PRODUCT MONOGRAPH

Pr Cipralex®

Escitalopram Oxalate Tablets

5, 10, 15, 20 mg as escitalopram

Antidepressant / Anxiolytic / Antiobsessional

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CIPRALEX®

Escitalopram Oxalate Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of administration	Dosage Form/ Strength	Nonmedicinal Ingredients
Oral	Tablets 5, 10, 15 and 20 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, talc, titanium dioxide (white E-171)

INDICATIONS AND CLINICAL USE

Adults

- Cipralex® (escitalopram oxalate) is indicated for the symptomatic relief of Major Depressive Disorder (MDD)

- The efficacy of Cipralex® in maintaining an antidepressant response, in patients with major depressive disorder who responded during an 8-week, acute-treatment phase while taking Cipralex® and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see **CLINICAL TRIALS**).

- Cipralex® is indicated for the symptomatic relief of anxiety causing clinically significant distress in patients with Generalized Anxiety Disorder (GAD).

- The efficacy of Cipralex® in maintaining anxiolytic response for at least 6 months in patients with GAD was demonstrated in a long-term placebo-controlled trial (in patients who had initially responded to Cipralex® during a 12-week open-label phase).

- Cipralex® is indicated for the symptomatic relief of obsessive-compulsive disorder (OCD). The obsessions and compulsions must be experienced as intrusive, markedly distressing, time consuming or interfering significantly with the person's social or occupational functioning.

- The efficacy of Cipralex® in maintaining an anti-obsessive response for up to 6 months, in patients with obsessive-compulsive disorder, was demonstrated in a long-term placebo-controlled trial in patients who initially responded to 16 weeks of Cipralex® open-label treatment (see **CLINICAL TRIALS**).

- Physicians who elect to use Cipralex® for extended periods should periodically re-evaluate the usefulness of the drug for individual patients.

Geriatrics:
Although there was no evidence from clinical studies suggesting that use in geriatric population is associated with differences in safety and effectiveness, a greater sensitivity of some older individuals to effects of escitalopram cannot be ruled out. A brief discussion can be found in the appropriate sections (e.g. **PHARMACOKINETICS, WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**)

Pediatrics:
Escitalopram is not indicated for use in patients below the age of 18 (see **WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm**).

CONTRAINDICATIONS

- Cipralex® (escitalopram oxalate) is contraindicated in patients with known hypersensitivity to escitalopram or any of the excipients of the drug product.

- **MONOAMINE OXIDASE INHIBITORS**
  Cases of serious reactions have been reported in patients receiving selective serotonin reuptake inhibitors (SSRIs) in combination with a monoamine oxidase inhibitor (MAOI) or the reversible MAOI (RIMA), moclobemide, and in patients who have recently discontinued an SSRI and have been started on a MAOI (see **DRUG INTERACTIONS**). With the co-administration of an SSRI with MAOI, there have been reports of serious, sometimes fatal reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible fluctuations of vital signs, and mental status changes, including extreme agitation progressing to delirium and coma. Some cases presented with features resembling serotonin syndrome.

  Therefore, escitalopram should not be used in combination with a MAOI or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should elapse after discontinuing escitalopram treatment before starting a MAOI.

- **PIMOZIDE**
  Escitalopram should not be used in combination with the antipsychotic drug pimozide, as results from a controlled study with racemic citalopram indicate that concomitant use is

associated with an increased risk of QTc prolongation compared to pimozide alone. This apparent pharmacodynamic interaction occurred in the absence of a clinically significant pharmacokinetic interaction; the mechanism is unknown (see **DRUG INTERACTIONS**).

WARNINGS AND PRECAUTIONS

GENERAL

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer antidepressants suggest that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional data

- **There are clinical trials and post-marketing reports with SSRIs and other newer antidepressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm and harm to others. The agitation-type events include: akathisia, agitation, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

  Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms

Patients currently taking escitalopram should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer antidepressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

DISCONTINUATION OF TREATMENT WITH ESCITALOPRAM

When discontinuing treatment, patients should be monitored for symptoms that may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances [including paraesthesias and electric shock sensations], agitation, anxiety, emotional indifference, impaired concentration, headache, migraine, tremor, nausea, vomiting and

sweating) or other symptoms that may be of clinical significance (see **ADVERSE REACTIONS**). A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

ESCITALOPRAM TREATMENT DURING PREGNANCY- EFFECTS ON NEWBORNS

Post-marketing reports indicate that some neonates exposed to SSRIs such as escitalopram and other antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. When treating a pregnant woman with escitalopram during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant and Nursing Women**; and **DOSAGE AND ADMINISTRATION**).

INTERFERENCE WITH COGNITIVE AND MOTOR PERFORMANCE

In a study with healthy volunteers, racemic citalopram did not impair cognitive function or psychomotor performance. However, psychotropic medications may impair judgement, thinking or motor skills. Consequently, patients should be cautioned against driving a car or operating hazardous machinery until they are reasonably certain that escitalopram does not affect them adversely.

The following additional PRECAUTIONS are listed alphabetically.

CARCINOGENESIS AND MUTAGENESIS

For animal data, see Part II: TOXICOLOGY section.

CARDIOVASCULAR

PATIENTS WITH CARDIAC DISEASE

Neither escitalopram nor racemic citalopram has been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical trials during the drug's premarketing assessment. However, the electrocardiograms (ECG) of patients participating in clinical trials with escitalopram and racemic citalopram indicate that the medications were not associated with the development of clinically significant ECG abnormalities. In line with other SSRIs, including racemic citalopram, escitalopram causes statistically significant, but clinically unimportant decrease in heart rate. In patients < 60 years old, the mean decrease with escitalopram was approximately 2.3 bpm, while in patients ≥ 60 years old, the mean decrease was approximately 0.6 bpm.

ENDOCRINE AND METABOLISM

DIABETIC PATIENTS

Neither escitalopram nor racemic citalopram has been systematically evaluated in diabetic patients; in the case of racemic citalopram, diabetes constituted an exclusion criterion. Rare events of hypoglycaemia were reported for racemic citalopram. Treatment with an SSRI in patients with diabetes may alter glycaemic control (hypoglycaemia and hyperglycaemia). Escitalopram should be used with caution in diabetic patients on insulin or oral hypoglycaemic drugs.

HEMATOLOGIC

BLEEDING DISORDERS

SSRIs and serotonin/norepinephrine reuptake inhibitors (SNRIs), including Cipralex®, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. There have been reports of bleeding events ranging from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening haemorrhages, associated with treatment with SSRIs and SNRIs.

Caution is advised in patients taking SSRIs and SNRIs, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, anticoagulants, platelet aggregation inhibitors, acetylsalicylic acid and NSAIDs), as well as in patients with a history of bleeding disorders or predisposing conditions (e.g., thrombocytopenia).

HEPATIC/BILIARY/PANCREATIC

HEPATIC IMPAIRMENT

Based on a study conducted with escitalopram in patients with mild to moderate hepatic impairment, the half-life was approximately doubled and the exposure was increased by approximately two third, compared to subjects with normal liver function. Consequently, the use of escitalopram in hepatically impaired patients should be approached with caution and a lower dosage is recommended (see **DOSAGE AND ADMINISTRATION**). No information is available about the pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). Escitalopram should be used with additional caution in patients with severe hepatic impairment.

NEUROLOGIC

SEIZURES

Escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from the clinical studies. In clinical trials with escitalopram, convulsions have been reported very rarely (2 out of 3981 patients) in association with treatment with escitalopram. From post-marketing data, the reporting of seizures with escitalopram is comparable to that of other antidepressants. Like other antidepressants, escitalopram should be used with caution in patients with a history of seizure disorder.

SEROTONIN SYNDROME/NEUROLEPTIC MALIGNANT SYNDROME (NMS)-LIKE EVENTS

On rare occasions serotonin syndrome or neuroleptic malignant syndrome-like events have occurred in association with treatment with SSRIs, including escitalopram, particularly when given in combination with other serotonergic and/or neuroleptic drugs. As these syndromes may result in potentially life-threatening conditions, treatment with Cipralex® should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. Cipralex® should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Serotonergic Drugs, Triptans**).

PSYCHIATRIC

SUICIDE

The possibility of a suicide attempt is inherent in depression and may persist until remission occurs. Therefore, high-risk patients should be closely supervised throughout therapy with consideration to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescription for escitalopram should be written for the smallest quantity of drug consistent with good patient management.

Because of the well established comorbidity between depression and other psychiatric disorders, the same precautions observed when treating patients with depression should be observed when treating patients with other psychiatric disorders (see **WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including self-Harm**).

ACTIVATION OF MANIA/HYPOMANIA

In placebo-controlled trials of Cipralex® (escitalopram oxalate) activation of mania/hypomania was reported in one patient of the n=715, treated with escitalopram and in none of the n=592 patients treated with placebo. Activation of mania/hypomania has also been reported in a small

proportion of patients treated with racemic citalopram, and with other marketed antidepressants. As with other antidepressants, escitalopram should be used with caution in patients with a history of mania/hypomania.

ELECTROCONVULSIVE THERAPY (ECT)
The safety and efficacy of the concurrent use of either escitalopram or racemic citalopram and ECT have not been studied.

RENAL

HYPONATREMIA
As with other antidepressants, cases of hyponatraemia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported with escitalopram and racemic citalopram as a rare adverse event. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume-depleted. Elderly female patients in particular seem to be a group at risk.

RENAL IMPAIRMENT
No information is available on the pharmacokinetic or pharmacodynamic effects of escitalopram on patients with renal impairment. Based on the information available for racemic citalopram, no dosage adjustment is needed in patients with mild to moderate renal impairment. Since no information is available on the pharmacokinetic or pharmacodynamic effects of either escitalopram or racemic citalopram in patients with severely reduced renal function (creatinine clearance < 30 mL/min), escitalopram should be used with caution in these patients (see **DOSAGE AND ADMINISTRATION**).

SPECIAL POPULATIONS

Pregnant and Nursing Women: The safety of escitalopram during human pregnancy and lactation has not been established. Therefore, escitalopram should not be used during pregnancy, unless the potential benefit to the patient outweighs the possible risk to the foetus.

Studies with escitalopram have not been performed in nursing mothers, but it is known that racemic citalopram is excreted in human milk and it is expected that escitalopram is also excreted into breast milk. Escitalopram should not be administered to nursing mothers unless the expected benefits to the patient outweigh the possible risk to the child.

Complications following late third trimester exposure to SSRIs:
Post-marketing reports indicate that some neonates exposed to SSRIs such as Cipralex® and other antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These

features are consistent with either a direct toxic effect of SSRIs and other newer antidepressants, or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS AND PRECAUTIONS - Serotonin Syndrome/Neuroleptic Malignant Syndrome**). When treating a pregnant woman with Cipralex® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

Risk of PPHN and exposure to SSRIs:
In one epidemiological case-control study on persistent pulmonary hypertension (PPHN) with n = 377 infants with PPHN and n = 836 matched control infants, PPHN was six times more common in babies whose mothers took an SSRI antidepressant after the 20th week of pregnancy compared to babies whose mothers did not take an antidepressant. The study was too small to determine relative risks among the specific SSRIs. This information is considered to be preliminary at this time. The absolute risk of PPHN in the general population is reported to be 1 – 2 per 1000.

Pediatrics:
Escitalopram is not indicated for use in patients below the age of 18 (see **WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm**).

Geriatrics: Approximately 5% of the 715 patients treated with escitalopram in clinical trials of depressive disorder were 60 years of age or over; elderly patients in these trials received daily doses between 10 and 20 mg. No overall significant differences in safety or effectiveness were observed between the elderly and younger subjects, but the number of elderly patients treated was insufficient to adequately assess for differential responses. Greater sensitivity of some older individuals to effects of escitalopram cannot be ruled out. In a multiple-dose pharmacokinetic study, the area under the curve (AUC) and half-life of escitalopram were increased by approximately 50% at steady-state in elderly subjects as compared to young subjects. Consequently, elderly patients should be administered lower doses and a lower maximum dose (see **PHARMACOKINETICS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

ADVERSE DRUG REACTION OVERVIEW

Adverse events information for Cipralex® (escitalopram oxalate) was collected from 715 patients with major depressive disorder (MDD) who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. During clinical trials, all treatment groups were comparable with respect to gender, age and race. The mean age of patients was 41 years (18 to 76 years). Of these patients, approximately 66% were females and 34% were males.

The adverse event information for Cipralex® in patients with generalized anxiety disorder (GAD) was collected from 832 patients exposed to escitalopram and from 566 patients exposed to placebo in 8-12 week double-blind, placebo-controlled trials. A total of 187 patients exposed to escitalopram and 188 patients exposed to placebo in a 24 to 76 week double-blind phase of a placebo-controlled long-term trial were also included. The demographics of the clinical trial population in GAD were similar to the population of patients included in MDD clinical trials.

The adverse event information for Cipralex® in patients with obsessive-compulsive disorder (OCD) was collected from two studies with double-blind, placebo-controlled treatment periods of up to 24 weeks. In the first study, a total of 227 patients were exposed to escitalopram and 114 patients were exposed to placebo in a 24-week double-blind, placebo-controlled, fixed-dose trial with assessments at weeks 12 and 24. In the second study, 322 patients who initially responded to 16 weeks of open-label escitalopram treatment were subsequently randomized to double-blind treatment with escitalopram (n=164) or placebo (n=158) for up to 24 weeks. In total, 391 patients were exposed to escitalopram and 272 patients were exposed to placebo in these two long-term studies. The mean age of patients with OCD included in the trials was approximately 36 to 38 years (ranging from 18 to 67 years). One trial included similar proportions of males and females and the other trial had a slightly higher proportion of females than males (57% females and 43% males).

