 mg film-coated tablets) 28 tablets
OGYI-T-9986/01	(Dalsan 20 mg film-coated tablets) 28 tablets
OGYI-T-9987/01	(Dalsan 40 mg film-coated tablets) 28 tablets

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

January 7, 2005

QUALITY CRITICAL REVIEW

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QUALITY CRITICAL REVIEW

I INTRODUCTION

As stated earlier, the application was in compliance with the following legal base: an abridged application according to article 10.1 (a) (iii) of Directive 2001/83/EC. The innovator's product (Seropram 20 mg film-coated tablets, H. Lundbeck) was authorised for marketing in Hungary in 1993. A bioequivalence study has been performed using the innovator product Cipramil, Seropram and Sepram. (H. Lundbeck and Bayer). The active substance was manufactured in-house.

II DRUG SUBSTANCE

S.1 General Information

S.1.1 Nomenclature: Citalopram (INN)
Other name: Citalopram hydrobromide
CA name: 1-[3-(dimethylamino)-propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-wasobenzo-furan-carbonitrile hydrobromide
Other name: (R,S)1-[3-(dimethylamino)-propyl]-1-(p-fluorophenyl)-5-phthalancarbo-nitrile
CAS NUMBER: 59729-32-7

S.1.2 Structure:
Molecular formula: $C_{20}H_{21}FN_2O$ x HBr
Molecular weight: 405.31 (324.39 + 80.91)

S.1.3 General Properties

Physical form: white or almost white, odourless crystalline powder
Solubility: sparingly soluble in water, freely soluble in chloroform, soluble in ethanol, very slightly soluble in diethyl ether.
Melting point: 183 – 185°C
Polymorphism: Only one crystalline form was known from the literature and has been found for all citalopram hydrobromide batches manufactured by EGIS.

S.2 Manufacture

S.2.1 Manufacturer:
Name: EGIS Pharmaceuticals Ltd.
Address: Budapest, Keresztúri út 30-38, H-1106 HUNGARY

S.2.2 Description of Manufacturing process and process controls

The applicant has provided a copy of Open and Restricted Part of the DMF dated August 2004.

The flow chart of the synthetic route was enclosed containing the main synthetic steps and the used starting materials detailing preparation of citalopram base and its HBr. Solvents, main reaction steps and their characteristics, quantities of raw materials, reaction conditions and standard yields were described for each step. Solvents used throughout the synthesis: see S.3.2.

S.2.3 Control of Materials:

Specifications of all reagents, starting materials and solvents were provided and found to be adequate. Certificates of analyswas were enclosed, the suppliers were named.

S.2.4 Control of Critical Steps and Intermediates

The critical steps were listed along with the requirements and tests.

Water determination (KF method) and peroxide content (Merck test-strip) of tetrahydrofurane.
Reaction end-point checking of complex formation (GC method).
Control test of cyclization (GC method).
pH test of alkalisation.
Loss on drying determination.
Foreign matter determination.

The only isolated intermediate was citalopram base. Specifications were given and found acceptable.

S.2.5. Process Validation and Evaluation

The manufacturer declared that the manufacturing process of the drug substance was validated in 2002 in accordance with "Qualification and validation" EU Guide to GMP Annex 15.

S.2.6. Manufacturing Process Development

The process developed by Chemical Research Department of EGIS at laboratory level has been taken as the basis of development. During the scale-up in 2001 and 2002, minor developments were carried out in order to avoid emulsion formation and to decrease molar excess of reagents. Critical steps and the critical parameters of the synthesis were identified. During the scale-up six batches of citalopram hydrobromide were manufactured.

The batch analysis results showed good quality of the product.

S.3 Characterisation

S.3.1. Elucidation of Structure and Other Characterwastics

The chemical structure of citalopram hydrobromide was identified and investigated by elementary analysis, infrared spectrum, NMR spectra and mass spectroscopy. The IR, NMR and MS-spectrum assignations were consistent with the declared chemical structure. The methods used for elucidation of structure were adequate. Typical spectra were enclosed.

Potential isomerism was discussed. Due to the asymmetric carbon atom in the molecule, two enantiomeric forms were theoretically possible. The synthetic route of EGIS results racemic form of the substance exclusively. The concentration of the identified, main possible impurity was in the starting material 1 below 0.01% in all batches, thus, this kind of impurity could be ruled out.

