PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Bio-ESCITALOPRAM

Escitalopram Oxalate Tablets

Tablets, 5, 10, 15, 20 mg escitalopram (as escitalopram oxalate), Oral

Manufacturer's standard

Antidepressant / Antiobsessional

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Hematologic	03/2023
7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential	03/2023
7 WARNINGS AND PRECAUTIONS, 7.1.1 Pregnant Women	03/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Bio-ESCITALOPRAM (escitalopram oxalate) is indicated in adults for:

- the symptomatic relief of Major Depressive Disorder (MDD).

  The efficacy of escitalopram in maintaining an antidepressant response, in patients with major depressive disorder who responded during an 8-week, acute-treatment phase while taking escitalopram and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see 14.2 Study Results).

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

  The efficacy of escitalopram in maintaining an anti-obsessive response for up to 6 months in patients with OCD was demonstrated in a long-term placebo-controlled trial in patients who initially responded to 16 weeks of escitalopram open-label treatment (see 14.2 Study Results).

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

1.1 Pediatrics

Pediatrics (<18 years of age): Bio-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).

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety and effectiveness (see 4.2 Recommended Dose and Dosage Adjustment, Geriatrics and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- Bio-ESCITALOPRAM is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Bio-ESCITALOPRAM is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation; 8.5 Post-Market Adverse Reactions, Cardiac Disorders; 9.4 Drug-Drug Interactions, QT Interval Prolongation).
- **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 discontinuedan SSRI and have been started on a MAOI (see 9.1 Serious Drug Interactions and 9.4 Drug-Drug Interactions, Monoamine Oxidase Inhibitors). 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, Bio-ESCITALOPRAM should not be used in combination with a MAOI or within 14 days of discontinuing treatment with a MAOI (including linezolid, an antibiotic which is a reversible non-selective MAOI, and methylene blue, which is a MAOI). Similarly, at least 14 days should elapse after discontinuing Bio-ESCITALOPRAM treatment before starting a MAOI.

- **Pimozide**
  Bio-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 9.4 Drug-Drug Interactions).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **Pediatrics:** Bio-ESCITALOPRAM is not indicated for use in children under 18 years of age. See 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm.
- **Pregnant Women**: Bio-ESCITALOPRAM should not be used during pregnancy unless the benefits markedly outweigh the risks, particularly during the third trimester as there are implications for neonatal health. See 7.1.1 Pregnant Women.
- **Elderly** - Use lower doses. Advise elderly patients of increased risk of falls. Elderly women are at increased risk of hyponatraemia, SIADH. See 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Patients with Cardiac Disease; Musculoskeletal, BoneFracture Risk; Renal, Hyponatraemia, and 7.1.4 Geriatrics.
- **Reduced dosing:** Use lower initial (5 mg) and maximum (10 mg) daily doses for:
  - elderly patients,
  - patients with mild to moderate hepatic impairment,
  - CYP2C19 poor metabolizers, or those taking cimetidine, omeprazole or other CYP2C19 inhibitors.
- **Proceed with caution in patients with:**
  - higher risk of hyponatraemia (e.g. elderly females; dehydrated or cirrhotic patients)
  - severe hepatic impairment,
  - severe renal impairment
  - a pre-existing slow heart rate.
- **Interactions (**See 9. DRUG INTERACTIONS.)
  - Do not co-administer with Monoamine Oxidase Inhibitors (contraindicated). Allow at least 14 days to elapse when switching to or from a MAOI.
  - Do not co-administer with pimozide (contraindicated), or citalopram.
  - Avoid or use caution if patient is concomitantly using:
    - potent CYP3A4 inhibitors,
    - other CNS medications,
    - other serotonergic agents,
    - drugs that prolong QT interval,
    - drugs that affect platelet function, or
    - drugs that cause hyponatraemia, or
    - alcohol.

- A drug metabolized primarily by CYP2D6, if it has a narrow therapeutic index.

- **Reduce dosage gradually.** Do not abruptly discontinue medication. Taper gradually when reducing dose or ending SSRI treatment, and monitor for discontinuation symptoms.

4.2 Recommended Dose and Dosage Adjustment

Adults (<65 years of age)

Major Depressive Disorder

Bio-ESCITALOPRAM should be administered once daily, in the morning or evening, with or without food:

- Usual adult dose: 10 mg/day, orally.
- Titration: If initial adverse events are a concern, start at 5 mg/day and titrate upwards as tolerated.
- Maximum dose: 20 mg/day (if needed, and tolerated).
- Use lowest effective dose and reassess periodically.

Obsessive Compulsive Disorder

- See dose recommendations under Major Depressive Disorder, above.

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 Bio-ESCITALOPRAM. Similarly, at least 14 days should be allowed after stopping Bio-ESCITALOPRAM before starting a MAOI (see 2 CONTRAINDICATIONS).

Discontinuation of Escitalopram Treatment
Adverse events are common within the first few days of SSRI treatment discontinuation and have also been reported following a missed dose or dose reduction.

- Do not discontinue treatment abruptly. A gradual dose reduction over several weeks, is recommended to reduce the risk of discontinuation symptoms.
- Patients should be monitored for discontinuation symptoms when stopping treatment or during dosage reduction.
- 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 7 WARNINGS AND PRECAUTIONS, General, Discontinuation Symptoms and 8.2 Clinical Trial Adverse Reactions, Adverse Reactions following Discontinuation of Treatment (orDose Reduction).

Special Populations

- **Pediatrics (<18 years of age):**
  Health Canada has not authorized an indication for pediatric use.

- **Geriatrics (≥65 years of age):**
  A longer half-life and decreased clearance have been demonstrated in the elderly (see 7.1.4 Geriatrics. See also 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics). Initial dosage is 5 mg once daily. Depending on individual response and tolerance the dose may

be increased to 10 mg daily.

- **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 <30 mL/min), Bio-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-PughCriteria C). Bio-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. Depending on the individual response, the dose may be increased to a maximum of 10 mg.

4.4 Administration

Bio-ESCITALOPRAM should be administered as a single oral daily dose, with or without food.

4.5 Missed Dose

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

5 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 800mg 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 lowerdose 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 moclobemidewere 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, seizure 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. Electrocardiogram 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 5, 10, 15 and 20 mg escitalopram (as escitalopram oxalate)	Croscarmellose sodium, colloidal silicon dioxide, hydroxylpropyl methyl cellulose, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose and titanium dioxide. Isopropyl alcohol and methylene chloride are present in traces amounts.

BIO-ESCITALOPRAM (escitalopram oxalate) is available as tablets:

5 mg: white, round, biconvex, film coated tablets with ‘EC’ debossed on one side and ‘5’ on other side. Available in bottles of 500’s.

10 mg: white, oval shaped, biconvex, film coated tablets with ‘EC’ debossed on one side separately by deep break line and ‘10’ on other side. Available in blisters of 30’s and bottles of 100’s and 500’s.

15 mg: white, oval shaped, biconvex, film coated tablets with ‘EC’ debossed on one side separated by deep break line and ‘15’ on other side. Available in bottles of 500’s.

20 mg: white, oval shaped, biconvex, film coated tablets with ‘EC’ debossed on one side separated by deep break line and ‘20’ on other side. Available in blisters of 30’s and bottles of 100’s and 500’s.

7 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 ageof 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.

  An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients aged 18 to 24 years with psychiatric disorders showed an increased riskof suicidal behaviours with antidepressants compared to placebo.