ADVERSE EVENTS OBSERVED IN CONTROLLED TRIALS

Adverse Events Associated with Discontinuation of Treatment

From the short-term (8-week) placebo-controlled, phase III studies in patients suffering from MDD, the incidence of discontinuation was: 17.3% (124/715) on escitalopram, 15.7% (64/408) on citalopram and 16.4% (97/592) on placebo. Discontinuation due to adverse events was more common in the active treatment groups (5.9% in escitalopram and 5.4% in citalopram) than in the placebo group (2.2%).

The events that were associated with discontinuation of escitalopram in 1% or more of patients at a rate of at least twice that of placebo were: nausea (1.5% vs. 0.2%) and ejaculation failure (1.8% vs. 0.0% of male patients).

Among the 832 GAD patients who received escitalopram 10-20 mg/day in placebo-controlled trials, 7.8% discontinued treatment due to an adverse event, as compared to 3.2 % of 566 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with escitalopram, and for which the rate was higher than the placebo rate, were: dizziness (1.2% vs. 0.2%), fatigue (1.1% vs. 0.2%) and nausea (1.8% vs. 0.2%).

During the first 12 weeks of treatment in the 24-week placebo controlled trial, discontinuation of treatment due to adverse events was reported for 9% and 11% of the 227 OCD patients who were treated with 10 mg/day or 20 mg/day escitalopram, respectively, compared to 5% of the 114 patients receiving placebo. All patients who discontinued treatment due to adverse events in the escitalopram groups did so in the first 12 weeks. Eight percent of patients receiving placebo

discontinued treatment due to an adverse event during the 24-week period. Adverse events that were associated with discontinuation of at least 1% of patients treated with escitalopram, and for which the rate was higher than the placebo rate, were: nausea (1.8% vs. 0.0%), insomnia (1.8% vs. 0.9%), and erectile dysfunction (1.1% vs. 0.0%).

Most Frequent Adverse Events
Adverse events that occurred in escitalopram-treated patients in the course of the short-term, placebo-controlled trials with an incidence greater than, or equal to, 10% were: headache and nausea. The incidence of headache was higher in the placebo group, which suggests that this is a non-specific symptom related to the underlying condition or treatment administration. The point prevalence of nausea increased during the first week (as expected with an SSRI) and then decreased to approach placebo levels by the end of the studies.

CLINICAL TRIAL ADVERSE DRUG REACTION

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

MAJOR DEPRESSIVE DISORDER

Table 1 enumerates the incidence of treatment emergent adverse events that occurred in 715 depressed patients who received escitalopram at doses ranging from 10 to 20 mg/day in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients. Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1.

TABLE 1
TREATMENT-EMERGENT ADVERSE EVENTS*
INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
FOR MAJOR DEPRESSIVE DISORDER

Body System/Adverse Event	Percentage of Patients Reporting	
	Escitalopram (n = 715)	Placebo (n = 592)
Cardiac Disorders		
Palpitations	1.4	1.2
Ear and Labyrinth Disorders		
Vertigo	1.4	0.8

TABLE 1 TREATMENT-EMERGENT ADVERSE EVENTS* INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR MAJOR DEPRESSIVE DISORDER		
Body System/Adverse Event	**Percentage of Patients Reporting**	
	Escitalopram (n = 715)	**Placebo (n = 592)**
Gastrointestinal Disorders		
Nausea	15.2	8.1
Diarrhoea	8.4	5.2
Dry mouth	6.6	4.6
Constipation	3.5	1.2
Dyspepsia	3.1	2.9
Abdominal pain upper	1.5	0.8
Stomach Discomfort	1.1	0.3
General Disorders and Administration Site Conditions		
Fatigue	4.9	2.7
Pyrexia	1.1	0
Infections and Infestations		
Nasopharyngitis	4.6	3.4
Influenza	4.3	4.1
Sinusitis	2.1	1.9
Gastroenteritis	1.8	0.7
Herpes simplex	1.3	0.3
Investigations		
Weight increased	1.8	1.5
Metabolism and Nutrition Disorders		
Decreased appetite	2.4	0.7
Increased appetite	1.7	1.4
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1.4	0.5
Pain in extremity	1.4	0.8
Nervous System		
Dizziness	6.3	3.6
Somnolence	4.1	1.2
Sedation	2.4	0.7
Migraine	1.5	1.5
Tremor	1.5	0.7
Lethargy	1.0	0.2
Paraesthesia	1.0	0.7
Sinus headache	1.0	0.3

TABLE 1 TREATMENT-EMERGENT ADVERSE EVENTS* INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR MAJOR DEPRESSIVE DISORDER		
Body System/Adverse Event	**Percentage of Patients Reporting**	
	Escitalopram (n = 715)	**Placebo (n = 592)**
Psychiatric Disorders		
Insomnia	8.2	3.6
Anxiety	2.2	2.0
Libido decreased	2.1	0.3
Anorgasmia	1.8	0.2
Abnormal dreams	1.3	0.8
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	2.1	1.0
Yawning	1.5	0.2
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	3.4	1.4
Night sweats	1.7	0.3
Rash	1.0	0.8
Vascular Disorders		
Hot flush [2]	2.2	0.0
Hot flush [1]	1.0	0.7
Reproductive System and Breast Disorders		
Ejaculation delayed[2]	3.6	0.0
Ejaculation failure[2]	2.7	0.0
Erectile dysfunction[2]	2.7	0.0
Ejaculation disorder[2]	1.3	0.0

*Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients.
[1]Denominator used was for females only (n=490 for escitalopram; n=404 for Placebo).
[2]Denominator used was for males only (n=225 for escitalopram; n=188 for Placebo).

The following events had a higher incidence in the placebo group compared to the escitalopram group: vomiting, abdominal pain, flatulence, upper respiratory tract infection, bronchitis, back pain, neck pain, headache.

Adverse reactions observed with escitalopram are in general mild and transient. They are most frequent during the first and/or second week of treatment and usually decrease in intensity and frequency with continued treatment and do not generally lead to a cessation of therapy.

In a clinical trial involving patients with Major Depressive Disorder that compared fixed doses of escitalopram (10mg/day and 20/mg/day) with placebo, the most common adverse events that occurred in patients treated with escitalopram are shown in Table 2.

TABLE 2
INCIDENCE OF COMMON ADVERSE EVENTS[1]
FOR MAJOR DEPRESSIVE DISORDER, STUDY MD-01

Adverse Event	Percentage of Patients Reporting		
	Placebo (n = 122)	**Escitalopram 10 mg/day (n =119)**	**Escitalopram 20 mg /day (n =125)**
Diarrhoea	7.4	10.1	14.4
Nausea	6.6	22.7	13.6
Insomnia	1.6	10.9	11.2
Mouth dry	7.4	10.9	9.6
Dizziness	3.3	10.1	9.6
Ejaculation failure	0.0	0.0	7.3
Nasopharyngitis	1.6	5.0	7.2
Constipation	1.6	2.5	5.6
Dyspepsia	1.6	5.9	4.0
Pharyngolaryngeal pain	0.0	5.9	1.6

[1] Events included are those occurring in 5% or more of patients treated with escitalopram (10 mg/day or 20 mg/day), and for which the incidence was greater than the incidence in placebo-treated patients.

Male and Female Sexual Dysfunction with SSRIs
While sexual dysfunction is often part of depression and other psychiatric disorders, there is increasing evidence that treatment with selective serotonin reuptake inhibitors (SSRIs) may induce sexual side effects. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with SSRIs may be underestimated.

Table 3 shows the incidence rates of sexual side effects in patients with major depressive disorder in placebo-controlled short-term trials.

TABLE 3 INCIDENCE OF SEXUAL SIDE EFFECTS IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR MAJOR DEPRESSIVE DISORDER		
Adverse Event	**Percentage of Patients Reporting**	
	Escitalopram (n =715)	**Placebo (n = 592)**
Libido decreased	2.1	0.3
Anorgasmia	1.8	0.2
In Males only		
Ejaculation delayed	3.6	0.0
Ejaculation failure	2.7	0.0
Erectile dysfunction	2.7	0.0
Ejaculation disorder	1.3	0.0

GENERALIZED ANXIETY DISORDER

Table 4 enumerates the incidence of treatment emergent adverse events that occurred among 832 patients who received escitalopram in placebo-controlled trials for up to 8-12 weeks in duration. Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients. Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1.

The most frequent adverse events that occurred in escitalopram-treated patients in the course of the short-term, placebo-controlled trials with an incidence greater than, or equal to, 10% were: nausea, headache and insomnia.

TABLE 4 TREATMENT-EMERGENT ADVERSE EVENTS* INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR GENERALIZED ANXIETY DISORDER (8-12 WEEKS)		
Body System/Adverse Event	**Percentage of Patients Reporting**	
	Escitalopram (n = 832)	**Placebo (n = 566)**
Cardiac Disorders		
Palpitations	1.3	0.4
Tachycardia	1.3	0.7

TABLE 4 TREATMENT-EMERGENT ADVERSE EVENTS* INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR GENERALIZED ANXIETY DISORDER (8-12 WEEKS)		
Body System/Adverse Event	**Percentage of Patients Reporting**	
	Escitalopram (n = 832)	**Placebo (n = 566)**
Ear and Labyrinth Disorders		
Tinnitus	1.1	0.7
Vertigo	1.0	0.2
Gastrointestinal Disorders		
Nausea	19.4	9.0
Diarrhoea	9.6	5.8
Dry mouth	7.3	4.6
Constipation	3.7	3.5
Vomiting	2.8	1.4
Abdominal pain upper	2.2	1.2
Flatulence	1.6	0.9
Toothache	1.3	0.0
General Disorders and Administration Site Conditions		
Fatigue	9.9	2.7
Irritability	1.9	0.9
Chills	1.2	0.0
Infections and Infestations		
Nasopharyngitis	5.3	5.0
Sinusitis	1.8	1.8
Gastroenteritis	1.3	1.2
Investigations		
Weight increased	1.1	0.9
Metabolism and Nutrition Disorders		
Decreased appetite	2.5	0.7
Anorexia	1.2	0.2
Increased appetite	1.0	0.9
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.0	2.5
Myalgia	1.9	0.7
Pain in extremity	1.3	0.7
Neck pain	1.2	0.9
Shoulder pain	1.0	0.7

TABLE 4
TREATMENT-EMERGENT ADVERSE EVENTS*
INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS
FOR GENERALIZED ANXIETY DISORDER (8-12 WEEKS)

Body System/Adverse Event	Percentage of Patients Reporting	
	Escitalopram (n = 832)	Placebo (n = 566)
Nervous System Disorders		
Headache	23.7	18.6
Dizziness	7.9	5.6
Somnolence	7.6	5.5
Paraesthesia	2.2	1.1
Sedation	2.2	0.2
Lethargy	1.6	0.4
Psychiatric Disorders		
Insomnia	10.1	3.7
Libido decreased	3.6	2.1
Anorgasmia	2.8	0.4
Abnormal dreams	1.8	0.9
Loss of libido	1.6	0.0
Orgasm abnormal	1.6	0.0
Nightmare	1.3	0.7
Restlessness	1.3	0.0
Depression	1.2	1.2
Sleep disorder	1.0	0.5
Renal and Urinary Disorders		
Pollakiuria	1.2	0.4
Reproductive System and Breast Disorders		
Ejaculation delayed[1]	5.6	0.8
Erectile dysfunction[1]	1.9	0.4
Respiratory, Thoracic and Mediastinal Disorders		
Yawning	2.3	0.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	4.7	1.2
Night sweats	1.1	0.2
Pruritus	1.0	0.9

*Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients.
[1]Denominator used was for males only (n=324 for escitalopram; n=241 for Placebo).

The following events had a higher incidence in the placebo group compared to the escitalopram group: dyspepsia, abdominal pain, upper respiratory tract infection, influenza, anxiety, dysmenorrhoea, pharyngolaryngeal pain, sinus congestion.

In general, the safety profile was similar in the long-term (24-76 weeks) placebo-controlled study when compared to short-term (8-12 week) trials.

In a clinical trial of patients with generalized anxiety disorder that compared 10 mg/day and 20 mg/day escitalopram with placebo, the most common adverse events that occurred in patients treated with escitalopram are shown in Table 5.

TABLE 5
INCIDENCE OF COMMON ADVERSE EVENTS[1]
FOR GENERALIZED ANXIETY DISORDER, STUDY 99815‡

Adverse Event	Percentage of Patients Reporting		
	Placebo (n = 139)	**Escitalopram 10 mg/day (n =136)**	**Escitalopram 20 mg /day (n =133)**
Nausea	12.9	22.1	23.3
Fatigue	4.3	11.0	17.3
Dizziness	5.8	13.2	13.5
Diarrhoea	4.3	11.8	10.5
Insomnia	2.9	12.5	10.5
Hyperhidrosis	2.9	9.6	9.0
Ejaculation delayed	0.0	6.7	7.3
Dry Mouth	2.2	6.6	6.8
Somnolence	2.9	3.7	6.8
Yawning	0.0	0.7	5.3

[1] Events included are those occurring in 5% or more of patients treated with escitalopram (10 mg/day or 20 mg/day), and for which the incidence was greater than the incidence in placebo-treated patients.