Possibility of polymorphism was also discussed. In accordance with the literature only one crystalline form was found for all batches manufactured by EGIS using the following analytical methods:

Differential Scannig Calorimetry,
IR spectroscopy,
X-ray diffraction.

S.3.2. Impurities

Degradation products and process related impurities:
Altogether 3 different starting materials (Stm), 6 impurities of Stm 1 (ImpStm1a, ImpStm1b, ImpStm1c, ImpStm1d, ImpStm1e, ImpStm1f), 1 by-product (Impurity 1) and 2 degradation products (*ImpCHba,ox* in alkaline and oxidative solution*, ImpCHac* in acidic solution) were taken into consideration. The recommended limits for these impurities were not more than (NMT) 0.1% while levels actually found were always below 0.01%.

Total impurity content**:** NMT 0.2 %.

Impurity data of four batches as well as limits of detection (LOD) for the above foreign substances were provided. The actual impurity values found were always below the limits set.

Residual solvents
The four solvents used during the synthesis were duly identified. The residual content of the single solvent (Sol1) applied in the last step of the process could be controlled by the "Loss on Drying" test with a limit of 0.5 % in accordance with ICH Guideline Q3C 3.5.

Residues of the other process solvents (together with the above one) were controlled with a validated HS-GC method at the stage of citalopram base. Limits of quantitation (LOQ) values were determined and provided.

The IPC limits of Sol2 – Sol3 have been set in accordance with the CPMP/QWP/450/03 guide.

Data for the above residual solvents of three validation and three production batches have been submitted. The values found were always below the LOD for Sol2 and Sol3, 4-6 ppm for Sol4 and 1500-2150 ppm (0,15-0,22%) for Sol1.

Residual catalysts: not applicable for no catalysts were used in the manufacturing process.

S.4 Control of drug substance

S.4.1. Specification

The citalopram hydrobromide active pharmaceutical ingredient has not been included in any Pharmacopoeia. Requirements were developed partly in-house for methods referenced as "EGIS method", while general pharmacopoeial procedures and limits referenced as "Ph.Eur" were used in another cases.

General purity requirements such as appearance of solution, heavy metals, sulphated ash, loss on drying, water content as well as titration assay were set according to from Ph.Eur. EGIS requirements (HPLC and an alternative GC one) were developed for related substances. Particle size was controlled also by EGIS method and proper requirements (lower and upper limits) were presented also for the latter.

S.4.2. Analytical Procedures

Tests outlined in S.4.1 were regularly carried out to control the quality of the drug substance. The methods and specifications were in accordance with ICH Guideline Q6A. Citalopram hydrobromide assay was carried out by a potentiometric titration with a requirement of 99-101% calculated on the dried substance.

Related substances were controlled by three chromatographic methods. In-house standards were developed and used. Two validated GC limit test methods were selective to Stm2 and Stm3 impurities with a limit of 1000 ppm and 25 ppm, respectively. According to the toxicological report, Stm3 was mutagenic, genotoxic and carcinogenic substance. The 25 ppm limit was in accordance with the draft Guideline on genotoxic impurities (CPMP/SWP/5199/02). Limits of 0.1% for other related substances (controlled by a HPLC method) were in line with ICH Guideline Q3A.

The only solvent used in the last step of the synthesis was Sol1 (class 3). As mentioned above, it could be controlled by the loss on drying test with a limit of 0.5 %. It was acceptable according to the ICH Guideline Q3C, point 3.5.

Other process solvents (Sol2 – Sol4) were controlled with a validated HS-GC method at the production stage of citalopram base. The specification limits were in accordance with CPMP/QWP/450/03 and ICH Q3C guidance. Since the values found in residual solvents were very low, it was acceptable not to control these residual solvents in the final product.

All methods were described in detail, typical chromatograms were enclosed.

S.4.3. Validation of the Analytical Procedures

Validation of the HPLC method used for determination of related substances was performed with respect to the following characteristics: specificity, selectivity, linearity, accuracy, precision, LOD, LOQ and stability of solutions.

Specificity of the method was checked using an *Impurity Reference Standard* solution. All components were resolved and no interfering peaks were detected. Representative chromatograms were enclosed.

Analytical validation for each residual solvent (Sol1 – Sol4) was performed with respect to the following characteristics: selectivity, LOD, LOQ, linearity and range, accuracy, precision, method ruggedness and robustness. Representative chromatograms were enclosed.