Discontinuation Symptoms
Adverse events are common when an SSRI dose is reduced and treatment discontinued, particularly if discontinuation is abrupt. When discontinuing treatment, patients should be monitored for symptoms that may be associated with discontinuation (e.g., dizziness, abnormaldreams, 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 8.2 Clinical Trial 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 8.2 Clinical Trial Adverse Reactions, Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction) and 4.2 Recommended Dose and Dosage Adjustment, Discontinuation of Escitalopram Treatment).

ESCITALOPRAM Treatment during Pregnancy- Effects on Newborns
In animal reproduction studies, escitalopram has been shown to have adverse effects on embryo/fetal and postnatal development, when administered at doses greater than human therapeutic doses (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity). There are no adequate and well-controlled studies in pregnant women; therefore, Bio-ESCITALOPRAM should only be used during pregnancy if the potential benefit to the patient justifies the potential risk to the foetus.

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 Bio-ESCITALOPRAM during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see 7.1.1 Pregnant Women and 7.1.2 Breast-feeding).

Carcinogenesis and Mutagenesis

For animal data, see 16 NON-CLINICAL TOXICOLOGY, Genotoxicity and Carcinogenicity.

Cardiovascular

Patients with Cardiac Disease

Neither Bio-ESCITALOPRAM nor racemic citalopram has been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoseswere generally excluded from clinical trials during the drug's premarketing assessment. In line with other SSRIs, including racemic citalopram, escitalopram oxalate causes statistically significant, but clinically unimportant decrease in heart rate. In patients <60 years old, the mean decrease with escitalopram oxalate was approximately 2.3 bpm, while in patients ≥ 60years old, the mean decrease was approximately 0.6 bpm (see 8.2 Clinical Trial Adverse Reactions, Cardiovascular parameters). Consequently, caution should be observed when Bio-ESCITALOPRAM is initiated in patients with pre-existing slow heart rate.

QT Interval Prolongation

Escitalopram has been found to cause a dose-dependent prolongation of the QT interval (see also 2 CONTRAINDICATIONS; 8.5 Post-Market Adverse Reactions, Cardiac Disorders; and 9.4 Drug-Drug Interactions, QT Interval Prolongation).

Driving and Operating Machinery

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

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). Bio-ESCITALOPRAM should be used with caution in diabetic patients on insulin or oral hypoglycaemic drugs.

Hematologic

Abnormal Bleeding

SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs), including escitalopram, may increase the risk of bleeding events by causing abnormal platelet aggregation. Concomitant use of acetylsalicylic acid (ASA), nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to the 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. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis,and petechiae to life-threatening haemorrhages.

SSRIs/SNRIs, including Bio-ESCITALOPRAM , may increase the risk of postpartum haemorrhage (see 7.1 Special Populations, 7.1.1 Pregnant Women, Complications following late third trimester exposure to SSRIs).

Patients should be cautioned about the risk of bleeding associated with the concomitant use of Bio-ESCITALOPRAM and NSAIDs, ASA, or other drugs that affect coagulation (see 9.4 Drug-Drug Interactions). Caution is advised in patients with a history of bleeding disorder or predisposing conditions (e.g., thrombocytopenia).

Hepatic/Biliary/Pancreatic

Hepatic Impairment
Based on a study conducted with escitalopram oxalate in patients with mild to moderate hepatic impairment, the half-life was approximately doubled and the exposure was increased by approximately two thirds, compared to subjects with normal liver function. Consequently, the use of Bio-ESCITALOPRAM in hepatically impaired patients should be approached with caution and a lower dosage is recommended (see 4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment). No information is available about the pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). Bio-ESCITALOPRAM should be used with additional caution in patients with severe hepatic impairment.

Musculoskeletal

Bone Fracture Risk
Epidemiological studies show an increased risk of bone fractures following exposure to some antidepressants, including SSRIs/SNRIs. The risks appear to be greater at the initial stages of treatment, but significant increased risks were also observed at later stages of treatment. The possibility of fracture should be considered in the care of patients treated with Bio-ESCITALOPRAM. Elderly patients and patients with important risk factors for bone fractures should be advised ofpossible adverse events which increase the risk of falls, such as dizziness and orthostatic hypotension, especially at the early stages of treatment but also soon after withdrawal.

Preliminary data from observational studies show association of SSRIs/SNRIs and low bone mineral density in older men and women. Until further information becomes available, a possible effect on bone mineral density with long-term treatment with SSRIs/SNRIs, including Bio-ESCITALOPRAM, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

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 oxalate, 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, Bio-ESCITALOPRAM should be used with caution in patients with a history of seizure disorder. Bio-ESCITALOPRAM should be discontinued if a patient develops seizures for the first time, or if there is an increase in seizure frequency (in patients with a previous diagnosis of epilepsy). SSRIs should be avoided in patients with unstable epilepsy, and patients with controlled epilepsy should be closely monitored.

Serotonin Toxicity/Neuroleptic Malignant Syndrome (NMS)
On rare occasions, serotonin toxicity, also known as serotonin syndrome, has been reported with escitalopram oxalate, particularly during combined use with other serotonergic drugs (see 9.4 Drug-Drug Interactions).

Serotonin toxicity is characterized by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter criteria, serotonin toxicity diagnosis is likely when, in the presenceof at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38°C and ocular clonus or inducible clonus

Neuroleptic malignant syndrome has also been rarely reported with escitalopram oxalate, particularly during combined use with neuroleptic/antipsychotic drugs. The clinical manifestations of neuroleptic malignant

syndrome often overlap with those of serotonin toxicity, including hyperthermia, hypertonia, altered mental status, and autonomic instability. In contrast to serotonin toxicity, patients with neuroleptic malignant syndrome may present with “lead pipe”muscle rigidity as well as hyporeflexia.

The concomitant use of Bio-ESCITALOPRAM with monoamine oxidase inhibitors, including linezolid and methylthioninium chloride (methylene blue), is contraindicated (see 2 CONTRAINDICATIONS). Bio-ESCITALOPRAM should be used with caution in patients receiving other serotonergic drugs or antipsychotics/neuroleptics. If concomitant treatment with Bio-ESCITALOPRAM and other serotonergic drugs and/or antipsychotics/neuroleptics is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug- Drug Interactions). Serotonin toxicity and neuroleptic malignant syndrome may result in potentially life-threatening conditions. If serotonin toxicity or neuroleptic malignant syndrome is suspected, discontinuation of Bio-ESCITALOPRAM should be considered.

Ophthalmologic

Angle-Closure Glaucoma
As with other antidepressants, Bio-ESCITALOPRAM can cause mydriasis, which may trigger an angle - closure attack in a patient with anatomically narrow ocular angles. Healthcare providers should inform patients to seek immediate medical assistance if they experience eye pain, changes in vision or swelling or redness in or around the eye.

Psychiatric

Suicide/Suicidal Thoughts and Clinical Worsening
Depression is associated with an increased risk of suicidal thoughts, self -harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvementmay not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. 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.

Other psychiatric conditions for which Bio-ESCITALOPRAM is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes.

Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and toseek medical advice immediately if these symptoms present (see 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes,Including Self-Harm).

Activation of Mania/Hypomania
In placebo-controlled trials of escitalopram oxalate activation of mania/hypomania was reported in one patient of the n=715, treated with escitalopram oxalate 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, Bio-ESCITALOPRAM should be used with caution in patients with a history of mania/hypomania.