OBSESSIVE COMPULSIVE DISORDER

Table 6 enumerates the incidence of treatment emergent adverse events that occurred among 227 patients who received escitalopram in the first 12 weeks of a 24-week placebo-controlled trial. Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients. Reported adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1.

The most frequent adverse events that occurred in escitalopram-treated patients in the course of the short-term, placebo-controlled trials with an incidence greater than, or equal to, 10% were: headache, nausea and fatigue.

TABLE 6
TREATMENT-EMERGENT ADVERSE EVENTS*
INCIDENCE IN A PLACEBO-CONTROLLED CLINICAL TRIAL
FOR OBSESSIVE COMPULSIVE DISORDER
(FIRST 12 WEEKS OF A 24-WEEK TRIAL)

Body System/Adverse Event	Percentage of Patients Reporting	
	Escitalopram (n = 227)	Placebo (n = 114)
Eye Disorder		
Visual disturbance	1.3	0.0
Gastrointestinal Disorders		
Nausea	23.3	12.3
Diarrhoea	6.6	4.4
Dry mouth	6.2	4.4
Constipation	2.6	2.6
Vomiting	2.6	0.9
General Disorders and Administration Site Conditions		
Fatigue	14.1	5.3
Asthenia	1.3	0.9
Infections and Infestations		
Nasopharyngitis	6.6	3.5
Sinusitis	2.2	0.9
Rhinitis	1.3	0.0
Investigations		
Weight increased	1.3	0.0
Metabolism and Nutrition Disorders		
Decreased appetite	2.2	0.9

TABLE 6
TREATMENT-EMERGENT ADVERSE EVENTS* INCIDENCE IN A PLACEBO-CONTROLLED CLINICAL TRIAL FOR OBSESSIVE COMPULSIVE DISORDER (FIRST 12 WEEKS OF A 24-WEEK TRIAL)

Body System/Adverse Event	Percentage of Patients Reporting	
	Escitalopram (n = 227)	Placebo (n = 114)
Musculoskeletal and Connective Tissue Disorders		
Neck pain	1.8	1.8
Back pain	1.3	0.9
Nervous System		
Headache	19.4	16.7
Dizziness	7.9	5.3
Somnolence	8.4	5.3
Tremor	3.5	1.8
Migraine	1.3	0.0
Psychiatric Disorders		
Libido decreased	4.8	0.9
Restlessness	2.2	0.9
Sleep disorder	1.8	0.9
Abnormal dreams	1.3	0.0
Reproductive system and breast disorders		
Ejaculation delayed[2]	7.6	0.0
Menorrhagia[1]	1.5	0.0
Respiratory, Thoracic and Mediastinal Disorders		
Yawning	1.8	0.0
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.7	1.8
Vascular Disorders		
Hot flush [1]	1.5	0.0

*Events included are those occurring in 1% or more of patients treated with escitalopram, and for which the incidence in patients treated with escitalopram was greater than the incidence in placebo-treated patients.
[1]Denominator used was for females only (n=135 for escitalopram; n=63 for Placebo).
[2]Denominator used was for males only (n=92 for escitalopram; n=51 for Placebo).

The following events had a higher incidence in the placebo group compared to the escitalopram group: abdominal pain upper, irritability, influenza, anorexia, increased appetite, insomnia, anxiety, erectile dysfunction.

In general, the safety profile of the placebo-controlled study at 24 weeks was similar to the one observed in the first 12 weeks of the trial.

In both phases of the long-term study of patients who were randomized to receive 24 weeks of double-blind treatment with escitalopram or placebo, following response to an initial 16 weeks of open-label escitalopram treatment, the safety profile of escitalopram was similar to the safety profile in the above mentioned placebo controlled trial. Adverse events reported by at least 2% of patients after the open-label period and during the first 2 weeks after randomization were: dizziness (15.8% placebo vs 0.6% escitalopram); nausea (5.7% placebo vs 0.6% escitalopram); headache (4.4% placebo vs 1.8% escitalopram); and insomnia (3.2% placebo vs 0.6% escitalopram).

The most common AEs that occurred during treatment with 10 mg/day and 20 mg/day escitalopram in this clinical trial are shown in Table 7.

TABLE 7
INCIDENCE OF COMMON ADVERSE EVENTS[1] FOR OBSESSIVE COMPULSIVE DISORDER (FIRST 12 WEEKS OF 24-WEEK TRIAL, STUDY 10205)

Adverse Event	Percentage of Patients Reporting		
	Placebo (n = 114)	Escitalopram 10 mg/day (n =113)	Escitalopram 20 mg /day (n =114)
Nausea	12.3	19.5	27.2
Fatigue	5.3	11.5	16.7
Somnolence	5.3	6.2	10.5
Ejaculation delayed	0.0	4.5	10.4
Diarrhoea	4.4	4.4	7.0
Dizziness	5.3	8.8	7.0
Nasopharyngitis	3.5	7.1	6.1
Libido decreased	0.9	2.7	7.0
Dry mouth	3.5	4.4	5.3
Hyperhidrosis	1.8	6.2	5.3

[1] Events included are those occurring in 5% or more of patients treated with escitalopram (10 mg/day or 20 mg/day), and for which the incidence was greater than the incidence in placebo-treated patients.

In general, the adverse event profile that occurred among the patients who received escitalopram during the 24 weeks of the trial was similar to the profile observed in the first 12 weeks of the trial.

Weight Changes
Patients treated with escitalopram in short-term controlled trials did not differ from placebo-treated patients with regards to clinically important change in body weight. In one 24-week randomized clinical trial in patients with Social Anxiety Disorder, 8.0% of patients treated with escitalopram and 3.2% of patients treated with placebo experienced weight gain of 7% or more.

Cardiovascular parameters
Escitalopram and placebo groups in MDD and GAD patients were compared with respect to mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The analyses did not reveal any clinically important changes in blood pressure associated with escitalopram treatment. In line with other SSRIs, including racemic citalopram, escitalopram causes statistically significant, but clinically unimportant decrease in heart rate. In MDD patients < 60 years old, the mean decrease with escitalopram was approximately 2.3 bpm, while in patients ≥ 60 years old, the mean decrease was approximately 0.6 bpm.

Electrocardiograms from escitalopram and placebo groups in MDD and GAD patients were compared with respect to mean change from baseline in various ECG parameters and the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. Escitalopram was not associated with the development of clinically significant ECG abnormalities.

ADVERSE REACTIONS FOLLOWING DISCONTINUATION OF TREATMENT (OR DOSE REDUCTION)

There have been reports of adverse reactions upon the discontinuation of SSRIs such as escitalopram (particularly when abrupt), including but not limited to the following: dizziness, abnormal dreams, sensory disturbances (including paraesthesias and electric shock sensations), agitation, anxiety, emotional indifference, impaired concentration, headache, migraine, tremor, nausea, vomiting and sweating or other symptoms which may be of clinical significance (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Patients should be monitored for these or any other symptoms. A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response. These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other selective serotonin reuptake inhibitors (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS DURING TREATMENT FOR UP TO 44 WEEKS

The Treatment-Emergent Adverse Event incidence profile of escitalopram in a longer term study in patients with major depressive disorder (MDD) consisting of a 36-week placebo-controlled relapse observation phase in responders of a preceding 8-week acute treatment phase was similar to that observed in short-term studies.

LESS COMMON CLINICAL TRIAL ADVERSE DRUG REACTIONS

Untoward events associated with the exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. Reported adverse events were classified using the Medical Dictionary for Regulatory Activities, version 9.1.

The events listed below present treatment emergent adverse events reported during the clinical development program of escitalopram in depressed patients (n=896), which includes a long-term clinical trial; in GAD patients included in short-term (8-12 weeks) trials (n=832) and in one GAD long-term (24-76 weeks) trial (n=187); and in OCD patients included in a long-term (24 weeks with assessments at 12 weeks and 24 weeks) trial (n=227). Excluded from this list are those already listed in Tables 1 (MDD), 4 (GAD) or 6 (OCD first 12 weeks of a 24 week trial).

It is important to emphasise that, although the events reported occurred during treatment with escitalopram, they were not necessarily caused by it. The events are categorized by body system and listed according to the following criteria: *frequent:* adverse events that occurred on one or more occasions in at least 1/100 patients; *infrequent:* adverse events that occurred in less than 1/100 patients but at least in 1/1000 patients; *rare:* adverse events that occurred in less than 1/1000 but at least in 1/10000 patients.

Blood and Lymphatic System Disorders
Infrequent: Anaemia, lymphadenopathy. *Rare:* Lymphadenitis

Cardiac Disorders
Rare: Atrial fibrillation, atrial ventricular block first degree, bradycardia, extrasystoles, myocarditis, nodal rhythm, sinus bradycardia.

Congenital, Familial and Genetic Disorders
Rare: Epidermal naevus, Gilbert's syndrome.

Ear and Labyrinth Disorders
Infrequent: Ear disorder, ear pain, tinnitus. *Rare:* Cerumen impaction, deafness, Meniere's disease, motion sickness, tympanic membrane perforation.

Endocrine Disorders
Rare: Goitre, hyperthyroidism, thyroiditis.

Eye Disorders
Infrequent: Accommodation disorder, blepharospasm, conjunctivitis, dry eye, eye pain, eye pruritus, mydriasis, photopsia, vision blurred. *Rare:* Asthenopia, chromatopsia, eye haemorrhage, eye irritation, eye swelling, eyelid oedema, iritis, keratoconus, myopia, night blindness, retinal detachment, scotoma, vitreous detachment.

Gastrointestinal Disorders
Infrequent: Abdominal discomfort, abdominal distension, Crohn's disease, dysphagia, enteritis, epigastric discomfort, food poisoning, frequent bowel movements, gastrointestinal pain, gastrooesophageal reflux disease, gastritis, haemorrhoids, lip dry, rectal haemorrhage. *Rare:* Anal fissure, colitis ulcerative, colonic polyp, eructation, gingival pain, haematemesis, haematochezia, ileitis, oral pain, pruritus ani, reflux gastritis, stomatitis, tongue black hairy, tongue disorder, tooth disorder, tooth erosion.

General Disorders and Administration Site Conditions
Infrequent: Chest discomfort, chest pain, feeling abnormal, feeling jittery, influenza like illness, malaise, oedema, oedema peripheral, pain, respiratory sighs, sluggishness, thirst. *Rare:* Early satiety, face oedema, feeling hot, hunger, local swelling, performance status decreased, sensation of blood flow.

Immune System Disorders
Infrequent: Anaphylactic reaction, house dust allergy, hypersensitivity, seasonal allergy. *Rare:* Allergic oedema.

Infections and Infestations
Infrequent: Acute sinusitis, bronchitis acute, cystitis, ear infection, eye infection, folliculitis, fungal infection, gastrointestinal infection, laryngitis, lung infection, pelvic inflammatory disease (gs = Gender Specific), otitis media, pharyngitis, pharyngitis streptococcal, pneumonia, respiratory tract infection, skin infection, tooth abscess, tonsillitis, tooth infection, urinary tract infection, vaginal candidiasis (gs), viral infection, viral upper respiratory tract infection, vulvovaginal mycotic infection (gs). *Rare:* Appendicitis, bronchitis viral, carbuncle, cellulitis, dental caries, erysipelas, furuncle, genitourinary chlamydia infection, gingival infection, impetigo, infection parasitic, mastitis, onychomycosis, otitis externa, peritonsillar abcess, pyelonephritis acute, rash pustular, salmonellosis, staphylococcal infection, streptococcal infection, tracheitis, vaginal infection, varicella, wound infection.

Injury, Poisoning and Procedural Complications
Infrequent: Animal bite, ankle fracture, arthropod bite, contusion, excoriation, fall, injury, intentional overdose, joint dislocation, joint injury, joint sprain, limb injury, mouth injury, procedural pain, road traffic accident, skin laceration, sunburn, thermal burn. *Rare:* Arthropod sting, back injury, concussion, electric shock, eye injury, facial bones fracture, foot fracture, ligament injury, muscle rupture, neck injury, post-traumatic pain, radius fracture, rib fracture, sports injury, tooth injury, ulna fracture, whiplash injury.

Investigations
Infrequent: blood glucose increased, blood pressure increased, body temperature increased, heart rate increased, weight decreased. *Rare:* Arthroscopy, blood bilirubin increased, blood cholesterol increased, blood uric acid increased, blood urine present, electrocardiogram PR shortened, haemoglobin decreased, hepatic enzyme increased, pregnancy test positive (gs).

Metabolism and Nutrition Disorders
Infrequent: Food craving. *Rare:* Dehydration, gout, hypercholesterolaemia, hypermagnesaemia, hyperphagia, latent tetany.

Musculoskeletal and Connective Tissue Disorders
Infrequent: Arthritis, joint stiffness, muscle contracture, muscle spasms, muscle tightness, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal stiffness, osteoarthritis, pain in jaw. *Rare:* Chest wall pain, costochondritis, exostosis, fibromyalgia, finger deformity, ganglion, intervertebral disc protrusion, musculoskeletal pain, plantar fasciitis, rheumatoid arthritis, sacroiliitis, sensation of heaviness, tendon disorder.

Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps)
Infrequent: Breast neoplasm. *Rare:* Benign breast neoplasm, lipoma, marrow hyperplasia, skin papilloma, uterine leiomyoma (gs).