The two GC methods used for determination of related substances Stm2 and Stm3 were limit tests, thus, the analytical validation has been performed only with respect to specificity, LOD and LOQ. Representative chromatograms were enclosed.

The assessment of the validation procedure was found to be in compliance with ICH guidelines Q2A and Q2B. Thus, the methods were adequate to control the substance on a routine baswas as well as in stability study.

S.4.4. Batch Analyses

Certificates of Analysis of three batches of citalopram hydrobromide manufactured in 2002 (Batch numbers identified) were. The batch sizes varied (mean ± 5%). The quality of the substance met the specification of the manufacturer in all cases.

The results confirm batch to batch consistency and uniformity of the quality of the substance as well as indicate that the process was under control.

S.4.5. Justification of Specification

The parameters and requirements of the substance specification were found properly justified.

- Identity and general impurity test and the assey specifications were set in accordance with Ph.Eur. monographs.

- The specification limits for related substances were in accordance with batch results, ICH Guideline Q3A and also CPMP/SWP/5199/02 for Stm2. The applied GC and HPLC methods were sensitive and selective to quantify organic impurities.
- Loss on drying test with the limit of NMT 0.5 % was set in accordance with the batch results and with ICH Guideline Q3C. It was suitable to control also the class3 Sol1.
- Other process solvents (Sol2 – Sol4) were controlled at the production stage of Citalopram base. The IPC limits of these solvents have been set in accordance with CPMP/QWP/450/03. Thus, it was justified not to have requirements for residual solvents in the final substance specification.
- The particle size distribution limit was in accordance with batch results.

S.5 Reference Standards or Materials

Primary (Lot No identified) and secondary working standards of the substance as well as impurity standards (ImpStm1a, ImpStm1b, ImpStm1c, ImpStm1d, ImpStm1e, ImpStm1f, Stm1, Stm2, Stm3, non-isolated intermediates Imp1, ImpCHac and ImpCHba,ox) were developed in-house and used.

Acceptable *Certificates of Analysis* and chemical, spectroscopic evidences of the structure of all reference standards were attached.

S.6 Container Closure System

The batches were supplied in a clear, slightly transparent LDPE bag, inside another LDPE bag, inside a reeled paper-board fiber drum which had two pulp closing plates (one at the bottom and one at the top). The bottom plate can be opened and closed by a metal patent closure.

The raw materials for the two LDPE bags met the requirements of the FDA and BGA for pharmaceutical utilization and certified by the Hungarian National Scientific Institution on Food and Nutrition (OÉTI) under the certification number 729/1997.

The clear, slightly transparent LDPE bag, which was in direct contact with the drug substance meets the requirements of Ph. Eur. 4 (chapter 3.1.4.) and USP (chapter 661).

The choice of the primary container was justified by accelerated and long-term stability tests carried out on the substances in the proposed primary container of the quality specified in this section.

S.7 Stability

S. 7.1. Stability Summary and Conclusion

Three batches of the substance were investigated. The batches were stored in the sales package under two conditions according to ICH Guidelines Q1A and Q1B (accelerated: 40°C/75% RH and long term: 25°C/60% RH). Separately a direct UV irradiation and a "Sun-test" were carried out.

Test parameters were: identity (IR), appearance, water (KF method), related substances by HPLC and assay (titration).

Test methods were the same as for release.

Six months of accelerated and 24 months of long term stability testing were complete at the time of this assessment. Data were enclosed. The results showed no changes in physical tests. The citalopram hydrobromide content was found unchanged and the impurity levels were within the specification.

Stress Tests: one batch underwent various treatments using different stress conditions (long term hydrolysis at elevated temperature in acidic and alkaline media, oxidation, diffuse light irradiation, direct UV radiation and thermal test under vacuo) in order to study the possible causes of degradation and the degradation products actually formed. Using a gradient HPLC/MS and HPLC methods (described in detail) a preliminary view could be outlined on the chemical composition of the main degradation products.

Re-test period: 1 year re-test period was proposed when stored below 25°C. It was acceptable.

S.7.2. Post-approval Stability Protocol and Stability Commitment

The manufacturer committed itself to continue stability tests and place the first three production batches on long term stability studies through the proposed re-test period (or at least 18 months) using the same stability protocol as that for primary batches.

III DRUG PRODUCT

P.1 Description and composition of the drug product

The 10 mg film-coated tablets are white, odourless, round and slightly convex with a 771 mark on one side and stylised E on the other side.