A major depressive episode may be the initial presentation of bipolar disorder. Patients with bipolar disorder may be at an increased risk of experiencing manic episodes when treated with antidepressants

alone. Therefore, the decision to initiate symptomatic treatment of depression should only be made after patients have been adequately assessed to determine if they are at risk for bipolar disorder.

Electroconvulsive Therapy (ECT)
The safety and efficacy of the concurrent use of either Bio-ESCITALOPRAM or racemic citalopram and ECThave not been studied, and therefore, caution is advisable.

Renal

Hyponatraemia
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. Caution should be exercised in patients at risk,such as the elderly, or patients with cirrhosis, or if used in combination with other medications which may cause hyponatraemia.

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), Bio-ESCITALOPRAM should be used with caution in these patients (see 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment).

Reproductive Health: Female and Male Potential

- **Fertility**

  Male Fertility
  Animal data have shown that some SSRIs, may affect sperm quality (see 16 NON- CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Male Fertility).Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed.

- **Sexual Function**

  Selective serotonin reuptake inhibitors (SSRIs) may cause symptoms of sexual dysfunction. Patients should be informed that there have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs. See 8.2 Clinical Trial Adverse Reactions, Male and Female Sexual Dysfunction with SSRIs.

- **Teratogenic Risk**

  See 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women and Newborns:
Bio-ESCITALOPRAM should not be used during pregnancy, unless the potential benefit to the patient outweighs the possible risk to the foetus.

Complications following late third trimester exposure to SSRIs:
Newborns should be observed if maternal use of Bio-ESCITALOPRAM continues into the later stages of pregnancy, particularly in the third trimester. If Bio-ESCITALOPRAM is used until or shortly before birth, discontinuation effects in the newborn are possible. Post-marketing reports indicate that some neonates exposed to SSRIs such as escitalopram oxalate 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, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either discontinuation effects or excess serotonergic activity. In a majority of instances, such complications begin immediately or soon (<24 hours) after delivery. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Neuroleptic Malignant Syndrome (NMS)).

When treating a pregnant woman with Bio-ESCITALOPRAM during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Risk of PPHN and exposure to SSRIs:
Epidemiological studies on persistent pulmonary hypertension of the newborn (PPHN) have shown that the use of SSRIs (including escitalopram oxalate) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. PPHN occurs in 1-2 per 1,000 livebirths in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy (Odds Ratio 6.1, 95% CI 2.2-16.8). A study using data from the Swedish Medical Birth Register for 831,324 infants born in 1997-2005 found an increased risk of PPHN of approximately 2-fold associated with patient-reported maternal use of SSRIs in the first trimester of pregnancy (Risk Ratio 2.4, 95% CI 1.2-4.3), and an increased risk of PPHN of approximately 4-fold associated with a combination of patient-reported maternal use of SSRIs in the first trimester and an antenatal SSRI prescription in later pregnancy (Risk Ratio 3.6, 95% CI 1.2-8.3).

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

7.1.2 Breast-feeding

Studies with escitalopram oxalate 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. Bio-ESCITALOPRAM should not be administered to nursing mothers unless the expected benefits to the patient outweigh the possible risk to the child; in which case the infant should be closely monitored.

7.1.3 Pediatrics

Pediatrics (<18 years of age): Bio-ESCITALOPRAM is not indicated for use in patients below the age of 18 (see 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behaviouraland Emotional Changes, Including Self-Harm).

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Approximately 5% of the 715 patients treated with escitalopram oxalate 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 ascompared to young subjects. Consequently, elderly patients should be administered lower doses and a lower maximum dose (see 10.3 Pharmacokinetics, Special Populations and Conditions, Geriatrics and 4.2 Recommended Dose and Dosage Adjustment, Geriatrics).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse events information for escitalopram oxalate was collected from 715 patients with major depressive disorder (MDD) who were exposed to escitalopram oxalate andfrom 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 andrace. 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 escitalopram oxalatein 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 oxalate 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 oxalate treatment were subsequently randomized to double-blind treatment with escitalopram oxalate (n=164) or placebo (n=158) for up to 24 weeks. In total, 391 patients were exposed to escitalopram oxalate 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 oxalate, 15.7% (64/408) on

citalopram and 16.4% (97/592) on placebo. Discontinuation due to adverse eventswas more common in the active treatment groups (5.9% in escitalopram oxalate and 5.4% in citalopram) than in the placebo group (2.2%). The events that were associated with discontinuation of escitalopram oxalate in 1% or more of patients at a rate of at least twice thatof placebo were: nausea (1.5% vs. 0.2%) and ejaculation failure (1.8% vs. 0.0% of male patients).

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 oxalate, respectively, compared to 5% of the 114 patients receiving placebo. All patients who discontinued treatment due to adverse events in the escitalopram oxalate groups did so in the first 12 weeks. Eight percent of patientsreceiving 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 withescitalopram oxalate, 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 thisis 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.

8.2 Clinical Trial Adverse Reactions

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

Major Depressive Disorder
Table 2 enumerates the incidence of treatment-emergent adverse events that occurred in 715 depressed patients who received escitalopram oxalate 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 in1% or more of patients treated with escitalopram oxalate, and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo -treated patients. Reported adverse events were classified using the Medical Dictionary for RegulatoryActivities (MedDRA), version 9.1.

Table 2 - Treatment-Emergent Adverse Events* Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder

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

Body System Adverse Event	Percentage of Patients Reporting	
	Escitalopram oxalate (n = 715)	Placebo (n = 592)
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
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 oxalate group: vomiting, abdominal pain, flatulence, upper respiratory tractinfection, bronchitis, back pain, neck pain, headache.

Adverse reactions observed with escitalopram oxalate 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 MDD 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 3.

Table 3 – Incidence of Common Adverse Events[1] for Major Depressive Disorder, Study MD-01

Adverse Event	Percentage of Patients Reporting		
	Placebo (n = 122)	Escitalopram oxalate 10 mg/day (n = 119)	Escitalopram oxalate 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. Furthermore, there have been reports of long-lasting sexual dysfunction where these symptoms have continued despite discontinuation of SSRIs. This is adifficult 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 4 shows the incidence rates of sexual side effects in patients with MDD in placebo-controlled short-term trials.

Table 4 – Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials for Major Depressive Disorder

Adverse Event	Percentage of Patients Reporting	
	Escitalopram oxalate (n = 715)	Placebo (n = 592)
Libido decreased	2.1	0.3
Anorgasmia	1.8	0.2
<u>In Males only</u>		
Ejaculation delayed	3.6	0.0
Ejaculation failure	2.7	0.0
Erectile dysfunction	2.7	0.0
Ejaculation disorder	1.3	0.0

Obsessive Compulsive Disorder

Table 5 enumerates the incidence of treatment-emergent adverse events that occurred among227 patients who received escitalopram oxalate 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 oxalate, and for which the incidence in patients treated with escitalopram oxalate was greater than the incidence in placebo-treated patients. Reported adverse events were classified using the MedDRA, version 9.1.