Nervous System
Infrequent: Amnesia, balance disorder, burning sensation, carpal tunnel syndrome, coordination abnormal, dizziness postural, disturbance in attention, dysgeusia, hyperreflexia, hypersomnia, hypertonia, hypoaesthesia, memory impairment, muscle contractions involuntary, restless legs syndrome, sciatica, syncope, tension headache. *Rare:* dysaesthesia, dysphasia, facial paresis, facial spasm, head discomfort, hypogeusia, myoclonus, paralysis, psychomotor hyperactivity, sensory disturbance, sleep talking, syncope vasovagal.

Pregnancy, Puerperium and Perinatal Conditions
Infrequent: Pregnancy (gs).

Psychiatric Disorders
Infrequent: Agitation, apathy, bruxism, confusional state, crying, depersonalization, depressed mood, derealisation, disorientation, early morning awakening, emotional disorder, hallucination

auditory, initial insomnia, libido increased, mental disorder, middle insomnia, mood swings, nervousness, obsessive-compulsive disorder, panic attack, suicidal ideation, suicide attempt, tension, thinking abnormal. *Rare:* Aggression, emotional distress, euphoric mood, flat affect, generalized anxiety disorder, hallucination, hypomania, indifference, major depression, paranoia, psychomotor retardation, tic.

Renal and Urinary Disorders
Infrequent: Dysuria, haematuria, micturition urgency, urinary hesitation. *Rare:* Bladder dilatation, bladder discomfort, chromaturia, nocturia, renal pain, urinary incontinence.

Reproductive System and Breast Disorders
Infrequent: Amenorrhoea (gs), epididymitis (gs), menstrual disorder (gs), menstruation irregular (gs), metrorrhagia (gs), orchitis noninfective (gs), painful erection (gs), pelvic pain, premenstrual syndrome (gs), postmenopausal haemorrhage (gs), sexual dysfunction, testicular pain (gs). *Rare:* Breast discharge, breast pain, breast tenderness, genital pain, menopausal symptoms (gs), uterine spasm (gs), vaginal discharge (gs), vaginal haemorrhage (gs).

Respiratory, Thoracic and Mediastinal Disorders
Infrequent: Asthma, cough, dyspnoea, epistaxis, nasal congestion, postnasal drip, rhinitis allergic, rhinorrhoea, throat irritation, wheezing. *Rare:* Allergic sinusitis, choking, dysphonia, nasal polyps, rhinitis perennial, throat tightness, trachoeal disorder.

Skin and Subcutaneous Tissue Disorders
Infrequent: Acne, alopecia, dermatitis allergic, dermatitis contact, dry skin, eczema, increased tendency to bruise, rash, urticaria. *Rare:* Cold sweat, dermal cyst, dermatitis, dermatitis acneiform, dermatitis atopic, hand dermatitis, ingrowing nail, photosensitivity reaction, rash maculo-papular, skin irritation, skin nodule, skin odor abnormal, skin warm.

Social Circumstances
Infrequent: Drug abuser. *Rare:* Family stress, stress at work.

Surgical and Medical Procedures
Infrequent: Tooth extraction. *Rare:* Colon polypectomy, gingival operation, scar excision.

Vascular Disorders
Infrequent: Flushing, haematoma, hypertension, hypotension, orthostatic hypotension, peripheral coldness, varicose vein. *Rare:* Circulatory collapse, pallor, vein disorder.

LONG-TERM TRIAL (GAD)

In general, the safety profile was similar in the long-term placebo-controlled study (24-76 weeks). The following events (single or duplicate cases), which are not listed in tables 4 and 5 or reported above in the short-term trials, have been reported: aneurysm, arteriosclerosis, dermatitis

bullous, hypercholesterolaemia, hypocalcaemia, hypokalaemia, joint dislocation, migraine, nasal septum deviation, psoriasis, scoliosis, torticollis.

LONG-TERM PLACEBO-CONTROLLED TRIAL IN ESCITALOPRAM RESPONDERS (OCD)

In general, the safety profile was similar in the long-term (24-week) placebo-controlled phase of the trial in which patients who initially responded to 16 weeks of open-label escitalopram treatment were randomized to treatment with escitalopram or placebo for up to 24 weeks. The following events (single or duplicate cases), which are not reported elsewhere, have been reported: abdominal pain lower, acute tonsillitis, blood pressure decreased, dental operation, depressive symptoms, dysarthria, dyspareunia, epicondylitis, facial pain, haematochezia, hordeolum, infrequent bowel movements, laceration, lacrimation increased, limb operation, negative thoughts, neuralgia, pain inflammation activated, subcutaneous abscess, tendon injury, wisdom teeth removal.

POST-MARKET ADVERSE DRUG REACTIONS

Adverse events not listed above that have been reported to be temporally (but not necessarily causally) associated with escitalopram treatment since its market introduction include:

Aggression, alanine aminotransferase increased, amblyopia, amenorrhoea not otherwise specified (NOS), angioedema, anxiety aggravated, appetite decreased NOS, aspartate aminotransferase increased, atrial fibrillation, blood alkaline phosphatase NOS increased, blood cholesterol increased, blood glucose increased, blood pressure increased, burning sensation NOS, cardiac arrest, cerebrovascular accident, clonic convulsion, coma, completed suicide, confusional state, contusion, convulsions NOS, death NOS, delirium, diplopia, disorientation, drug level NOS increased, dysarthria, dysgeusia, dyskinesia, dysphasia, ecchymosis, electrocardiogram QT prolonged, emotional distress, epidermal necrolysis, epistaxis, erectile dysfunction NOS, extrapyramidal disorder, facial palsy, feeling abnormal, fluid retention, gait abnormal NOS, galactorrhoea, gastrointestinal haemorrhage, gingival bleeding, grand mal convulsion, haematemesis, hallucination visual, hepatitis NOS, hyperventilation, hypoglycaemia NOS, injury NOS, INR increased, irritability, leukocytosis, leukopenia NOS, liver function tests NOS abnormal, loss of consciousness, memory impairment, menometrorrhagia, muscle cramps, myocardial infarction, myocardial ischaemia, neuroleptic malignant syndrome, neurotransmitter level altered, night sweats, nightmare, orthostatic hypotension, pancreatitis NOS, panic attack, panic reaction, petit mal epilepsy, platelet count decreased, priapism, pulmonary embolism, pyrexia, renal failure acute, restlessness, rhabdomyolysis, rhinorrhoea, serotonin syndrome, SIADH, speech disorder, stomatitis, tardive dyskinesia, thrombocytopenia, torsades de pointes, trismus, urinary incontinence, vasovagal attack, ventricular tachycardia, vision blurred, visual disturbance NOS, weakness.

DRUG INTERACTIONS

Serious Drug Interactions
● **Monoamine Oxidase Inhibitors: see CONTRAINDICATIONS.**
● **Pimozide: see CONTRAINDICATIONS.**

OVERVIEW

Escitalopram is the active enantiomer of racemic citalopram. The pharmacokinetic studies described in the following sections, whether using escitalopram or racemic citalopram, were carried out in young healthy, mostly male volunteers. In addition, many of the studies utilized single doses of the specific concomitant medication, with multiple dosing of escitalopram or citalopram. Thus, data are not available in patients who would be receiving the concomitant drugs on an ongoing basis at therapeutic doses.

DRUG-DRUG INTERACTIONS

Monoamine Oxidase Inhibitors (MAOIs)

Combined use of escitalopram and MAO inhibitors is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome**).

Cytochrome P450 Isozymes

Citalopram: Based on the results of broad in vitro and in vivo testing, racemic citalopram is neither the source nor the cause of any clinically important pharmacokinetic drug-drug interactions. In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -1A2, -2D6, -2C9, -2C19 and –2E1. Accordingly, escitalopram would be expected to have little inhibitory effect on in vivo drug metabolism mediated by the cytochrome P-450 isozymes. In addition, pharmacokinetic interaction studies with racemic citalopram have also demonstrated no clinical important interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), warfarin (CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor).

Escitalopram: Using *in vitro* models of human liver microsomes, the biotransformation of escitalopram to its demethylated metabolites was shown to depend on three parallel pathways (CYP2C19, CYP3A4 with a smaller contribution from CYP2D6) (see **DOSAGE AND ADMINISTRATION, CYP2C19 Poor metabolizers**).

Studies also indicate that escitalopram is a very weak or negligible inhibitor of human hepatic isoenzyme CYP1A2, 2C9, 2C19, 2E1, and 3A4, and a weak inhibitor of 2D6. Although escitalopram has a low potential for clinically significant drug interactions, caution is recommended, when escitalopram is co-administered with drugs that are mainly metabolized by CYP2D6, and that have a narrow therapeutic index.

The possibility that the clearance of escitalopram will be decreased when administered with the following drugs in a multiple-dose regimen should be considered:

- potent inhibitors of CYP3A4 (e.g., fluconazole, ketoconazole, itraconazole, erythromycin), or
- potent inhibitors of CYP2C19 (e.g., omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine). Caution should be exercised at the upper end of the dosage range of escitalopram when it is co-administered with CYP2C19 inhibitors.

In addition, a single-dose study of escitalopram co-administered with a multiple-dose regimen of cimetidine, a non-specific CYP inhibitor, led to significant changes in most of the pharmacokinetic parameters of escitalopram.

The overall metabolic pathways for escitalopram and citalopram are qualitatively similar and the interaction potential for escitalopram is expected to closely resemble that of citalopram. Thus, this allows for extrapolation to previous studies with citalopram.

CNS drugs
Drug interactions have not been specifically studied between either escitalopram or racemic citalopram and other centrally acting drugs. Given the primary CNS effects of escitalopram, caution should be used as with other SSRIs when escitalopram is taken in combination with other centrally acting drugs.

Serotonergic Drugs:
Based on the mechanism of action of escitalopram and the potential for serotonin syndrome, caution is advised when Cipralex® is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, lithium, tramadol, or St. John's Wort (see WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome (NMS)-like events). Concomitant use of Cipralex® and MAO inhibitors (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor) is contraindicated (see CONTRAINDICATIONS).

Triptans ($5HT_1$ agonists):
Cases of life-threatening serotonin syndrome have been reported during combined use of selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) and triptans. If concomitant treatment with Cipralex® and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS AND PRECAUTIONS: Serotonin Syndrome/Neuroleptic Malignant Syndrome (NMS)-like events).

Racemic Citalopram
As escitalopram (Cipralex®), is the active isomer of racemic citalopram (Celexa®), the two drugs should not be taken together.

Alcohol use
The interaction between escitalopram and alcohol has not been studied. Although racemic citalopram did not potentiate the cognitive and psychomotor effects of alcohol in volunteers, the concomitant use of alcohol in depressed patients taking escitalopram is not recommended.

Polymorphism
It has been observed that poor metabolizers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolizers. (See **DOSAGE AND ADMINISTRATION, CYP2C19 Poor metabolizers**). Although no significant change in exposure was observed in poor metabolizers with respect to CYP2D6, caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolized by this enzyme, and that have a narrow therapeutic index.

Interaction data which include studies conducted with escitalopram

Table 8. Established or Predicted Drug-Drug Interactions with escitalopram

Escitalopram	Reference	Effect	Clinical Comment
Cimetidine	CT	Co-administration of cimetidine (400 mg twice daily for 5 days), a moderately potent CYP2D6, 3A4 and 1A2 inhibitor, with escitalopram (single dose of 20 mg on day 4) resulted in an increase in escitalopram AUC and C_{max} of approximately 70% and 20%, respectively.	Caution should be exercised when used concomitantly with cimetidine. A reduction in the dose of escitalopram may be necessary based on clinical judgement.
Imipramine/ Desipramine: substrate for CYP2D6	CT	Co-administration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 50% increase in desipramine concentrations	The clinical significance of this finding is unknown. Consequently, concomitant treatment with escitalopram and imipramine/desipramine should be undertaken with caution
Metoprolol: substrate for CYP2D6	CT	Co-administration of 20 mg/day of escitalopram for 21 days with metoprolol (a CYP2D6 substrate) resulted in a 50% increase in the peak plasma levels of the -adrenergic blocker with no clinically significant effects on blood pressure or heart rate	
Omeprazole: CYP2C19 inhibitor	CT	Co-administration of omeprazole (30 mg once daily for 6 days), a CYP2C19 inhibitor, with escitalopram (single dose of 20 mg on day 5) resulted in an increase in escitalopram AUC and C_{max} of approximately 50% and 10%, respectively.	Caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole). A reduction in the dose of escitalopram may be necessary based on clinical judgement.