The 20 mg film-coated tablets were white, odourless, round and slightly convex with stylised E and 772 mark on one side and a bisector notch on the other side.

The 40 mg film-coated tablets were white, odourless, round and slightly convex with stylised E and 773 mark on one side and a bisector notch on the other side.

One film-coated tablet contains:

	Unit formula (mg/tablet)	Unit formula (mg/tablet)	Unit formula (mg/tablet)	Function of the component	Reference
C o r e					
Citalopram In the form of citalopram hydrobromide	10.0 12.95	20.0 24.99	40.0 49.98	Active pharmaceutical ingredient	EGIS specification Code identified
Cellulose, microcrystalline	Filling ingredient				Ph. Eur.
Lactose monohydrate As Lactose spray dried DCL 11	7.20	14.4	28.8	Filling ingredient	Ph. Eur.
Magnesium stearate	Lubricant				Ph.Eur.
Colloidal anhydrous silica	Glidant				Ph. Eur.
C o a t i n g					
Hypromellose	Coating agent				Ph. Eur.
Macrogol 6000	Plasticizer				Ph. Eur.
Titanium dioxide E171	Colouring agent				Ph. Eur.
Total weight of the film-coated tablet	91.8	183.6	367.2		

No overages were applied.

The qualitative composition of the film-coated tablets of the three different strengths was the same.

The quantitative composition of the 10 mg, 20 mg and 40 mg preparation was dose-proportional.

The film-coated tablets were packed in blisters composed of PVC / 60g/m^2 PVdC foil fastened with 20 μm aluminium foil.

The blisters and the patient information leaflet were packed into folded cardboard box.

P.2 Pharmaceutical Development

The aim was to develop pharmaceutical products which were essentially similar to the H. Lundbeck's original citalopram hydrobromide preparations containing different doses of the active ingredient and meet the general tablet requirements of the European Pharmacopoeia.

Drug Substance (active pharmaceutical ingredient)

The applicant identified the properties of the drug substance.

There were no special properties which were of relevance for product performance.

Citalopram hydrobromide was freely soluble in water and showed no polymorphism.

Excipients

The excipients of Dalsan film-coated tablets were materials commonly used in pharmaceutical preparations. Functions of the excipients were duly identified (see above).

Drug Product (medicinal product):

Formulation development:

The formulations were designed to attain film-coated tablets with essential similarity to the reference formulations, i.e. the 20 mg and 40 mg film-coated tablets of H. Lundbeck.

With respect to the relatively low active ingredient content of the preparation, the aim was to develop a direct compression technology for processing of the product to be marketed.

Experiments for designing the composition were accomplished with tablet core of 20 mg strength.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final formulation were included in the documentation.

Satisfactory comparative dissolution data for two batches of reference products marketed with different names in different countries have been provided.

Bioavailability

Because of the proportionality of the 10 mg, 20 mg and 40 mg film-coated tablets in the bio-equivalence study the 40 mg preparation was only used. The study was conducted with a production scale batch manufactured as detailed in Module 3.2.P.3 and with the composition as detailed in Module 3.2.P.1.

The batch numbers of Dalsan 40 mg film-coated tablet used for bioequivalence study and that of the reference product Cipramil 40 mg tablets (H. Lundbeck A/S) used for bioequivalence study were identified. (For detailed data see Module 5, 5.3.2.1.)

Overages

No overages were applied.

Physico-chemical and Biological properties

The parameters of the core tablets controlled (description, colour, odour, dimensions, resistance to crushing, friability, breaking surface, average mass, uniformity of mass, identity test, impurity test, disintegration time, water content, active ingredient content) as well as the parameters of the film-tablets controlled (description, colour, odour, dimensions, resistance to crushing, breaking surface, average mass, uniformity of mass, identity test, impurity test, disintegration time, water content, active ingredient dissolution, active ingredient content, uniformity of content, microbiological test) and requirements presented in this section were adequate in terms of ensuring the constant quality of the products.

Manufacturing Process Development

Satisfactory, exhaustive data on development of manufacturing process have been presented including the various scale-up processes and validation processes.

Detailed data were given on results of IPC tests and analytical tests at the time of release and after storage for several months at different temperature and relative humidity for tablet core as well as for the film-coated tablet both for laboratory scale and scale-up batches of all the three strengths. The packaging applied during stability testing was brown glass bottle with PE cap.

During the scale-up a minor change in technology compared to laboratory scale process was performed, namely the hand-sieving of the active ingredient was dropped out and after the pre-homogenization the pre-homogenate together with the external phase was screened by oscillatory regranulator.