The most frequent adverse events that occurred in escitalopram oxalate-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 5 – Treatment-Emergent Adverse Events* Incidence in a Placebo-Controlled Clinical Trial for Obsessive Compulsive Disorder (first 12 weeks of a 24-weektrial)

Body System Adverse Event	Percentage of Patients Reporting	
	Escitalopram oxalate (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
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

Body System Adverse Event	Percentage of Patients Reporting	
	Escitalopram oxalate (n = 227)	Placebo (n = 114)
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	5.7	1.8
Hyperhidrosis		
Vascular Disorders		
Hot flush [1]	1.5	0.0

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

The following events had a higher incidence in the placebo group compared to the escitalopram oxalate 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 oxalate or placebo, following response to an initial 16 weeks of open-label escitalopram oxalate treatment, the safety profile of escitalopram oxalate was similar to the safety profile in the above mentioned placebo controlled trial. Adverse eventsreported by at least 2% of patients after the open-label period and during the first 2 weeks afterrandomization were: dizziness (15.8% placebo vs. 0.6% escitalopram oxalate); nausea (5.7% placebo vs. 0.6% escitalopram oxalate); headache (4.4% placebo vs. 1.8% escitalopram oxalate); and insomnia (3.2% placebo vs. 0.6% escitalopram oxalate).

The most common adverse events that occurred during treatment with 10 mg/day and 20 mg/day escitalopram oxalate in this clinical trial are shown in Table 6.

Table 6 – 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 oxalate 10 mg/day (n = 113)	Escitalopram oxalate 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 oxalate (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 oxalate during the 24 weeks of the trial was similar to the profile observed in thefirst 12 weeks of the trial.

Weight Changes
Patients treated with escitalopram oxalate in short-term controlled trials did not differ from placebo-treated patients with regards to clinically important change in body weight. In one24-week randomized clinical trial in patients with Social Anxiety Disorder, 8.0% of patientstreated with escitalopram oxalate and 3.2% of patients treated with placebo experienced weight gain of 7% or more.

Cardiovascular parameters
Escitalopram oxalate and placebo groups in MDD 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 oxalate treatment. In line with other SSRIs, including racemic citalopram, escitalopram oxalate causes statistically significant, but clinically unimportant decrease in heart rate. In MDD patients <60 years old, themean decrease with escitalopram oxalate was approximately 2.3 bpm, while in patients ≥ 60 years old, the mean decrease was approximately 0.6 bpm.

Adverse Reactions Following Discontinuation of Treatment (or Dose Reduction)

There have been reports of adverse reactions upon the discontinuation of SSRIs such as escitalopram oxalate (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.

These events are generally self-limiting. Symptoms associated with discontinuation have been reported for other SSRIs.

Adverse Reactions During Treatment for up to 44 weeks
The treatment-emergent adverse event incidence profile of escitalopram oxalate in a long-term study in

patients with 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 observedin short-term studies.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.3 Less Common Clinical Trial Adverse Reactions

Untoward events associated with the exposure were recorded by clinical investigators usingterminology 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 MedDRA, version 9.1.

The events listed below present treatment-emergent adverse events reported during the clinical development program of escitalopram oxalate in depressed patients (n=896), which includes a long-term clinical trial; and in OCD patients included in a long-term (24 weeks with assessments at 12 weeks and 24 weeks) trial (n=227). Excludedfrom this list are those already listed in Tables 2 (MDD) or 5 (OCD first 12 weeks of a 24-week trial).

It is important to emphasise that, although the events reported occurred during treatment with escitalopram oxalate, 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 thatoccurred 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, nightblindness, 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:* Earlysatiety, 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:* Arthropodsting, 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, hyponatraemia, 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 Disorders
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, taste disturbance, 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, mania, 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, testicularpain (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, tracheal 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 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 oxalate treatment were randomized to treatment with escitalopram oxalate 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.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

8.5 Post-Market Adverse Reactions

The following adverse events have been identified during post -approval use of escitalopram oxalate. These events are reported voluntarily from a population of uncertain size, and it is not possibleto reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 7 – Spontaneous Adverse Events

System Organ Class	Adverse Event
Blood and Lymphatic Disorders	Leukocytosis, Leukopenia, Thrombocytopenia
Cardiac Disorders	Cardiac arrest, Electrocardiogram QT prolonged, Myocardial infarction, Myocardial ischaemia, Ventricular arrhythmia, Torsades de pointes, Ventricular tachycardia
Endocrine Disorders	Alanine aminotransferase increased, Aspartate aminotransferase increased, Hyperprolactinemia, SIADH
Eye Disorders	Amblyopia, Diplopia, Visual Disturbance
Gastrointestinal Disorders	Gastrointestinal haemorrhage, Gingival bleeding, Pancreatitis
General Disorders and Administration Site Conditions	Death NOS, Feeling abnormal, Gait abnormal, Irritability, Pyrexia
Hepatobiliary Disorders	Hepatitis
Investigations	Blood alkaline phosphatase increased, Drug level increased, Electrocardiogram QT prolonged, INR increased, Liver function tests abnormal, Neurotransmitter level altered, Platelet count decreased
Metabolism and Nutrition Disorders	Fluid retention, Hypoglycaemia
Musculoskeletal and Connective Tissue Disorders	Muscle cramps, Rhabdomyolysis, Trismus

Nervous System Disorders	Akathisia, Cerebrovascular accident, Clonic convulsion, Coma, Dysarthria, Dyskinesia, Dysphasia, Extrapyramidal disorder, Facial palsy, Grand mal convulsion, Loss of consciousness, Neuroleptic malignant syndrome, Movement disorder, Petit mal epilepsy, Serotonin syndrome, Speech disorder, Tardive dyskinesia, Vasovagal attack
Psychiatric Disorders	Delirium, Hallucination visual, Panic reaction, Psychomotor restlessness, Restlessness, Suicidal behavior
Renal and Urinary Disorders	Renal failure acute, Urinary retention
Reproductive System and Breast Disorders	Female: Menometrorrhagia, postpartum haemorrhage* Male: Galactorrhoea, Priapism
Respiratory, Thoracic and Mediastinal Disorder	Hyperventilation, Pulmonary embolism, Rhinorrhoea
Skin and Subcutaneous Tissue Disorders	Angioedema, Ecchymosis, Epidermal necrolysis, Stevens-Johnson syndrome

** This event has been reported for the therapeutic class of SSRIs/SNRIs.*

Cardiac Disorders

QT interval prolongation

Escitalopram has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes havebeen reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases. In a double-blind, placebo-controlled ECG study in healthy subjects, the change from baseline in QTc (Fridericia-correction) was 4.3 msec (90% CI: 2.2, 6.4) at the 10 mg/day dose and 10.7 msec (90% CI: 8.6, 12.8) at the 30 mg/day dose. Based on the established exposure - response relationship, the predicted QTc (Fridericia-correction) change from placebo arm (95% confidence interval) under the C_{max} for the dose of 20 mg is 6.6 (7.9) msec. Statistically significant decreases in heart rate of mean 2-5 bpm were also observed during treatment with escitalopram oxalate at 10 mg and 30 mg in these healthy subjects (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS, Cardiovascular, QT Interval Prolongation; and 9.4 Drug-Drug Interactions, QT Interval Prolongation).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- **Monoamine Oxidase Inhibitors: see 2 CONTRAINDICATIONS.**
- **Pimozide: see 2 CONTRAINDICATIONS**

9.2 Drug Interactions Overview

Escitalopram is the active enantiomer of racemic citalopram. The pharmacokinetic studies described in the following sections, whether using escitalopram oxalate 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 oxalate or citalopram. Thus, data are not available in patients who would be receiving the concomitant drugs on an ongoing basis at therapeutic doses.

9.3 Drug-Behavioural Interactions

See 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm.