Escitalopram	Reference	Effect	Clinical Comment
Ritonavir: substrate for CYP3A4	CT	Combined administration of a single dose of ritonavir (600 mg), a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram	

Legend: CT = Clinical Trial

Interaction studies conducted with racemic citalopram

Table 9. Established or Predicted Drug-Drug Interactions with racemic citalopram

Racemic citalopram	Reference	Effect	Clinical Comment
Carbamazepine	CT	Carbamazepine, titrated to 400 mg/day, was given for 21 days alone and then in combination with racemic citalopram (40 mg/day) for an additional 14 days. Citalopram did not affect the plasma levels of carbamazepine, a CYP3A4 substrate, or its metabolite, carbamazepine-epoxide	Since carbamazepine is a microsomal enzyme inducer, the possibility that carbamazepine may increase the clearance of escitalopram should be considered if the two drugs are given concomitantly
Digoxin	CT	Administration of racemic citalopram (40 mg/day for 21 days) did not affect the pharmacokinetics of digoxin (single dose of 1 mg). The serum levels of citalopram were slightly lower in the presence of digoxin but with no clinical relevance	
Ketoconazole	CT	Combined administration of racemic citalopram (40 mg single dose) and the potent CYP3A4 inhibitor ketoconazole (200 mg single dose) decreased the C_{max} of ketoconazole by 21% and did not affect the pharmacokinetics of racemic citalopram	
Levomepromazine	CT	Co-administration of racemic citalopram (40 mg/day for 10 days) and a CYP2D6 inhibitor, levomepromazine (single dose of 50 mg) did not affect the pharmacokinetics of either drug	

Racemic citalopram	Reference	Effect	Clinical Comment
Lithium	CT	Co-administration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) did not affect the pharmacokinetics of either drug	Since lithium may increase serotonergic neurotransmission, concomitant treatment with escitalopram should be undertaken with caution
Pimozide	CT	In a double-blind crossover study in healthy young adults, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values at T_{max} of approximately 12 msec compared to pimozide when given with placebo	The mechanism of this apparent pharmacodynamic interaction is not known. Concomitant use of citalopram or escitalopram and pimozide is contraindicated.
Theophylline	CT	Co-administration of racemic citalopram (40 mg/day for 21 days) with the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline	
Triazolam	CT	Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either drug	
Warfarin	CT	Administration of racemic citalopram (40 mg/day for 21 days) did not affect either the pharmacokinetics or the pharmacodynamics (prothrombin time) of a single 25 mg dose of warfarin, a CYP3A4 and CYP2C9 substrate	

Legend: CT = Clinical Trial

DRUG-FOOD INTERACTION

Various scientific publications have acknowledged that the main components in grapefruit juice may act as CYP3A4 inhibitors. Escitalopram is also metabolized by other isoenzymes not affected by grapefruit juice, namely CYP2C19 and CYP2D6. Although there is a theoretical possibility of pharmacokinetic drug interactions resulting from co-administration of escitalopram with grapefruit juice, the onset of an interaction is considered unlikely.

DRUG-HERB INTERACTIONS

St-John's Wort: In common with other SSRIs and newer antidepressants, pharmacodynamic interactions between escitalopram and the herbal remedy St-John's Wort may occur and may result in undesirable side effects.

DRUG-LABORATORY TEST INTERACTIONS

Interactions with laboratory test have not been established.

DOSAGE AND ADMINISTRATION

DOSING CONSIDERATION

- **Cipralex® (escitalopram oxalate) is not indicated for use in children under 18 years of age** (see **WARNINGS AND PRECAUTIONS, Potential Association with Behavioural and Emotional Changes, Including Self-Harm**).

- **General:** Escitalopram should be administered as a single daily dose, with or without food.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

ADULTS

MAJOR DEPRESSIVE DISORDER
Escitalopram should be administered as a single oral dose of 10 mg daily. Depending on individual patient response, an increase in the dose to a maximum of 20 mg daily should be considered. Where initial sensitivity to adverse events may be a concern, escitalopram could be started at 5 mg daily and titrated upwards as tolerated.

GENERALIZED ANXIETY DISORDER
Escitalopram should be administered as a single oral dose of 10 mg daily. Depending on individual patient response, an increase in the dose to a maximum of 20 mg daily should be considered. Where initial sensitivity to adverse events may be a concern, escitalopram could be started at 5 mg daily and titrated upwards as tolerated. During long-term therapy, the dosage should be maintained at the lowest effective level and patients should be periodically reassessed to determine the need to continue treatment.

OBSESSIVE COMPULSIVE DISORDER
Escitalopram should be administered as a single oral dose of 10 mg daily. Depending on individual patient response, an increase in the dose to a maximum of 20 mg daily should be considered. Where initial sensitivity to adverse events may be a concern, escitalopram could be started at 5 mg daily and titrated upwards as tolerated. During long-term therapy, the dosage

should be maintained at the lowest effective level and patients should be periodically reassessed to determine the need to continue treatment.

TREATMENT OF PREGNANT WOMEN DURING THE THIRD TRIMESTER

Post-marketing reports indicate that some neonates exposed to SSRIs such as Cipralex® and other newer antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **WARNINGS AND PRECAUTIONS)**. When treating pregnant women with Cipralex® during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cipralex® in the third trimester.

ELDERLY PATIENTS

A longer half-life and decreased clearance have been demonstrated in the elderly, therefore lower doses and a lower maximum dose should be considered. It may be desirable to start at 5 mg daily and titrate upwards as needed and tolerated.

RENAL IMPAIRMENT

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Since no information is available on the pharmacokinetic or pharmacodynamic effects of either escitalopram or racemic citalopram in patients with severely reduced renal function (creatinine clearance < 30mL/min), escitalopram should be used with caution in these patients.

HEPATIC IMPAIRMENT

Dosages should be restricted to the lower end of the dose range in patients with mild to moderate hepatic insufficiency. Accordingly, an initial single oral dose of 5 mg daily is recommended. Subsequently, the dose may be increased based on the patient's response and clinical judgement. A daily dose of 10 mg is the recommended maximum dose for most patients with hepatic impairment. No information is available about the pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). Escitalopram should be used with additional caution in patients with severe hepatic impairment.

CYP2C19 POOR METABOLIZERS

The metabolism of escitalopram is mainly mediated by CYP2C19. For patients who are known to be poor metabolizers with respect to CYP2C19, an initial dose of 5 mg daily is recommended. The dose may be increased based on the patient's response and clinical judgement.

LONG-TERM TREATMENT

During long-term therapy, the dosage should be maintained at the lowest effective level and patients should be periodically reassessed to determine the need to continue treatment.

SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR (MAOI)

At least 14 days should elapse between discontinuation of a MAOI and initiation of therapy with escitalopram. Similarly, at least 14 days should be allowed after stopping escitalopram before starting a MAOI (see **CONTRAINDICATIONS**).

DISCONTINUATION OF ESCITALOPRAM TREATMENT

Symptoms associated with the discontinuation or dosage reduction of escitalopram have been reported. Patients should be monitored for these and other symptoms when discontinuing treatment or during dosage reduction (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

A gradual reduction in the dose over several weeks rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

CHILDREN

See Potential Association with Behavioural and Emotional Changes, Including Self-Harm under **PRECAUTIONS AND WARNINGS**.

MISSED DOSE

In the event that a dose is missed, the patient should take the next dose when it is due.

OVERDOSAGE

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone (doses unknown); the majority of cases have involved multiple drug overdose. Doses up to 800 mg of escitalopram alone have been taken without any severe symptoms.

In clinical trials with racemic citalopram, there were no reports of fatal citalopram overdoses of up to 2000 mg. Post-marketing reports of drug overdoses involving racemic citalopram have included fatalities with citalopram alone. In many cases, details regarding the precise dose of racemic citalopram or combination with other drugs and/or alcohol are often lacking. However, three fatalities with known overdoses of racemic citalopram alone have been reported in the literature (doses of 2800 mg, 2880 mg, and 3920 mg), although survival has also been reported with overdoses of up to 5200 mg.

In comparing the data from racemic citalopram with that of escitalopram, it is important to be aware that the latter product is expected to have similar pharmacodynamic effects at a lower dose of the racemic product.

Fatal cases of serotonin syndrome have been reported in patients who took overdoses of moclobemide (Manerix®) and racemic citalopram. The plasma concentrations of moclobemide were between 16 and 90 mg/L (therapeutic range: 1 to 3 mg/L) and those of racemic citalopram between 0.3 and 1.7 mg/mL (therapeutic concentration: 0.3 mg/L). This indicates that a

relatively low dose of citalopram, given with an overdose of moclobemide represents a serious risk for the patient.

Symptoms most often accompanying overdose of racemic citalopram included dizziness, sweating, nausea, vomiting, tremor, and somnolence. In more rare cases, observed symptoms included confusion, loss of consciousness, convulsions, coma, sinus tachycardia, cyanosis, hyperventilation and rhabdomyolysis and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

MANAGEMENT OF OVERDOSE

As with racemic citalopram, there is no specific antidote to escitalopram. Treatment is symptomatic and supportive. Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered as soon as possible after oral ingestion. Cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive measures.

Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit.

In managing overdosage, the possibility of multiple drug involvement must be considered.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Escitalopram (S-citalopram) is the active enantiomer of the racemic drug citalopram. *In vitro* and *in vivo* studies have suggested that escitalopram is a highly potent and selective serotonin reuptake inhibitor (SSRI), which acts by specific competitive inhibition of the membrane transporter of serotonin (5-hydroxytryptophan, 5-HT). In addition to its high affinity to the primary binding site, escitalopram also binds with a 1000 fold lower affinity to a secondary binding site on the serotonin transporter. The clinical significance of this binding has not been established.

Escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, dopamine D_1 and D_2 receptors, $_1$, $_2$, - adrenoreceptors, histamine H_1, muscarinic cholinergic, benzodiazepine, gamma aminobutyric acid (GABA) and opioid receptors. Escitalopram does not bind to, or has low affinity for various ion channels including Na^+, Cl^-, K^+ and Ca^{++} channels.

PHARMACOKINETICS

The single and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic with a

mean terminal half-life of about 27-32 hours. With once daily dosing, steady-state plasma levels are achieved within approximately 1 week. At steady state, the plasma concentration of escitalopram in young healthy subjects was approximately 2.6 times that observed after a single dose.

ABSORPTION AND DISTRIBUTION: Following the administration of an oral dose (10 mg or 20 mg) of escitalopram to healthy volunteers, peak plasma levels occur at about 4 hours after dosing. Absorption of escitalopram is expected to be almost complete after oral administration and is not affected by food. After a single oral administration of escitalopram 10 mg, the apparent volume of distribution of (Vd,β,/F) is about 12 L/kg to 26 L/kg. The binding of escitalopram to human plasma proteins is independent of drug plasma levels and average 55 %.

METABOLISM AND ELIMINATION: The plasma clearance following oral administration is about 0,6 L/min with approximately 7% due to renal clearance. Escitalopram is metabolized in the liver to S-demethylcitalopram (S-DCT) and to S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. After multiple-dose administration of escitalopram, the mean plasma concentrations of the metabolites S-DCT and S-DDCT are usually 28-31% and <5% of the parent compound concentration, respectively. Results from in vitro studies suggest that the metabolites (S-DCT and S-DDCT) do not contribute significantly to the clinical actions of escitalopram.

In vitro studies using human liver microsomes indicated that the biotransformation of escitalopram to its demethylated metabolites depends primarily on CYP2C19 and CYP3A4 with a smaller contribution from CYP2D6. The apparent hepatic clearance of drug amounts to approximately 90% of the administered dose. Following oral administration of escitalopram, the fraction of drug recovered as escitalopram and the metabolite S-DCT is about 8% and 10% respectively.

SPECIAL POPULATIONS

Elderly patients: Escitalopram pharmacokinetics in subjects older than 65 years of age was compared to younger subjects in a single/multiple-dose study (n=18 subjects ≥65). After a single dose, plasma escitalopram levels were similar in young and elderly subjects. At steady state in elderly subjects, escitalopram Cmax, AUC and half-life values were increased by approximately 35, 50 and 50%, respectively, while the clearance values were decreased. In this population, lower doses and a lower maximum dose of escitalopram are recommended (see **WARNINGS AND PRECAUTIONS** AND **DOSAGE AND ADMINISTRATION**).

Gender: In a multiple dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in the weight-adjusted values of the area under the curve (AUC), Cmax, and half-life between the male and the female subjects. No adjustment in dosage is recommended on the basis of gender difference.

Reduced Hepatic Function: In patients with mild to moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was approximately doubled (66 hours vs. 36 hours), and the exposure was about two-third higher than in subjects with normal liver function. Consequently, the doses in the lower end of the recommended range of escitalopram should be used for patients with hepatic dysfunction. No information is available about the pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). Escitalopram should be used with additional caution in patients with severe hepatic impairment (see **WARNINGS AND PRECAUTIONS** AND **DOSAGE AND ADMINISTRATION**).

Reduced Renal Function: No information is available about the pharmacokinetics of escitalopram in patients with reduced renal function. In n=7 patients with mild to moderate renal function impairment, oral clearance of racemic citalopram was reduced by 17% compared to normal subjects, with no clinically significant effect on the kinetics. No adjustment of dosage is recommended for such patients. At present no information is available about the pharmacokinetics of either escitalopram or racemic citalopram for the chronic treatment of patients with severely reduced renal function (creatinine clearance <30 mL/min) (see **WARNINGS AND PRECAUTIONS** AND **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Escitalopram tablets should be stored in a dry place at room temperature (15^{o} and 30^{o}C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Escitalopram tablets contain escitalopram oxalate corresponding to 5 mg, 10 mg, 15 mg or 20 mg escitalopram, and the following non medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, talc, titanium dioxide (white E-171).

AVAILABILITY OF DOSAGE FORMS

5 mg tablets: Each film-coated, white, round tablet, marked with "EK" on one side, contains: escitalopram 5 mg (as escitalopram oxalate). Blister packages of 30. Bottle of 100.

10 mg tablets: Each film-coated, white, oval, scored tablet, marked with "EL" on one side, contains: escitalopram 10 mg (as escitalopram oxalate). Blister packages of 7 and 30. Bottle of 100. Bottle of 200.

15 mg tablets: Each film-coated, white, oval, scored tablet, marked with "EM" on one side, contains: escitalopram 15 mg (as escitalopram oxalate). Blister packages of 30. Bottle of 100.

20 mg tablets: Each film-coated, white, oval, scored tablet, marked with "EN" on one side, contains: escitalopram 20 mg (as escitalopram oxalate). Blister packages of 30. Bottle of 100.