Container Closure System

Materials for immediate packaging of the film-coated tablets (PVC/PVdC//Al blister) were well known materials for packaging solid dosage forms and were shown to support adequately the use and the stability of the product as demonstrated in section 3.2.P.8.

Compatibility

No compatibility tests were carried out because the film-coated tablets contain well known excipients and the composition fulfils the stability requirements as demonstrated by laboratory tests.

The quantitative composition of the tablets was dose-proportional.

The film-coated tablets were packed in blisters composed of PVC/PVDC foil fastened with aluminium foil. The blisters were packed into a cardboard box as secondary packaging.

The pharmaceutical development was in accordance with the CPMP Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96).

P.3 Manufacture

The products were manufactured and batches of the finished products were released by EGIS Pharmaceuticals Ltd, 1106 Budapest, Keresztúri út 30-38. Hungary.

A satisfactory formula has been provided for the manufacture of a batch size of 200 000 pieces of 10 mg and 20 mg and 100 000 pieces of Dalsan 40 mg film-coated tablets. The ready-to-press homogenisate was compressed by a direct compaction procedure.

The applicant has provided the detailed description of the manufacturing process including the homogenisation of the inner phase costituents, sieving, final homogenisation, parameters of the pressing device, the in-process control, preparation of the coating suspension,

Packaging:

Bulk film-coated tablets of acceptable quality were packed with an automatic packaging machine for blister packs. Blisters were made of PVC/PVdC/Al foil. Blisters with the patient information leaflets were put into folded cardboard boxes.

The Dalsan film-coated tablets were manufactured using standard manufacturing processes in accordance with current GMP. The method of manufacture was in accordance with Note for Guidance on Manufacture of the finished dosage form (CPMP/QWP/486/95).

A flow chart of the process has been provided and accepted by the reviewers.

Control of Critical Steps was specified in detail and found acceptable.

Process validation

Dalsan film-coated tablets were produced in three different strengths, with a proportional composition. The composition of the ready-to-press homogenisate was the same for all the three strengths and only the sizes and masses of the tablets were different.

Validation of the manufacturing process of the film-coated tablets has been performed in two separate stages:

1. Validation of the manufacturing process of the ready to press homogenisate
2. Validation of the manufacturing process of the film-coated tablets.

Validation of the manufacturing process of the ready to press homogenisate:

On the basis of the critical quality characteristics (drug substance content and blend uniformity), the critical operations (final blending) and the critical parameters (the time of the final blending and the rpm of the final blender), the validation points have been determined.

The validation of the manufacturing process of Dalsan ready-to-press homogenisate was performed in a prospective way according to requirements of the validation protocol. Three successive Dalsan ready-to-press homogenisate batches were tested.

The test results showed that the measured values and the RSD values met the specified limits in all the tests. All acceptance criteria of a successful validation specified in the validation protocol were fulfilled. The results of validation proved, that the manufacturing process of Dalsan homogenisate was suitable to produce the homogenisate conforming the specifications with high reliability and batch to batch consistency.

Validation of the manufacturing process of the film-coated tablets:

The validation critical points were been determined on the basis of the critical quality, the critical operations, the critical parameters for the tabletting and the critical parameters for the film-coating operation.

The validation of the manufacturing process of the film-coated tablets was performed in a prospective way on the basis of the analysis of three successive batches of all three strengths. The test results of all nine batches meet the specified limits in the case of all tested parameters.

On the basis of the test results it can be stated that all the acceptance criteria of the validation specified in the validation protocol were fulfilled. The manufacturing process was suitable to produce repeatedly and with high reliability the product conforming to EGIS specification.

Both the Process Validation Report and the Process Validation Plan for all the three strengths fulfil the requirements of the CPMP's Note for Guidance on Process Validation (CPMP/QWP/848/96).

P.4 Control of excipients

All the inactive ingredients of Dalsan film-coated tablets have monographs in Ph.Eur. The manufacturer of the finished product tested each batch of raw materials. Names of the suppliers and Certificates of analysis of the batches used for the manufacture of Dalsan have been enclosed.

TSE Risk Materials: Dalsan film-coated tablets contain two ingredients (lactose monohydrate and magnesium stearate) derived from animals. Lactose monohydrate was sourced from an identified supplier. A public statement (EMEA/CPMP/571/02) from the EMEA on TSE of lactose prepared using calf rennet, and TSE statements from this supplier were provided confirming compliance to EMEA/CPMP/571/02.