9.4 Drug-Drug Interactions

The drugs listed in the tables below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Monoamine Oxidase Inhibitors (MAOIs)
Combined use of Bio-ESCITALOPRAM and MAOIs is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Neuroleptic Malignant Syndrome (NMS)). In patients receiving SSRIs in combination with a MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes, including extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome or neuroleptic malignant syndrome. Bio-ESCITALOPRAM should not be used in combination with a MAOI, (including linezolid, an antibiotic which is a reversible non- selective MAOI, and methylene blue, which is a MAOI) or within 14 days of discontinuing treatment with a MAOI. Similarly, at least 14 days should elapse after discontinuing Bio-ESCITALOPRAM treatment before starting a MAOI (see 2 CONTRAINDICATIONS).

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 4.2 Recommended Doseand Dosage Adjustment, 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 metabolizedby 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.

Central Nervous System (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 withother centrally acting drugs.

Serotonergic Drugs:
Based on the mechanism of action of escitalopram and the potential for serotonin syndrome, caution is advised when Bio-ESCITALOPRAM is co-administered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, SSRIs, lithium,St. John's Wort, dextromethorphan, and opioids (including methadone, buprenorphine and tramadol, fentanyl and its analogues, tapentadol, meperidine and pentazocine) (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Neuroleptic Malignant Syndrome (NMS)). Concomitant use of Bio-ESCITALOPRAM and MAOIs (including linezolid, an antibioticwhich is a reversible non-selective MAOI) is contraindicated (see 2 CONTRAINDICATIONS).

Triptans ($5HT_1$ agonists):
Cases of life-threatening serotonin syndrome have been reported during combined use of SSRIs/SNRIs and triptans. If concomitant treatment with Bio-ESCITALOPRAM and a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiationand dose increases (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Neuroleptic Malignant Syndrome (NMS)).

Drugs Affecting Platelet Function (e.g., NSAIDs, ASA and other anticoagulants) Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies ofthe case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of a nonsteroidal anti- inflammatory drugs (NSAID), acetylsalicylic acid (ASA) or other anticoagulants may potentiate the risk of bleeding.

Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are co-administered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Bio-

ESCITALOPRAM is initiated or discontinued (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding).

Citalopram
As escitalopram is the active isomer of racemic citalopram, 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, theconcomitant use of alcohol in depressed patients taking escitalopram is not recommended.

QT Interval Prolongation
Pharmacokinetic and pharmacodynamic studies of escitalopram combined with other medicinal products that prolong the QT interval have not been performed. An additive effect of escitalopram and these medicinal products cannot be excluded. Therefore, co-administration ofescitalopram with medicinal products that have a clear QT interval prolonging effect, such as Class IA and III antiarrhythmics, certain antipsychotics (e.g., ziprasidone), tricyclic antidepressants, opioids (e.g., methadone), certain antimicrobial agents (e.g., moxifloxacin), is discouraged. The concomitant use of Bio-ESCITALOPRAM with drugs that can disrupt electrolyte levels is discouraged. Drugs that decrease electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids. The above lists of potentially interacting drugs are not comprehensive (see 2 CONTRAINDICATIONS and 8.5 Post-Market Adverse Reactions, Cardiac Disorders).

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 4.2 Recommended Doseand Dosage Adjustment, 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 oxalate

Table 8 - Established or Predicted Drug-Drug Interactions with Escitalopram

Drug (proper/common name)	Source of Evidence	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 oxalate (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. A maximum dose of 10 mg/day escitalopram should not be exceeded.

imipramine / desipramine: substrate for CYP2D6	CT	Co-administration of escitalopram oxalate (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 oxalate for 21 days with metoprolol (a CYP2D6 substrate) resulted in a 50% increase in the peak plasma levels of the β-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 oxalate (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. A maximum dose of 10 mg/day escitalopram should not be exceeded.
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 oxalate (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

Drug (proper/common name)	Source of Evidence	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.	

Drug (proper/common name)	Source of Evidence	Effect	Clinical Comment
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.	
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.	

Drug (proper/common name)	Source of Evidence	Effect	Clinical Comment
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

9.5 Drug-Food Interactions

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.

9.6 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.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 serotoninreuptake 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.

10.2 Pharmacodynamics

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, 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.

10.3 Pharmacokinetics

The single and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. 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:

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.

Distribution:

After a single oral administration of escitalopram 10 mg, the apparent volume of distribution of ($V_{d,\beta}$/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:

Escitalopram is metabolized in the liver to S-demethylcitalopram (S-DCT) and to S-didemethyl citalopram (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 themetabolites (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 witha smaller contribution from CYP2D6. The apparent hepatic clearance of drug amounts to approximately 90% of the administered dose. Following oral administration of escitalopram, thefraction of drug recovered as escitalopram and the metabolite S-DCT is about 8% and 10% respectively.

Elimination:

Biotransformation of escitalopram is mainly hepatic with a mean terminal half-life of about 27-32 hours. The plasma clearance following oral administration is about 0.6 L/min with approximately 7% due to renal clearance.

Cardiac Safety:

See 8.5 Post-Market Adverse Reactions, Cardiac Disorders.

Special Populations and Conditions

- **Pediatrics:** Bio-ESCITALOPRAM is not indicated for use in patients below the age of 18 (see 7 WARNINGS AND PRECAUTIONS, General, Potential Association with Behavioural and Emotional Changes, Including Self-Harm).
- **Geriatrics:** 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). Aftera single dose, plasma escitalopram levels were similar in young and elderly subjects. At steady state in elderly subjects, escitalopram C_{max}, area under the curve (AUC) and half-life values were increased by approximately 35, 50 and 50%, respectively, whilethe clearance values were decreased. In this population, lower doses and a lower maximum dose of Bio-ESCITALOPRAM are recommended (see 7.1.4 Geriatrics and 4.2 Recommended Dose and Dosage Adjustment, Geriatrics (≥65 years of age)).
- **Sex:** In a multiple dose study of escitalopram oxalate (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 AUC, C_{max}, and half-life between the male and the female subjects. No adjustment in dosage is recommendedon the basis of gender difference.

- **Hepatic Insufficiency:** 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 Bio-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). Bio-ESCITALOPRAM should be used with additional caution in patients with severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic, Hepatic Impairment and 4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment).
- **Renal Insufficiency:** 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 forthe chronic treatment of patients with severely reduced renal function (creatinine clearance <30 mL/min) (see 7 WARNINGS AND PRECAUTIONS, Renal, Renal Impairment and 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment).

11 STORAGE, STABILITY AND DISPOSAL

Bio-ESCITALOPRAM (escitalopram oxalate) tablets should be stored in a dry place at room temperature (15 °C to 30 °C).

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

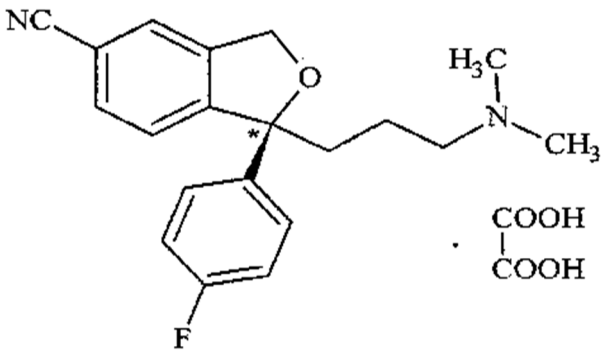
Drug Substance

Proper name: Escitalopram oxalate

Chemical name: S-(+)-1-[3-(dimethylamino) propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate

Molecular formula and molecular mass: $C_{20}H_{21}FN_2O.\ C_2H_2O_4$
414.4 g/mol

Structural formula:



** Chiral centre*

Physicochemical properties: White to off-white powder
Melting Point: 147°-151 °C
pKa: 3.86 (1% solution)

Solubility:

S. No	Aqueous media	% drug dissolved
01	0.1N HCl	99.90
02	Acetate buffer	100.2
03	Phosphate buffer	94.58
04	Phosphate buffer	102.81
05	Water	99.80

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

See 14.2 Study Results.