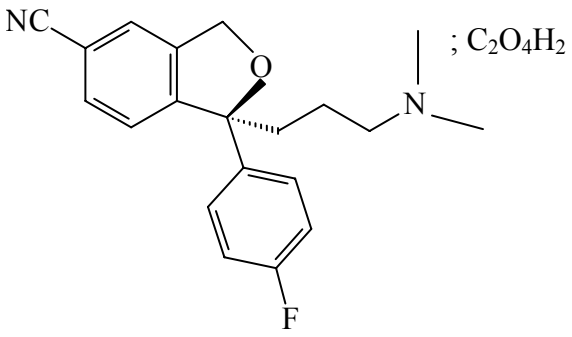
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name:	Escitalopram oxalate
Code Name:	Lu 26-054
Chemical Name:	S(+)-1-[3-(Dimethylamino)propyl]-1-(*p*-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, oxalate
Molecular Formulas:	$C_{20}H_{21}FN_2O$, $C_2H_2O_4$

Structural Formula:



Molecular Weight:	414.42
Physical form:	White to off-white, crystalline material having no more than a slight odour.
Melting Point:	147°-152°C
pKa:	9.5 (microtitration)
Solubility:	Water (sparingly soluble) Ethanol (sparingly soluble) Ethyl acetate (slightly soluble) Methanol (freely soluble) Dimethyl sulfoxide (freely soluble) Isotonic saline (soluble)
Partition Coefficient:	Log P (octanol/phosphate buffer pH 7.4) - 1.34

CLINICAL TRIALS

MAJOR DEPRESSIVE DISORDER (MDD)

The efficacy of escitalopram in the treatment of depression was established in three 8-week placebo-controlled, parallel groups, multi-centre studies in patients who met the DSM-IV criteria for major depression. Two of the studies included racemic citalopram as a treatment arm. The primary efficacy endpoint in all 3 studies was mean change from baseline to 8-week endpoint on the Montgomery Asberg Depression Rating Scale (MADRS), adjusted for effects of baseline score, treatment and centre. All three studies consisted of a 1-week single-blind placebo lead-in period, followed by an 8-week, double-blind treatment period.

ESCITALOPRAM FIXED-DOSE STUDIES

Study 1
A total of 377 primary care patients with major depressive disorder were treated with 10 mg/day escitalopram (N=188) or placebo (N=189). The 10 mg/day escitalopram treatment group showed significantly greater improvement than placebo on the adjusted MADRS mean change from baseline to 8-week end-point (-16.3 vs. –13.6, respectively).

Study 2
In another study, a total of 485 outpatients with major depressive disorder were treated with 10 mg escitalopram (N=118), 20 mg escitalopram (N=123), 40 mg racemic citalopram (N=125), or placebo (N=119) for 8 weeks. Both the 10 mg and 20 mg escitalopram treatment groups showed significantly greater improvement than placebo on the MADRS mean change from baseline to 8-week endpoint (-12.8 and -13.9 vs. –9.4, respectively).

ESCITALOPRAM FLEXIBLE-DOSE STUDY

Study 3
A total of 468 primary care patients with major depressive disorder were treated with 10-20 mg escitalopram (N=155), 20-40 mg racemic citalopram (N=159), or placebo (N=154) for 8 weeks. During the first four weeks of active treatment, all doses were fixed at 10 mg escitalopram or 20 mg racemic citalopram. A dose increase to 20 mg and 40 mg, respectively, was permitted from Week 4 onward. The escitalopram 10-20 mg treatment group showed significantly greater improvement than placebo on the adjusted MADRS mean change from baseline to 8-week end-point (-15.0 vs. –12.11, respectively).

ESCITALOPRAM LONGER TERM RELAPSE OBSERVATION STUDY

The efficacy of Cipralex® in maintaining an antidepressant response in patients with major depressive disorder was demonstrated in a longer term study consisting of a 36-week placebo controlled relapse observation phase in responders of a preceding 8-week acute treatment phase. In a longer term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who

had responded during an initial 8-week, open-label treatment phase with escitalopram 10 or 20 mg/day, were randomized to continuation of escitalopram at their same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined by having a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

GENERALIZED ANXIETY DISORDER (GAD)

Studies 4, 5, 6

The efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD) was established in three, 8-week, multicenter, flexible-dose, placebo-controlled studies that compared escitalopram 10-20 mg/day to placebo in outpatients between 18 and 80 years of age who met the DSM-IV criteria for GAD. The primary efficacy endpoint in all 3 studies was mean change from baseline to 8-week endpoint on the Hamilton Anxiety Scale (HAMA) total score.

All three studies consisted of a 1-week single-blind placebo run-in period, followed by an 8-week, double-blind treatment period. During the first four weeks of active treatment, all doses were fixed at 10 mg escitalopram. A dose increase to 20 mg was permitted from Week 4 onward if clinically indicated.

The escitalopram 10-20 mg treatment group showed significantly greater improvement ($p \leq 0.05$) than placebo on the mean change from baseline to 8-week end-point in the HAMA total score (LOCF) in the three studies (-9.6 escitalopram vs. -7.7 placebo [study 4]; -9.2 escitalopram vs. -7.6 placebo [study 5]; -11.3 escitalopram vs. -7.4 placebo [study 6]).

The response rates at Week 8 of treatment (LOCF), as defined using a CGI-I score of 1 (very much improved) or 2 (much improved) or a ≥50% improvement in HAMA total score as the response criterion, were as follows:

TABLE 10 RESPONSE RATES AT WEEK 8 OF TREATMENT IN SHORT-TERM PLACEBO CONTROLLED CLINICAL TRIALS FOR GENERALIZED ANXIETY DISORDER (STUDIES 4, 5, 6)						
	Study 4		**Study 5**		**Study 6**	
Parameter	**PBO (n=128)**	**ESC (n=124)**	**PBO (n=138)**	**ESC (n=143)**	**PBO (n=153)**	**ESC (n=154)**
Proportion of patients with a ≥50% improvement in HAMA total score (responders, %)	28.9	49.2**	29.0	39.9	28.8	53.2**
Proportion of patients with a CGI-I score of 1 or 2[1] (responders, %)	41.4	48.4	34.1	49.0*	37.3	57.8**
Statistically significantly different from placebo: *p≤0.05; **p≤0.001						

[1] 1=very much improved; 2=much improved

Study 7

In an additional multicenter, placebo-controlled study, escitalopram was administered at fixed dose of 5, 10 and 20 mg/day for 12 weeks following a 1-week single-blind placebo run-in period. An SSRI currently indicated for the treatment of GAD was included in the study as an active control. In this 12-week pairwise comparison of three escitalopram active treatment groups, one SSRI active control group and placebo group, there was a significant advantage on the primary measure of the mean change from baseline in HAMA total score (LOCF) for escitalopram 10 and 20 mg compared with placebo (-16.8 escitalopram 10 mg vs. -14.2 placebo [p<0.01]; -16.4 escitalopram 20 mg vs. -14.2 placebo [p<0.05]). Escitalopram 5 mg as well as the active control SSRI were numerically, but not statistically significantly superior to placebo (-15.5 escitalopram 5 mg vs. -14.2 placebo; -14.7 SSRI vs. -14.2 placebo).

Study 8

In a long-term multicenter study, 373 patients with GAD who had responded during an initial 12-week open-label escitalopram treatment phase, were randomized to placebo or escitalopram (20mg/day) for a minimum potential double-blind treatment period of 24 weeks (with a maximum of potential treatment period of 76 weeks, depending on the date of enrolment). There were statistically significantly (p≤0.001) more relapses on placebo (56%) than on escitalopram (19%).

OBSESSIVE COMPULSIVE DISORDER (OCD)

Study 9

The efficacy of escitalopram in the treatment of Obsessive-Compulsive Disorder (OCD) was established in a multicenter 24-week placebo-controlled fixed-dose study (with efficacy assessments at Week 12 and Week 24) that compared the efficacy of 10 mg/day or 20mg/day escitalopram with placebo in outpatients between 18 and 67 years of age who met the DSM-IV-TR criteria for OCD. An SSRI currently indicated for the treatment of OCD was included in the study as an active control. The primary efficacy endpoint was mean change from baseline to 12-week on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) total score.

A total of 455 outpatients with OCD were treated with 10 mg escitalopram (n=112), 20 mg escitalopram (n=114), SSRI (n=116) or placebo (n=113). At 12 weeks, escitalopram 20 mg/day and the active control SSRI showed significantly greater improvement than placebo (p=0.002 and p=0.014, respectively) on the mean change from baseline in the Y-BOCS total score (LOCF). Improvement in the 10 mg/day group was numerically, but not statistically, superior to the placebo group (p=0.052). The mean treatment differences relative to placebo were -1.97 and -3.21 for escitalopram 10 mg /day and 20 mg/day, respectively and -2.47 for the active control SSRI.

Secondary efficacy outcomes were supportive of the primary efficacy outcome. At Week 12 there were improvements in patient functioning with escitalopram and active SSRI control compared to placebo as measured by CGI responder rates[a] and the social life, family life and work items of the Sheehan Disability Scale.

Study 10

The efficacy of Cipralex® in maintaining an anti-obsessive response in patients with OCD was demonstrated in a long-term study in which 322 patients meeting the DSM-IV-TR criteria for OCD, who had responded during an initial 16-week, open-label treatment phase with escitalopram (10 or 20 mg/day), were randomized to continuation of escitalopram at their same dose, or to placebo, for 24 weeks. Response during the open-label phase was defined by having a ≥25% reduction from baseline in Y-BOCS total score. Relapse during the double-blind phase was defined as either an increase from randomization to any single visit in Y-BOCS total score of 5 points or more or an unsatisfactory treatment effect, as judged by the investigator.

Patients who relapsed were withdrawn from the study. There were statistically significantly (p≤0.001) more relapses on placebo (52%) than on escitalopram (23%).

[a] For the CGI-Improvement, response was defined as “much improved” or “very much improved”.

DETAILED PHARMACOLOGY

Escitalopram is the S (+) enantiomer of citalopram. At clinically relevant doses, the pharmacological activity of the racemic citalopram is mediated through the S (+) enantiomer. Tolerance to the inhibition of serotonin reuptake is not induced by long-term (up to 5 weeks) treatment of rats with escitalopram. No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted on rats with escitalopram and racemic citalopram showed a similar profile. The pharmacodynamic and pharmacokinetic properties of escitalopram are shown to parallel those of the racemate citalopram.

ANIMAL DATA

IN VITRO EXPERIMENTS

Neuronal reuptake of serotonin, norepinephrine and dopamine
Escitalopram selectively blocks the reuptake of ^{3}H-5-HT in rat brain synaptosomes *in vitro* with an IC_{50} value of 2.1 nM compared to 275 nM for the R-enantiomer and 3.9 nM for racemic citalopram. As suggested by these inhibitory potencies, escitalopram is expected to be two-fold more potent than racemic citalopram, the R-enantiomer being several fold less potent.

The effects of racemic citalopram, the S- and R-enantiomers and the corresponding demethylated metabolites (DCT, S-DCT and R-DCT, respectively) on accumulation of ^{3}H-5-HT into rat whole brain synaptosomes, ^{3}H-dopamine (DA) into rat striatal synaptosomes, and ^{3}H-norepinephrine (NE) into rat frontal and temporal cortices were compared.

The results show that escitalopram and racemic citalopram are both potent and selective 5-HT reuptake inhibitors with no effect on the reuptake of NE and DA. Although the N-demethylated DCT metabolites of escitalopram and racemic citalopram are also selective inhibitors of the 5-HT reuptake, they are significantly less potent than the parent compounds. The didemethylated metabolites (DDCT) were devoid of 5-HT inhibitory potency.

Defining selectivity as the ration between NE and 5-HT reuptake inhibitory potency, escitalopram is considered to be the most selective serotonin reuptake inhibitor that has been developed for clinical use (NE/5-HT uptake of escitalopram vs. racemic citalopram = 1700 vs. 3400).

Effect of neurotransmitter receptors
Escitalopram has no or very low affinity for a series of receptors including 5-HT_{1A}, 5-HT_2, dopamine D_1 and D_2 receptors, α_1-, α_2-, β-adrenoreceptors, histamine H_1, muscarinic cholinergic, benzodiazepine, and opioid receptors; nor has it an action on MAO except at extremely high concentrations achievable only *in vitro*.

BEHAVIOURAL EFFECTS

Escitalopram has shown efficacy in several animal models predictive of antidepressant and anxiolytic activities. Effects of escitalopram, racemic citalopram and R-citalopram in male mice were studied in the forced swim test. Escitalopram as well as citalopram dose-dependently reversed immobility induced by forced swimming, whereas R-citalopram was inactive.

A potent anxiolytic-like profile has been shown for escitalopram in animal models mimicking features of generalized anxiety (the two-compartment black and white box models in mice and rats) and panic anxiety (the foot shock-induced ultrasonic vocalisation model in adult rats).

The 5-HT precursors tryptophan, *d,l*-5-HTP and *l*-5HTP induce in mice a characteristic 5-HT syndrome (tremor, hyperactivity and abduction of the hind limbs). Individual behavioural changes are scored for each animal resulting in a total score that corresponds to a complete 5-HT syndrome. Concomitant acute treatment with a 5-HT reuptake inhibitor potentiates the behavioural response to the precursors. Table 13 below shows relative potencies (ED_{50}) of escitalopram, racemic citalopram and corresponding metabolites.

Table 11. Potentiation of 5-HTP-induced behavioural changes in mice. Effects of racemic citalopram and S- and R-enantiomers and the corresponding demethylated metabolites.