Supplier of magnesium stearate was also identified. A Certificate of Suitability was enclosed proving that stearic acid used for the production of magnesium stearate was in compliance with the Ph.Eur. general monograph 1483.

P.5 Control of drug product

P.5.1. Specification

The specifications of Dalsan film-coated tablets for release and for the end of shelf-life were identical. The active substance identification comprised TLC and HPLC methods. Titanium dioxide was also identified. The assay of the active ingredient and the Content Uniformity test were HPLC methods, applying the Ph. Eur. 2.9.6 requirements for the latter. Impurity analysis, adequate Ph. Eur. dosage-form and microbial impurity control tests were applied. A dissolution (6 units) test with an in-house limit and water determination were also applied.

The specifications and control tests of the finished products were set in accordance with the ICH guideline 3AQ11a.

P.5.2-3 Analytical Procedures/Validation

The documentation contained adequate validation procedures and results covering all aspects of the above specification.

P.5.4. Batch analysis

Certificates of analysis were presented for three batches of 10 mg, 20 mg and 40 mg film-coated tablet strengths. Analytical data for all batches presented were within the specification limits and confirmed both the consistency of production and good performance of the analysis methods. It can be concluded that the analytical tests were suitable, manufacturing process and analysis were well controlled.

P.5.5. Characterization of impurities

According to purity test results of citalopram hydrobromide active substance batches it was found that the impurities of the starting materials were always below the disregard limit, so they were only potential impurities. That was the reason why these impurities were not specified but used only to prove the selectivity of the HPLC method.

Comparative impurity profiles of Dalsan film-coated tablets and the reference products Cipramil film-coated tablets were enclosed. The sum of impurities both in Dalsan and Cipramil film-coated tablets was less than 0.1 % and there was no individual impurity higher than 0.1% either in Dalsan or in Cipramil film-coated tablets. Although some impurities of Dalsan film-coated tablets cannot be found in the reference tablets, their levels (0.029%, 0.014% and 0.010%) were far below the qualification threshold.

P.6 Reference Standards or Materials

Citalopram hydrobromide working standard has been used for the analytical tests of the finished products. Certificate of analysis of the batch used as working standard was enclosed.

P.7 Container Closure System

Immediate packaging: colourless, transparent PVC/PVDC blister strip covered with aluminium foil. The PVC/PVDC (60 g/m^2) blister strip and the Al foil were manufactured and supplied by internationally respected firms, which was a guarantee for the constant and consistent quality. The manufacturers provided certificates on their products with respect to their suitability for pharmaceutical use. Specifications and test methods of hard PVC foil coated with 60 g/m^2 PVDC and of the aluminium foil were provided. The chemical characteristic of PVC foil coated with 60 g/m^2 PVDC was examined based on Ph.Eur. 3.1.11. The IR spectroscopy investigation method was described, the spectrum was enclosed. The type of blister proposed for routine storage has been used for the stability studies supporting the shelf life.

The choice of the immediate (primary) packaging was justified by stability tests (see P.8) carried out on the finished products in the proposed primary container of the quality specified in this section.

Secondary packaging: cardboard box. The basic function of boxes was the general protection of drugs. The surface of boxes was printed. The text contains the most important information about the product and the manufacturer.

P.8 Stability

Stability data were presented on three production batches of all three strengths. According to the "Note for guidance for stability testing" the drug product batches were manufactured from different batches of the drug substance.

All batches were packed in PVC/PVdC/Al blister, the packaging proposed for marketing.

The stability programme (number of batches, test conditions and time points) has been done according to the Note for Guidance on Stability testing of new drug substances and products (Q1A).

The tests cover those features susceptible to change during storage and likely to influence quality, safety and/or efficacy of the product.

The specifications and methods were the same as described in Module 3.2.P.5.1 and 3.2.P.5.2, respectively.

No significant changes were found either in the physical or in the chemical characteristics of the product during the 12 months storage period of long-term and intermediate and the 6 months accelerated stability trials.

Proposed shelf-life: 2 years with no special storage condition.

According to the results this was acceptable without statistical evaluation.

No In-use stability data have been submitted. It was accepted, for that type of packaging there is no need for such studies.

Post approval stability protocol and commitment:

The long-term stability trials will be continued until the desired shelf-life (5 years) reached.