14.2 Study Results

Major Depressive Disorder (MDD)

The efficacy of escitalopram oxalate in the treatment of depression was established in three 8-week placebo-controlled, parallel groups, multicentre studies in patients who met the DSM-IVcriteria for major depression. Two of the studies included racemic citalopram as a treatment arm. The primary efficacy end-point in all 3 studies was mean change from baseline to 8 -weekend-point on the Montgomery Åsberg 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 MDD were treated with 10 mg/day escitalopram oxalate (N=188) or placebo (N=189). The 10 mg/day escitalopram oxalate treatment group showed significantly greater improvement than placebo on the adjusted MADRS mean changefrom baseline to 8-week end-point (-16.3 vs. -13.6, respectively).

Study 2

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

Escitalopram flexible-dose study

Study 3

A total of 468 primary care patients with MDD were treated with 10-20 mg escitalopram oxalate (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 oxalate or 20 mg racemic citalopram. A dose increase to 20 mg and 40 mg, respectively, was permitted from Week 4 onward. The escitalopram oxalate 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 long-term relapse observation study

The efficacy of escitalopram oxalate in maintaining an antidepressant response in patients with MDD was demonstrated in a long-term study consisting of a 36-week placebo controlled relapse observation phase in responders of a preceding 8-week acute treatment phase. In a long-term trial, 274 patients meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for MDD, who had responded during an initial 8 -week, open-label treatment phase with escitalopram oxalate 10 or 20 mg/day, were randomized to continuation of escitalopram oxalate 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 increaseof the MADRS total score to ≥22, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram oxalate experienced a significantly longer time torelapse over the subsequent 36 weeks compared to those receiving placebo.

Obsessive compulsive disorder (OCD)

Study 9

The efficacy of escitalopram oxalate in the treatment of OCD was established in a multicenter 24-week placebo-controlled fixed-dose study (with efficacy assessments at Week 12 and Week24) that compared the efficacy of 10 mg/day or 20 mg/day escitalopram oxalate with placebo inoutpatients between 18 and

67 years of age who met the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (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 end-point 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 oxalate (n=112), 20 mg escitalopram oxalate (n=114), SSRI (n=116) or placebo (n=113). At 12 weeks, escitalopram oxalate 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 using 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 oxalate 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 the CGI-I responder rate[1] and the Sheehan Disability Scale functional impairment scores (social life, family life and work) with escitalopram oxalate andactive SSRI control compared to placebo.

Study 10
The efficacy of escitalopram oxalate 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 oxalate (10 or 20 mg/day), were randomized to continuation of escitalopram oxalate 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. Non-responders left the study.

Relapse during the double-blind phase was defined as either an increase from randomizationto 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 oxalate (23%).

Secondary efficacy outcomes were supportive of the primary efficacy outcome. There were improvements in CGI-I total score and the Sheehan Disability Scale functional impairment scores (social life, family life and work) with escitalopram oxalate compared to placebo.

[1] For the CGI-Improvement, response in the OCD studies was defined as “much improved” or “very much improved”.

14.3 Comparative Bioavailability Studies

A randomized, two-treatment, two-period, crossover, single dose, oral comparative bioavailability study of Bio-ESCITALOPRAM 20 mg tablets (Biomed Pharma, Canada) and CIPRALEX® 20 mg tablets (Lundbeck Ltd., UK) was conducted in 22 healthy, adult, male volunteers under fasting conditions. Comparative bioavailability data from 19 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Escitalopram (1 x 20 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng·h/mL)	886.74 912.42 (23.63)	863.51 888.63 (27.13)	102.69	99.42 - 106.07
C_{max} (ng/mL)	26.09 26.79 (22.55)	26.32 26.86 (23.15)	99.13	94.56 - 103.93
T_{max}[3] (h)	3.95 (38.03)	3.58 (38.28)		

[1] Bio-ESCITALOPRAM (escitalopram, as escitalopram oxalate) tablets, 20 mg (Biomed Pharma, Canada).
[2] CIPRALEX® (escitalopram, as escitalopram oxalate) tablets, 20 mg (Lundbeck Ltd., UK).
[3] Expressed as the arithmetic mean (CV%) only.
Due to the long elimination half-life of escitalopram, AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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, DCTand DDCT, that is comparable to that found in humans. In addition, the rat has been used as an animal model to demonstrate enantiomeric stereo-selectivity for SSRI pharmacological action.

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

General Toxicology:

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/kgwere 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.

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 animalsvs. 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 infemales.

The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at NOELs 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.

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 atconcentrations in the micromolar range.

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 0.5-2.5µM 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 thehighest dose of escitalopram (corresponding to 15-21 times the C_{max} in human at a dose of 20mg/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.

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 effectand to determine its relevance to humans.

The studies have shown that (1) IV 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) IV infusion of the didemethyl metabolite of citalopram caused QTprolongation 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. Atthese 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 40 mg/day dose of citalopram
citalopram, 20 mg/kg **plus** didemethylcitalopram, 5 mg/kg	1950 ng/mL 300 ng/mL	83 ng/mL 5.2 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 generaland racemic citalopram in particular.

The NOEL 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 therat 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.

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 asa 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 animalsgiven 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 clinicalsigns including reduced weight gain, sedation and trembling. The no-observed-effect-level(NOEL) was about 5-10 mg/kg/day for both compounds.

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 tablebelow 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**	**Gender**	**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				

Study/ Species	**Dose ESC (mg/kg/day) oral route**	**Gender**	**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}**

[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 andanimals. The most important is the lesser degree of first pass metabolism in humans relative toanimals, which results in proportionately lower circulating levels of S-DCT and S-DDCT in humans.

Carcinogenicity:

Comprehensive carcinogenicity tests of racemic citalopram were conducted in the mouse and rat. Racemic citalopram showed no evidence of carcinogenic potential in the NMRI/BOM strainof 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.

Genotoxicity:

An extensive battery of *in vitro* and *in vivo* tests of racemic citalopram has 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 *invitro* Chinese hamster lung cell assay, in the presence and absence of metabolic activation.

Reproductive and Developmental Toxicology:

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 durationwas increased at 48 mg/kg/day.

Tests of the maternal and foetal toxicity and the peri- and post-natal toxicity of escitalopram were performed in rats. One high dose of racemic citalopram was included for comparison.

In an embryo-fetal developmental toxicity study with escitalopram (56, 112 or 150 mg/kg/day and racemic citalopram (70 mg/kg/day) in female rats during the period of organogenesis embryo-foetal effects (reduced foetal body weight and delays in ossification) were found only atdoses ≥112 mg/kg/day (approximately ≥56 times the maximum recommended human dose of 20 mg/day escitalopram on a body surface area [mg/m^2] basis). Similar effects were seen with racemic citalopram. These doses were also associated with maternal toxicity.

In a previous separate embryo-foetal developmental toxicity study with racemic citalopram embryo-fetal effects in terms of decreased foetal growth and survival, an increased incidenceof foetal abnormalities (including cardiovascular and skeletal defects, and delays in ossification) were noted at 112 mg/kg/day (approximately 18 times the maximum recommended human dose of 60 mg/day citalopram on a body surface area [mg/m^2] basis).