	ESC	*R-CIT*	*CIT*	*S-DCT*	*R-DCT*	*DCT*
5-HTP potentiation						
Mice, 30 min, SC	1.1	59	3.3	>50	>50	NT
***l*-5-HTP potentiation**						
Mice, 30 min, SC	1.7	>48	1.8	NT	NT	NT
5-HT syndrome						
Mice, 30 min, SC	>6.0	>190	>49	>50	>50	NT

NT=not tested

CARDIOVASCULAR STUDIES

Patch clamp experiments showed that escitalopram and racemic citalopram had some inhibitory effect on I_{kr} and I_{Na} channels, and on cardiac L-type calcium currents, but only at concentrations in the micromolar range, and so about 1000-fold higher than the concentrations required to produce a half-maximal action on 5-HT reuptake in the CNS. With respect to these actions, both escitalopram and racemic citalopram were very similar to other marketed SSRIs.

The electrophysiological effects of escitalopram, S-DDCT, R-DDCT, racemic citalopram, DDCT and other SSRIs have been examined in the Langendorff guinea pig heart model. From 0.5-2.5 μM all SSRIs caused an increase in the PQ interval, accompanied by negative inotropic activity. None of the SSRIs tested nor S-DDCT had an effect on the QT interval, whereas R-DDCT and DDCT did prolong it at the highest concentrations of 2.5 μM.

Doses of escitalopram of 1, 3 or 6 mg/kg were infused i.v. over 2 hours into conscious dogs. The serum levels reached at the end of the infusion did not induce convulsive attacks. Even the highest dose of escitalopram (corresponding to 15-21 times the C_{max} in human at a dose of 20 mg/day) was associated with a minor variation in the PR interval, which was considered to be within the physiological limits. The QT interval was not affected. There was no particular action on the ECG apart from some changes in the morphology of the precordial T waves, which has been seen with many other CNS drugs.

Escitalopram and its corresponding metabolites S-DCT and S-DDCT did not appear to have a harmful effect on the heart in these studies and their actions on cardiac conduction *in vivo* and *in vitro* were small and similar to or less than other SSRIs.

RESPIRATORY STUDIES

Escitalopram caused moderate acidosis (blood pH fell from about 7.34 to 7.21) in conscious dogs following intravenous administration. An intravenous dose of racemic citalopram decreases arterial blood pH by approximately 0.07. Escitalopram does not affect the respiratory rate in dogs.

PHARMACOKINETICS AND METABOLISM IN ANIMAL MODELS

Animal models have shown that the pharmacokinetics and metabolism of escitalopram does not depend on whether it is given on its own or together with the R-enantiomer in the racemate. In addition, results of studies carried out *in vitro* and *in vivo* show lack of inter-conversion between the two enantiomers. It is considered appropriate, therefore, to combine the kinetics and other information about escitalopram when given on its own with the other knowledge available of the body's handling and responses to the racemic citalopram.

ABSORPTION

Escitalopram appears to be readily absorbed. Similar to racemic citalopram, the kinetics of escitalopram in rats and dogs are characterized by rapid absorption, with T_{max} ranging from approximately 0.5-2 hours with difference due to species-specific first pass metabolism. Higher serum concentrations of R-citalopram were seen in both humans and rats after administration of racemic citalopram compared to escitalopram. Comparisons between studies indicate a high absolute bioavailability.

DISTRIBUTION

The lipophilicity of escitalopram is assumed to be a major determinant of its distribution pattern in tissues. Based on previous results on the distribution of racemic citalopram, it is assumed that escitalopram will follow two-compartment distribution characteristics. High levels of racemic citalopram and demethylated metabolites were generally found in the lungs, liver, and kidneys, and lower levels in the heart and brain. The apparent volume of distribution for racemic citalopram was approximately 10 to 25 L/kg. Similarly, the apparent volume of distribution ($V_{d,\beta}/F$) of escitalopram after oral administration to human is about 12 to 26 L/kg. Racemic

citalopram and the metabolites were shown to pass the placental barrier and were excreted in small amounts in milk of lactating mice.

The plasma protein binding of escitalopram is low with an average of 55%, compared to an average of 75% for racemic citalopram. Both in mice and dogs, tissue concentrations of parent racemic citalopram as well as those of the demethylated metabolites increased with increasing doses, although not necessarily in a dose-related manner. Levels of the didemethylated metabolites were higher in dogs than in mice in relation to the parent drug, resulting in smaller citalopram/didemethylcitalopram ratios in the dog, particularly in the heart and kidneys.

METABOLISM

As with racemic citalopram, the metabolism of escitalopram in animal species is assumed to be qualitatively the same as in humans. The demethylated metabolites of escitalopram (S-DCT, S-DDCT) have been measured in rats, dogs and humans. Escitalopram has been shown to be demethylated qualitatively by CYP3A4, 2C19 and 2D6. Escitalopram and S-DCT (main metabolite in humans and rats) are weak or negligible inhibitors of CYP1A2, 2C9, 2C19, 2E1, and 3A4. The metabolite S-DDCT (main metabolite in dogs) is a moderate inhibitor of CYP2C9 and 2C19. However, this is unlikely to be of clinical importance due to the low plasma levels of S-DDCT achieved clinically in humans. Alternatively, the nitrogen groups may be oxidised to form the N-oxide metabolite. The deamination leads to the propionic acid metabolite. Both parent and metabolites are partly excreted as glucuronides.

ELIMINATION

Following the administration of ^{14}C-labelled citalopram by oral gavage to rats, maximum excretion in urine occurred at 2-8 hours and in faeces at 8-24 hours. At a dose of 20 mg/kg, approximately equal amounts of the dose were excreted in the urine and feces, with total recovery being about 80% of the dose. In the 4- and 13-week toxicity studies the apparent serum elimination half-life of escitalopram was generally short: about 0.8-5.5 hours in rats and about 4-8 hours in dogs. The apparent increase of the elimination half-life in the dog with increasing doses is presumably due to the saturation of the first-pass metabolism. This is consistent with the results obtained with racemic citalopram. Of the three compounds (escitalopram, S-DCT, S-DDCT), S-DDCT appears to have the longest elimination half-life (about 8-36 hours) in animals.

TOXICOKINETICS

The pharmaco-/toxicokinetics of escitalopram observed in the 4- and 13-week studies performed in the rat appeared comparable after administration of either escitalopram or racemic citalopram. Plasma levels were also determined in several toxicity studies. The table below summarizes the toxicokinetic parameters from a 13-week study in rats relative to pharmacokinetic parameters in humans.

Study/ Species	Dose ESC (mg/kg/day) oral route	Gendre	C_{max} (nmol/l)	AUC_{0-t} (h·nmol/l)	Ration of AUC values animal/human			
					10 mg/day		20 mg/day[3]	
					C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
ESCITALOPRAM								
13-week rats (day 90)	10	M	181	643	2.9x	0.6x	1.4x	0.3x
	40		*1076*	*6552*	*17x*	*5.9x*	*8.2x*	*2.9x*
	120[1]		n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	10	F	775	1199	12x	1.1x	5.9x	0.5x
	40		*1383*	*9165*	*22x*	*8.3x*	*11x*	*4.1x*
	120[1]		2066	19609	33x	18x	16x	8.7x
multidose humans[2] (day 24)	10 mg/day	both	63	1109	-	-	-	-
	20 mg/day[3]		131	2250				
S-DCT								
13-week rats (day 90)	10	M	305	1094	13x	2.2x	6.9x	1.2x
	40		*1383*	*17843*	*58x*	*36x*	*31x*	*20x*
	120[1]		n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	10	F	302	739	13x	1.5x	6.9x	0.8x
	40		*734*	*10232*	*31x*	*21x*	*17x*	*12x*
	120[1]		1585	28668	66x	59x	36x	32x
multidose humans[2] (day 24)	10 mg/day	both	24	489	-	-	-	-
	20 mg/day[3]		44	883				
S-DDCT								
13-week rats (day 90)	10	M	48	367	16x	6.1x	13x	5.0x
	40		*316*	*5123*	*105x*	*85x*	*85x*	*69x*
	120[1]		n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	10	F	38	315	13x	5.3x	10x	4.3x
	40		*149*	*2510*	*50x*	*42x*	*40x*	*34x*
	120[1]		395	8535	132x	142x	107x	115x
multidose humans[2] (day 24)	10 mg/day	both	3.0	60	-	-	-	-
	20 mg/day[3]		3.7	74				

[1] The 120 mg/kg/day dose was reduced to 100 mg/kg/day for males on day 13 and further for both genders to 80 mg/kg/day during Week 6.
[2] n=17 (10 mg) or n=16 (30 mg)
[3] The 20 mg/day dose is estimated from the mean of the 10 and 30 mg/day results.
Numbers in *italics* refer to the NOEL (40 mg/kg/day) with respect to cardiac effects.
n.d.: not determined

Exposure margins of approximately up to 10 times the maximum therapeutic dose for the parent drug and up to about 30-140 times for the metabolites have been produced in the various toxicity

tests of escitalopram. The data indicate that the rat resembles man most closely in its metabolism. The R/S ratio in rats for citalopram and the metabolites, DCT and DDCT, is comparable to that found in humans. However, there are some quantitative differences in the pharmacokinetics and metabolism of citalopram and escitalopram in man and animals. The most important is the lesser degree of first pass metabolism in humans relative to animals, which results in proportionately lower circulating levels of S-DCT and S-DDCT in humans.

TOXICOLOGY

The studies on escitalopram were performed in one species, the rat. This species was considered the most appropriate as it has a R/S ratio for citalopram and the metabolites, DCT and DDCT, that is comparable to that found in humans. In addition, the rat has been used as an animal model to demonstrate enantiomeric stereoselectivity for SSRI pharmacological action.

Significant findings from toxicological studies with racemic citalopram in rats, mice and dogs are also described in this section.

ACUTE TOXICITY

After gavage administration, escitalopram 500 mg/kg caused deaths, prostration and tremors, 250 mg/kg had no effect. Citalopram also had no effect at 250 mg/kg, but 500 and 1000 mg/kg were both associated with some deaths and similar clinical signs.

Bolus IV injection of escitalopram at 22 mg/kg led to breathing difficulties within 30 minutes and 30 mg/kg caused convulsions and deaths. Citalopram had similar effects at those dose levels.

SUBCHRONIC AND REPEATED DOSE TOXICITY

Comparative 4- and 13-week and bridging oral tests have been conducted with escitalopram and racemic citalopram in the rat. A separate 60-day test was also carried out using the rat as a model.

In the 4-week experiment, the highest dose of both drugs (60 mg/kg/day) led to small retardation in weight gain, slight changes in liver function and phospholipidosis in various tissues. At a dose of 60 mg/kg/day, the signs of phospholipidosis were more marked in animals given racemic citalopram.

In the 13-week toxicity experiments in the rat, it was demonstrated that the pattern of toxic actions of escitalopram was similar to that of citalopram. Toxic actions mainly comprised hepatic enlargement and inflammation of the myocardium at high dose levels, plus typical phospholipidosis seen with many cationic amphophilic medicines. There were also clinical signs including reduced weight gain, sedation and trembling. The NOEL was about 5-10 mg/kg/day for both compounds.

Cardiotoxicity, Including Inflammation and Congestive Heart Failure
In the bridging study both escitalopram (80 mg/kg/day) and citalopram (160 mg/kg/day) were found to induce cardiotoxicity in the rat under the conditions of the study, although a higher incidence of changes was recorded in animals treated with escitalopram (2 out of 20 animals vs. 3 out of 40 animals, respectively).

The changes induced by both compounds were initially and mainly inflammatory (myocarditis) affecting the myocardium and atria in particular, and included congestive heart failure.

Male and female rats dosed with escitalopram at the high doses are affected to the same extent by myocarditis, although onset of lesions appears to be more rapid in males than in females.

The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-levels were approximately 8-fold greater than those achieved in clinical use, whereas AUC for escitalopram was only 3-4 fold higher than the exposure achieved in clinical use. The findings may be secondary to the effect on biogenic amines, which results in reduction in coronary flow and potential ischaemia. However, an exact mechanism of cardiotoxicity in rats is not clear. Clinical experience with racemic citalopram, and the clinical trials experience with escitalopram do not indicate that these findings have a clinical correlate.

Retinal Degeneration/Atrophy in Rats Given Racemic Citalopram
In the rat carcinogenicity study, a slight, dose-related increase in lens opacity was seen, affecting males only. In addition, increased incidence/severity of retinal degeneration/atrophy was seen in the high-dose group (80 mg/kg/day). The incidence was higher in females, however, more female than male rats survived the study. It was concluded by an independent pathologist that the retinal changes were most likely related to drug-induced pupillary dilatation (mydriasis), which increased the risk of retinal damage in the already light-sensitive albino rat.

Convulsions and Death in Dogs Given Racemic Citalopram
Toxicity studies in dogs revealed that citalopram administration led to fatal ventricular arrhythmias. Consequently, studies were undertaken to elucidate the mechanism of this effect and to determine its relevance to humans.

The studies have shown that (1) i.v. infusion of citalopram, at a dose of 20 mg/kg, led to convulsions. The blood levels of citalopram were 1950 ng/mL at this dose. In the presence of diazepam, also infused intravenously, higher doses of citalopram could be infused, namely up to 70 mg/kg (6800 ng/mL). (2) Intravenous infusion of the didemethyl metabolite of citalopram caused QT prolongation in a dose range of 5 to 22 mg/kg. The blood levels of the metabolite were 300 ng/mL at the 5 mg/kg dose. The QT prolongation was dose-dependent. (3) When citalopram, 20 mg/kg, and didemethylcitalopram, 5 mg/kg, were infused concomitantly (in the presence of diazepam in order to prevent convulsions), 5 out of 9 dogs died due to ventricular fibrillation. At these doses, the plasma levels of citalopram and didemethylcitalopram were 1950 ng/mL and 300 ng/mL, respectively.