One batch per year of all three strengths of tablets will be entered into the long-term stability trials (follow-up stability).

Stress tests of Dalsan 10mg, 20 mg and 40 mg film-coated tablets:

The composition of the three strengths were proportional and the concentrations of the sample solutions were the same, so the stress tests were performed on one (40 mg) batch of the tablets only.

Stress tests (elevated temperature, oxidative test as well as hydrolysis in various media at elevated temperature and photolysis) were carried out parallelly on one batch of the drug product, on the placebo and on a single batch of the drug substance, citalopram hydrobromide.

Conclusion: the products were not sensitive to heat, to humidity and to light. Considerable degradation occurred only in acidic and in basic hydrolytic conditions and during oxidation. The main degradation products were Chbaox and Chac (See previously, at the drug substance).

OVERALL CONCLUSIONS

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY

In summary, the data provided in Module 3 of the application dossier were considered satisfactory.

The Quality Overall Summary signed by (identified person, chemical engineer) was adequate.

For the questions arisen during the assessment procedure of the application, adequate responses were provided. Additional data have been submitted and built in the dossier by the applicant.

The approved ingredients and the method of manufacture of the finished products Dalsan 10 mg, Dalsan 20 mg and Dalsan 40 mg were considered suitable to produce a pharmaceutical product of the specified quality. All relevant quality characteristics of the active substance and the finished products (release and end of shelf-life) were specified. The proposed limits were acceptable. The description of the analytical procedures used was adequate, validation was plausible. The studies carried out on the finished products justify a 2 years shelf-life if packed in PVC/PVDC//Al blister. No special storage condition has been required.

MODULES 4 & 5

NONCLINICAL AND CLINICAL ASSESSMENT

TABLE OF CONTENTS

I. NON-CLINICAL ASSESSMENT

I.1 TOXICOLOGY

The National Institute of Pharmacy finds it acceptable that specific studies had not been performed, for the application was submitted in accordance with article 10.1 a (iii) of Directive 2001/83/EEC.

I.2 EXPERT REPORT

The Expert Report was written in 2003 by a recognised toxicologist registered by EUROTOX and American Board of Toxicology. The report is a sufficient update of the known toxicological profile of citalopram and we agree with the conclusions.

II. CLINICAL PHARMACOLOGY

II.1 PHARMACODYNAMICS

Abnormalities in serotonin (5-HT) levels in the brain have been hypothesized to predispose individuals to an increased risk of depressive illness. The link between depression and abnormal serotonin transmission has been strengthened by biochemical studies, and clinical observations. These findings suggest that compounds capable of modulating central serotonergic function may be effective in ameliorating depression.

Citalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) with a chemical structure unrelated to that of other SSRI's or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram, the most selective serotonin reuptake inhibitor, like other second generation antidepressant agents enhances serotoninerg neurotransmission through selective and potent inhibition of serotonin reuptake.

It has a very low affinity for a range of receptors including muscarinic acethylcholine receptors as well as 5-HT_{1A}, 5-HT_{1b}, 5-HT_2, dopamine$_1$ és dopamine$_2$, α_{1-}, α_{2-}, β_1- and β_2- adreno, histamine$_1$, benzodiazepine, gamma aminobutyric, opioid and monoamine oxidase inhibitor receptors. Citalopram potentiates morphin analgesia in rats probably via its effects on the serotonergic component of morphin's action.

Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

II.2 PHARMACOKINETICS

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose proportional in a dose range of 10-60 mg/day. Steady state plasma levels are achieved in 1-2 weeks. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Absorption of citalopram from the gastrointestinal tract is almost complete and independent of food intake (T_{max} /mean/: 3.8 hours). Oral bioavailability is about 80%. The plasma protein binding is below 80% for citalopram and its main metabolites. All the three active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma. The elimination half-life ($t_{½}$) is about 1.5 days.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients. Citalopram is eliminated more slowly in patients with reduced hepatic function. Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20mL/min).

II.3 ASSESSMENT OF BIOEQUIVALENCE

Citalopram is rapidly and completely absorbed following oral administration with peak plasma concentrations achieved after 2-4 hours for immediate release oral products. Bioavailability is unaffected by food. Kinetics are linear over the proposed dose range. Terminal elimination half life is 23-75 hours.

Clinical & analytical site

The trial wes performed in Canada. The Contract Research Organisation (CRO), the sites as well as the Principal Investigator were identified. The latter has had the adequate education and experiences.