In an embryo-fetal developmental toxicity study with racemic citalopram (0.8, 3.2 or 12.8 mg/kg/day in female rabbits during the period of organogenesis no effects on embryo-foetal development were noted. The NOEL for maternal toxicity was 3.2 mg/kg/day and 12.8 mg/kg/day for developmental toxicity.

When female rats were orally treated with escitalopram (6, 12, 24, or 48 mg/kg/day) or racemic citalopram (12 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 at 48 mg/kg/day for both compounds. The NOEL for maternal and reproductive toxicity of citalopram was 12 mg/kg/day. The corresponding NOEL and no-observed-adverse- effect-level for escitalopram for reproductive and maternal effects were 24 mg/kg/day, which is approximately 12 times the maximum recommended human dose on a mg/m^2 basis.

Male Fertility
Animal data have shown that some SSRIs induce a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess ofhuman exposure. Citalopram was further shown to be genotoxic to mouse germ cells at the recommended human doses after 4 weeks of chronic exposure, resulting in increased spermDNA strand breaks, aberrant primary spermatocytes and oxidative DNA damage. No animal data related to this aspect are available for escitalopram.

17 SUPPORTING PRODUCT MONOGRAPHS

1. ^{Pr}Cipralex® (escitalopram oxalate), Tablets, 5, 10, 15, 20 mg, submission control 253398, Product monograph, Lundbeck Canada Inc., Date of Revision: January 12, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrBio-ESCITALOPRAM

Escitalopram Oxalate Tablets

Read this carefully before you start taking **Bio-ESCITALOPRAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Bio-ESCITALOPRAM**.

What is Bio-ESCITALOPRAM used for?

Bio-ESCITALOPRAM is used to relieve the symptoms of depression or obsessive compulsive disorder (OCD) in adults. Your healthcare professional will keep evaluating if Bio-ESCITALOPRAM is still safe and effective for you if you take it for a long time.

How does Bio-ESCITALOPRAM work?

Bio-ESCITALOPRAM is known as an antidepressant and belongs to a group of medicines called selective serotonin reuptake inhibitors (SSRIs).

Bio-ESCITALOPRAM works by increasing the levels of a chemical in the brain called serotonin. Changes in the amount of serotonin in your brain can contribute to the development of depression and related diseases.

What are the ingredients in Bio-ESCITALOPRAM?

Medicinal ingredient: Escitalopram oxalate
Non-medicinal ingredients: Croscarmellose sodium, colloidal silicon dioxide, hydroxylpropyl methyl cellulose, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose and titanium dioxide. Isopropyl alcohol and methylene chloride are present in trace amounts.

Bio-ESCITALOPRAM comes in the following dosage forms:

As tablets containing 5 mg, 10 mg, 15 mg or 20 mg escitalopram (as escitalopram oxalate)

Do not use Bio-ESCITALOPRAM if:

- you are allergic to escitalopram oxalate
- you are allergic to any of the other ingredients in Bio-ESCITALOPRAM or to a component of the container
- you are also taking the medicine pimozide, used to treat schizophrenia
- you are currently taking or have recently taken medicines called monoamine oxidase antidepressants such as phenelzine sulphate, tranilcypromine or moclobemide, or othermonoamine oxidase inhibitors such as linezolid, methylene blue, selegiline.
- you have been told that you have QT interval prolongation or have been diagnosed with a congenital long QT syndrome

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Bio-ESCITALOPRAM. Talk about any health conditions or problems you may have, including if you:

- have heart problems
- have diabetes; Bio-ESCITALOPRAM may make it more difficult to control your blood sugar
- have liver or kidney problems
- have or have had a seizure disorder
- have or have had manic episodes or have been diagnosed with bipolar disorders
- are receiving Electroconvulsive Therapy (ECT)
- have a bleeding disorder or have been told that you have low platelets
- have a family history of QT/QTc prolongation (abnormal electrical activity of the heart).
- have electrolyte disturbances like low blood potassium, magnesium, or calcium levels) or conditions that could lead to this such as vomiting, diarrhea, dehydration
- had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- are taking any medications (prescription or non-prescription) or have taken within the last 14 days, especially monoamine oxidase inhibitors, pimozide, any other antidepressants, triptans used to treat migraines, lithium, opioids (including to treat pain, or drug dependence) or drugs containing tryptophan.
- ever had an allergic reaction to any medication or any of the ingredients mentioned in this leaflet.
- have habits of alcohol and/or street drug consumption.
- are taking St. John's Wort, an herbal product used to treat depression

Other warnings you should know about:

It is important that you and your healthcare professional talk regularly about how you are feeling while you are taking Bio-ESCITALOPRAM.

Bio-ESCITALOPRAM should not be used in children and adolescents under 18 years of age.

New or Worsened Emotional or Behavioural Problems
When you first start taking Bio-ESCITALOPRAM, or when your dose is changed, you might feel worse instead of better. You may get new or worsened feelings of agitation, hostility or anxiety.

Self-harm and suicide
Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. If you have thoughts of harming or killing yourself at any time, contact your healthcare professional or go to a hospital **right away**. This is more likely if you have had thoughts of harming orkilling yourself in the past. Tell your healthcare professional if you have had these thoughts before. This way, they will monitor you more closely while you are taking Bio-ESCITALOPRAM.

You may also find it helpful to tell a relative or close friend that you are depressed. Ask them to read this leaflet. Ask them to tell you if they think your depression is getting worse, or if they areworried about changes in your behaviour. Seek medical help if they notice these getting worse.

Activation of Mania
Tell your healthcare professional if you have or have had manic episodes in the past or if you have been diagnosed with bipolar disorder. Bio-ESCITALOPRAM should be used with caution if you have a history of mania/hypomania. Some patients with bipolar disorder (also known as manic depression) may enter into a manic phase when they start taking Bio-ESCITALOPRAM. Tell your healthcare professional if you experience symptoms of mania such as excessive physical activity, overactive behaviour or thoughts, increased energy, trouble sleeping, racing thoughts, reckless behaviour, excessive happiness or irritability, talking more or faster than usual.

Bleeding Problems
Before taking Bio-ESCITALOPRAM tell your healthcare professional if you have a bleeding disorder including low blood platelets. Drugs from the class that Bio-ESCITALOPRAM 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 blood clotting. Talk to your healthcare professional about drugs that might increase bleeding.

Pregnancy
Before taking Bio-ESCITALOPRAM, tell your healthcare professional if you are pregnant, think you might be pregnant or are planning to become pregnant. You should not take Bio-ESCITALOPRAM if you are pregnant unless you and your healthcare professional have discussed the risks and decided that you should take it. Tell your healthcare professional right away if you become pregnant while taking Bio-ESCITALOPRAM. If you take Bio-ESCITALOPRAM near the end of your pregnancy, you could have heavy vaginal bleeding shortly after giving birth.

Effects on Newborns
Some newborn babies whose mothers took medications such as Bio-ESCITALOPRAM during pregnancy have developed problems at birth. These problems include prolonged hospitalisation, breathing support and tube feeding. Symptoms can include:

- feeding and/or breathing difficulties
- bluish skin
- seizures
- body temperature changes
- vomiting
- low blood sugar
- tense or overly relaxed muscles
- vivid reflexes
- tremor
- jitteriness
- irritability
- weakness
- sleepiness, sleeping difficulties and constant crying.

In most cases, these medications were taken during the third trimester of pregnancy. These symptoms are caused by the medication itself or from the effects of suddenly stopping the medication. These symptoms normally go away over time. However, if your baby experiencesany of these symptoms, contact your healthcare professional as soon as you can.