As shown in the table below, there is a substantial difference in the plasma levels of citalopram and its metabolite in dogs and in humans at the recommended therapeutic doses.

Treatment	Dog ventricular fibrillation	Patients at steady state after a 60 mg/day dose of citalopram
citalopram, 20 mg/kg	1950 ng/mL	121 ng/mL
plus		
didemethylcitalopram, 5 mg/kg	300 ng/mL	6.2 ng/mL

In summary the safety profile of escitalopram is similar to racemic citalopram, other than a higher incidence of cardiac inflammation at proportional doses. Further, the clinical use of escitalopram is supported by the extensive clinical safety experience with the SSRIs in general and racemic citalopram in particular.

The No Effect Level in rats is 40 mg/kg/day PO, excluding phospholipidosis as observed with many cationic amphophilic medicines. At this dose level the C_{max} plasma levels of escitalopram in the rat during a 13-week study are 1076-1383 nM, i.e. approximately 8-11 fold the human exposure of 131 nM following repeated dosing at the maximum recommended dose of 20 mg/day.

REPRODUCTION STUDIES

Comparative tests of the maternal and foetal toxicity and the peri- and post-natal toxicity of escitalopram and racemic citalopram were performed in the rats.

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 16, 32, 48 and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at dose ≥32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

In the reproductive toxicity studies with racemic citalopram in female rats during the period of organogenesis (32, 56, or 112 mg/kg/day) and escitalopram (56, 112, or 150 mg/kg/day), embryo-foetal effects were found only at doses ≥ 112 mg/kg/day (approximately ≥ 60 times the maximum recommended human dose of escitalopram on a body surface bases). These effects included decreased foetal growth and survival, an increased incidence of foetal abnormalities (including cardiovascular and skeletal defects, and reversible delays in ossification). These doses were also associated with maternal toxicity.

When female rats were orally treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) or escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, the high doses were associated with increased offspring mortality in the first 4 days and persistent offspring growth retardation. The NOEL for maternal and reproductive toxicity of citalopram was 12 mg/kg/day. The corresponding NOEL and NOAEL for esitalopram for reproductive and maternal effects were 24 mg/kg/day.

MUTAGENIC POTENTIAL

An extensive battery of *in vitro* and *in vivo* tests of racemic citalopram have been conducted. Racemic citalopram did not show mutagenic activity in most of the *in vitro* tests (Ames Salmonella assay; chromosome aberration assay in cultured human lymphocytes; gene mutation assay in cultured mouse lymphoma L5178Y) and *in vivo* tests (micronucleus test; unscheduled DNA synthesis). However, racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. Racemic citalopram was clastogenic in the *in vitro* Chinese hamster lung cell assay, in the presence and absence of metabolic activation.

CARCINOGENICITY

Comprehensive carcinogenicity tests of racemic citalopram were done in the mouse and rat. Racemic citalopram showed no evidence of carcinogenic potential in the NMRI/BOM strain of mice at daily doses of 40-240 mg/kg (1.5 years) and in the COBS WI strain of rats at 8-80 mg/kg (2 years) other than an increased incidence of small intestine carcinoma in rats treated with 8 and 24 mg/kg/day of racemic citalopram. The latter doses are approximately equivalent to a dose of escitalopram 2-6 times the maximum recommended human daily dose based on mg/m^2 basis. No such effects were observed in rats treated with a 80 mg/kg/day dose. On the same grounds as used previously, it can be concluded that escitalopram is not carcinogenic.

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PART III: CONSUMER INFORMATION

Cipralex®
Escitalopram Oxalate Tablets

This leaflet is part III of a three-part "Product Monograph" published when Cipralex® was approved for sale in Canada and is designed specifically for Consumers. Please read this information before you start to take your medicine. Keep the leaflet while you are taking Cipralex® as you may want to read it again. This leaflet is a summary and will not tell you everything about Cipralex®. Contact you doctor or pharmacist if you have any questions about the drug. Always keep medicines out of the reach of children.

ABOUT THIS MEDICATION

What is the medication used for:
Cipralex® has been prescribed to you by your doctor to relieve your symptoms of depression, anxiety, or obsessive compulsive disorder. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

What it does:
Cipralex® belongs to a group of medicines known as antidepressants, more specifically to the family of medicines called SSRIs (Selective Serotonin Reuptake Inhibitors).

Cipralex® is thought to work by increasing the levels of a chemical in the brain called serotonin (5-hydroxytryptamine).

When it should not be used:
- Do not use Cipralex® at the same time as pimozide.
- Do not use Cipralex® if you are currently or have recently taken monoamine oxidase antidepressants (e.g. phenelzine sulphate, moclobemide).
- Do not take Cipralex® if you are allergic to it, or to any of the components of its formulation (for list of components see the section on "What Cipralex® contains").
- Stop taking Cipralex® and contact your doctor immediately if you experience an allergic reaction or any severe side effect.

What the medicinal ingredient is:
Escitalopram oxalate

What the non medicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methyl cellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400, talc, titanium dioxide (white E-171).

What dosage forms it comes in:
White 5 mg, 10 mg, 15 mg or 20 mg tablets in blister packs or bottles.

WARNINGS AND PRECAUTIONS

Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.

Cipralex® is not for use in children under 18 years of age.

New or Worsened Emotional or Behavioural Problems
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

Effects on Pregnancy and Newborns
Possible complications at birth (from taking any newer antidepressant, including Cipralex®):
Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) such as Cipralex® or other newer antidepressant during pregnancy have developed complications at birth requiring prolonged hospitalisation, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

Persistent Pulmonary Hypertension (PPHN) and newer antidepressants:
Preliminary information suggests that use of SSRIs during the second half of pregnancy may be associated with an increased rate of a serious lung condition (PPHN) that causes breathing difficulties in newborns soon after birth. According to the study, babies born with this condition were 6 times more likely than healthy babies to have been exposed to SSRIs. In the general population, PPHN is known to occur at a rate of about 1-2 per 1000 newborns.

If you are pregnant and taking an SSRI, or other newer antidepressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

Before you use Cipralex®, tell your doctor:

- All your medical conditions, including heart problems, history of seizures, manic-depressive illness, liver or kidney disease, diabetes or history of bleeding disorders.
- Any medications (prescription or non-prescription) which you are taking or have taken within the last 14 days, especially monoamine oxidase inhibitors, pimozide, any other antidepressants, triptans used to treat migraines, lithium, tramadol or drugs containing tryptophan.
- If you ever had an allergic reaction to any medication or any of the ingredients mentioned in this leaflet.
- If you are pregnant or thinking of becoming pregnant, or if you are breastfeeding.
- Your habits of alcohol consumption.
- If you drive a vehicle or perform hazardous tasks during your work.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

- Monoamine oxidase inhibitor (e.g., phenelzine, tranylcypromine, moclobemide or selegiline)
- Pimozide
- Linezolid (an antibiotic)

Other drugs that may interact with Cipralex® include:

- Other SSRIs (citalopram) or any other antidepressant (e.g., imipramine, desipramine)
- Lithium
- Tryptophan
- Cimetidine
- Triptans (e.g., sumatriptan, zolmitriptan, naratriptan)
- Tramadol
- Fluconazole
- Ketoconazole
- Itraconazole
- Racemic Citalopram (Celexa)
- Erythromycin
- Warfarin
- Omeprazole
- Any herbal product such as St. John's Wort
- Any medicine that affect the rate of clotting of the blood e.g., acetylsalicylic acid (ASA) or non-steroidal antiinflammatory drugs (NSAIDS) such as ibuprofen, naproxen, etc. and phenothiazines such as chlorpromazine.

Avoid drinking alcohol while taking Cipralex®

Drugs from the class that Cipralex® belongs to may increase the chance of a bleeding event such as nose bleeds, bruising and even life threatening bleeding. This is more likely if you have a history of a bleeding disorder or are taking other drugs that are known to affect your platelets.

Treatment with an SSRI in patients with diabetes may alter glycaemic control (hypoglycaemia and hyperglycaemia).

Tell your doctor all the medicines (prescription or over the counter) that you are using or thinking of taking.

PROPER USE OF THIS MEDICATION

Usual dose:

- It is important that you take Cipralex® exactly as your doctor has instructed.
- Usually your doctor will prescribe 10 mg per day, which you will take once daily preferably at the same time each day. If you are elderly, your doctor may prescribe a lower dose. This dose may be increased. Never change the dose of Cipralex® you are taking, or that someone in your care is taking unless your doctor tells you to.
- Swallow the tablets whole with a drink of water. Do not chew them. Cipralex® can be taken with or without food.
- You should continue to take Cipralex® even if you do not feel better, as it may take several weeks for your medication to work. Improvement may be gradual.
- Continue to take Cipralex® for as long as your doctor recommends it. Do not stop taking your tablets abruptly even if you begin to feel better, unless you are told to do so by your doctor. Your doctor may tell you to continue to take Cipralex® for several months. Continue to follow your doctor's instructions.

Overdose:

- If you have accidentally taken too much Cipralex® contact your doctor, the Regional Poison Control Centre or nearest hospital emergency department immediately, even if you do not feel sick. If you go to the doctor or the hospital, take the Cipralex® container with you.

Missed dose:

- If you miss a dose, do not worry. Do not take the missed tablet(s) - just take the next dose when it is due.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- Cipralex® may cause unwanted effects (side-effects). These may include nausea, increased sweating, diarrhoea, fatigue, fever, constipation, clogged or runny nose, sleep disturbance, loss of appetite, decreased interest in sex, decreased ability to

reach orgasm, erectile dysfunction, difficulties falling asleep, drowsiness, yawning, dizziness, dry mouth, heartburn, stomach pain and changes in heart rate.

- **Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, or to those in your care if you are a caregiver or guardian, consult your doctor immediately; do not discontinue your medication on your own.**

- Contact your doctor before stopping or reducing your dosage of escitalopram. Symptoms such as dizziness, abnormal dreams, electric shock sensations, agitation, anxiety, emotional indifference, difficulty concentrating, headache, migraine, tremor (shakiness), nausea, vomiting, sweating or other symptoms may occur after stopping or reducing the dosage of escitalopram. Such symptoms may also occur if a dose is missed. These symptoms usually disappear without needing treatment. Tell your doctor immediately if you have these or any other symptoms. Your doctor may adjust the dosage of escitalopram to reduce the symptoms.

- Side-effects are often mild and may disappear after a few days. If they are troublesome or persistent, or if you develop any other unusual side-effects while taking Cipralex®, please consult your doctor.

- Usually Cipralex® does not affect your ability to carry out normal daily activities. However, you should not drive a car or operate machinery until you are reasonably certain that Cipralex® does not affect you adversely.

- Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) such as Cipralex® or other newer antidepressant during pregnancy have developed complications at birth requiring prolonged hospitalisation, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, seizures, tense or overly relaxed muscles, jitteriness and constant crying. In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

  If you are pregnant and taking an SSRI, or other newer antidepressant, you should discuss the risks and benefits of the various treatment options with your doctor. It is very important that you do NOT stop taking these medications without first consulting your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Allergic reactions [skin rash, hives, swelling, trouble breathing]			√*
	Alteration of blood sugar control in patients with diabetes: Low blood sugar [symptoms of dizziness, lack of energy, drowsiness, headache, trembling, sweating] or High blood sugar [symptoms of increased thirst, increased urination, weakness, confusion, fruity breath odour)		√	
	Bruising or unusual bleeding from the skin or other areas		√	
	Hallucinations [strange visions or sounds]		√	
	Mania [overactive behaviour and thoughts]		√	
	Uncontrollable movements of the body or face		√	
	Inability to urinate		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	Serotonin syndrome [a combination of symptoms, possibly including: agitation, confusion, tremor, sudden jerking of muscles, high fever]		√*	
	Low sodium level in blood [symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles]		√	
Very Rare	Seizures [loss of consciousness with uncontrollable shaking ("fit")]			√*
	Liver disorder [symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine]		√*	
	Gastrointestinal bleeding [vomiting blood or passing blood in stools]		√*	
See Warnings & Precautions	New or Worsened Emotional or Behavioural Problems		√*	
	Akathisia [feeling restless and unable to sit or stand still]		√	

* If you think you have these side effects, it is important that you seek medical advice from your doctor immediately.

This list is not a complete list of side effects. If you have any unexpected effects while taking this drug, contact your doctor or pharmacist.

HOW TO STORE CIPRALEX®

- As with all medicines, keep Cipralex® out of the reach of children. Store your tablets at room temperature (15°-30°C) in a dry place.
- Keep the container tightly closed.
- There is an expiry date on the label. Do not use the medicine after this date.
- If your doctor tells you to stop taking your medicine you should return any leftover tablets to the pharmacist, unless the doctor tells you to keep them at home.

REMEMBER: This medicine is for YOU. Only a doctor can prescribe it, so never offer it to any other person, even if their symptoms seem to be the same as yours.

REPORTING SUSPECTED SIDE EFFECTS

NOTE: THIS IS NOT AN EMERGENCY NUMBER
To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
On-line: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: **Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.**

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Lundbeck Canada Inc., at:
1-800-586-2325

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