Study design

The bioequivalence study was conducted in August 2002 to support this application.

This was a two-way, single-dose, randomized crossover study. The number trial subjects (healthy male volunteers) and their age distribution were specified. Each subject received a 40 mg dose (one tablet) of one of the 2 citalopram formulations (Dalsan® 40 mg film tablet, EGIS Pharmaceuticals LTD as the test, i.e. investigational product and Cipramil® 40 mg Tablets, H.Lundbeck A/S as the reference product. Batch numbers were identified.

For each subject there were 2 dosing periods, separated by a washout period of at least 21 days.

Both formulations were administered with an identified amount of water following an overnight fast. Blood samples were collected in pre-determined time intervals.

The study was claimed to be compliant with the principles of GCP.

Citalopram bioanalytical characteristics

The limit of quantitation (LOQ) was 0.250 ng/ml for Citalopram. Intra-batch accuracy and precision were evaluated for each quality control level with six replicates. This was carried out for 1 run. The mean for each quality control level (QC LOW, QC MED, and QC HIGH) and the LOQ had a relative error ranging from –5.3% to 0.2% and coefficient of variation ranging from 2.8% to 6.1%. Inter-assay accuracy and precision were evaluated for each quality control level and the LOQ for five runs. The coefficient of variation for each quality control sample was determined with values ranging from 7.3% to 7.9%. The calibration curves ranged from 0.25 - 32.1 ng/ml. The method was well validated and a sufficient quality of validation report was provided. Plasma samples were analyzed for citalopram and its desmethyl metabolite by HPLC with MS/MS detection.

Data Analyis

$AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, $C_{max\ and}$ T_{max} were calculated according to normal standard procedures. Statistical evaluation was performed for $AUC_{(0\text{-}inf)}$, and C_{max} with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

> Analysis was also carried out for the desmetyl metabolites but, for it is non-relevant since in vitro studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram, these results of the desmetyl metabolites are not reported below.

Results

The results are tabulated below.

Parameter N=20	Test (mean±SD)	Reference (mean±SD)	% Ratio of Geometric Means	90 % Confidence Interval	Intra-Subject CV%
AUC_{0-T} (ng*hr/ml)	1863±354	1868.7±364	0.99	0.96-1.03	6.67
AUC_{inf} (ng*hr/ml)	2010±427	2010.8±429	0.99	0.96-1.03	6.28
C_{max} (ng/ml)	40.62±6.6	41.86±7.6	0.97	0.93-1.01	7.1
T_{max}	5.1±1.1	4.95±1.4			

Safety

During the study with the test formulation only one serious adverse event has occurred.

Event description and assessment: after one hour following the administration of test preparation, volunteer No 1 vomited, lost his consciousness and his heart arrested. The on site nurse notified the doctor on duty who diagnosed the volunteer having Torsado de Pointes and the patient was hospitalized immediately. From that point of time, the information is scarce because the patient did not give access to his medical records to the CRO. In fact, even the manifestation of Torsado de Pointes had not been confirmed. The chief investigator judged the relationship between the adverse event and citalopram unlikely.

The National Institute of Pharmacy was of the opinion first that further assurance is needed to exclude any possibility that the adverse event can be attributed to the test preparation, therefore requested the CRO to investigate the matter further. In response the CRO submitted an about 200 pages Canadian Law about patients rights and informed the NIP that, without the patient's approval they were not in the position to reopen the case. The NIP did not accept this answer either. To solve the deadlocked situation the NIP and EGIS LTD agreed to submit the available data to a Hungarian cardiologist with a considerable clinical background for a second opinion. This Professor, based on the available clinical data, concluded that the heart problem arose was due to the intensive vomiting. The assessor finds this conclusion reasonable, for vomiting is a typical adverse event observed during bioequivalence trial of selective serotonin reuptake inhibitors. Moreover, the observed citalopram concentration at the time of the adverse event (10.4 ng/ml) was low compared to the observed C_{max} (40-41 ng/ml).

Summary

Given that the three strengths (10, 20 and 40 mg) are based on a proportional formulation, that similar dissolution profiles occur for the three strengths, and as linear kinetics apply over the proposed dose range, it is acceptable that a bioequivalence study has not been performed with tables of the lower strengths.

II.4 CONCLUSION

Approval is recommended from the clinical (pharmacokinetic) point of view, since the applicant has properly demonstrated bioequivalence to the reference medicinal product.