Persistent Pulmonary Hypertension (PPHN):
If you take Bio-ESCITALOPRAM towards the end of your pregnancy, your newborn may be at risk of having a serious lung condition called Persistent Pulmonary Hypertension of the Newborn (PPHN). This causes breathing problems in newborns soon after birth. Newborn babies may breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your newborn baby, get immediate medical help for them.

Breastfeeding
Tell your healthcare professional if you are breastfeeding or planning to breastfeed. Bio-ESCITALOPRAM is released into breast milk. It is not known if this is safe for your baby. You should not breastfeed a baby if you are taking Bio-ESCITALOPRAM unless you and your healthcare professional have discussed the risks and decided that you should.

Effects on the electrical activity of the heart
Bio-ESCITALOPRAM has an effect on the electrical activity of the heart known as QT/QTc prolongation (abnormal electrical activity of the heart). This can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias) that could result in dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting or cardiac arrest. This is more likely in patients with risk factors, such as heart disease, heart attack, or in the presence of certain drugs that could interact with the activity of the heart. If you experience any symptoms of a possible heart rhythm disturbance (abnormal heart rate or rhythm), such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, you should seek immediate medical attention.

Serotonin Toxicity
Serotonin toxicity (also known as Serotonin syndrome): Bio-ESCITALOPRAM can cause Serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin toxicity if you take Bio-ESCITALOPRAM with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:
- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Effects on Sexual Function:
Taking medicines like Bio-ESCITALOPRAM may cause symptoms of sexual dysfunction. In some cases these symptoms have continued after stopping Bio-ESCITALOPRAM treatment. Talk to your healthcare professional if you experience symptoms such as a decrease in sexual desire, performance or satisfaction.

Risk of Bone Fractures
Taking Bio-ESCITALOPRAM may increase your risk of breaking a bone if you are elderly, have osteoporosis or other major risk factors for breaking a bone. You should take extra care to avoid falls especially if you get dizzy or have low blood pressure.

Angle-closure Glaucoma
Bio-ESCITALOPRAM can cause dilation of the pupil. This may cause an acute glaucoma attack in an individual with narrow ocular angles. Having your eyes examined before you take Bio-ESCITALOPRAM could help identify if you are at risk of having angle-closure glaucoma. Get immediate medical attention if you experience:
- eye pain
- changes in vision
- swelling or redness in or around the eye.

Driving and using machines
Bio-ESCITALOPRAM may impair your ability to drive or to use machines. Wait until you know how Bio-ESCITALOPRAM affects you before driving or using machines. Do not drive or use machines if Bio-

ESCITALOPRAM impairs your ability to do so safely.

Discontinuation Symptoms
Contact your healthcare professional before stopping or reducing your dosage of Bio-ESCITALOPRAM. If you stop or reduce the dosage of Bio-ESCITALOPRAM abruptly, or if you miss a dose, you may experience symptoms such as dizziness, abnormal dreams, sensory disturbances like electric shock sensations, agitation, anxiety, emotional indifference, difficulty concentrating, headache, migraine, tremor (shakiness), nausea, vomiting, sweating or other symptoms. Tell your healthcare professionalimmediately if you have these or any other symptoms. Your healthcare professional may adjust the dosage of Bio-ESCITALOPRAM to reduce the symptoms.

Tell your healthcare professional about all the medicines you take, including any drugs,vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not use Bio-ESCITALOPRAM if you are taking or have recently taken:
- Monoamine oxidase inhibitor such as phenelzine, tranylcypromine, moclobemide or selegiline, linezolid (as antibiotic) or Methylene blue (intravenous)
- Pimozide

The following may interact with Bio-ESCITALOPRAM:

- drugs to treat heart rhythm disturbances (antiarrhythmics)
- antipsychotics, used to treat schizophrenia
- opioids (including for pain, drug dependence or anesthesia) such as methadone, buprenorphine, tramadol, fentanyl, tapentadol, meperidine or pentazocine
- drugs to treat infections
- diuretics (water pills)
- laxatives (including enemas)
- other SSRIs (citalopram) or any other antidepressant (e.g., imipramine, desipramine) used to treat depressions
- lithium, used to treat mood disorder
- tryptophan, for sleep aid or treating anxiety
- cimetidine, for acidity problems
- triptans (e.g., sumatriptan, zolmitriptan, naratriptan) for migraine
- fluconazole, for treating fungal infection
- ketoconazole, for treating fungal infection
- itraconazole, for treating fungal infection
- warfarin, used to prevent clot of blood
- omeprazole, used to treat stomach problems
- any herbal product such as St. John's Wort
- certain medicines which may affect blood clotting and increase bleeding, such as oral anticoagulants (e.g., warfarin, dabigatran), acetylsalicylic acid (e.g., Aspirin®) and other non-steroidal anti-inflammatory drugs (e.g., ibuprofen)
- certain medicines used to treat cough, such as dextromethorphan.

Avoid drinking alcohol while taking Bio-ESCITALOPRAM.

How to take Bio-ESCITALOPRAM:
- Take Bio-ESCITALOPRAM exactly as your healthcare professional has told you
- Swallow tablets whole with water. Do not chew them.

- You can take Bio-ESCITALOPRAM with or without food
- Take Bio-ESCITALOPRAM once a day at the same time every day
- Continue taking Bio-ESCITALOPRAM even if you do not feel better. It may take several weeks for it to work and improvement may be gradual
- Keep taking Bio-ESCITALOPRAM for as long as your healthcare professional recommends. Do not stop taking Bio-ESCITALOPRAM abruptly even if you feel better unless your healthcare professional has told you to.
- Never take more Bio-ESCITALOPRAM than your healthcare professional has prescribed for you.
- Follow all instructions given to you by your healthcare professional.

Usual dose:

The usual dose is one 10 mg tablet once a day. Your healthcare professional might prescribe a lower dose to you if you are elderly, have liver problems or in other situations.

Overdose:

Some of the signs of an overdose could be dizziness, tremor, agitation, sweating, drowsiness, coma, nausea, vomiting, change in heart rhythm, decreased blood pressure and seizure.

If you think you, or a person you are caring for, have taken too much Bio-ESCITALOPRAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget a dose, take the next dose as planned. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using Bio-ESCITALOPRAM?

These are not all the possible side effects you may have when taking Bio-ESCITALOPRAM. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea,
- increased sweating,
- diarrhea,
- fatigue,
- fever,
- constipation,
- clogged or runny nose,
- sleep disturbance,
- loss of appetite,
- increased appetite,
- increased weight,
- decreased interest in sex,
- decreased ability to reach orgasm,
- erectile dysfunction,
- anxiety,

- restlessness,
- abnormal dreams,
- difficulties falling asleep,
- drowsiness,
- yawning,
- tremor (shakiness),
- prickling of the skin,
- dizziness,
- dry mouth,
- heartburn,
- pain in muscles and joints,
- stomach pain and changes in heart rate,
- bone fracture.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Allergic reactions: Red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes.			✓
Allergic reactions: Skin rash alone, hives alone.		✓	
Alteration of blood sugar control in patients with diabetes: Hypoglycemia (Low blood sugar): dizziness, lack of energy, drowsiness, headache, trembling, sweating or **Hyperglycemia** (high blood sugar): increased thirst, increased urination, weakness, confusion, fruity breath odour.		✓	
Bleeding problems: Bruising or bleeding from the skin, nose or other areas for longer than usual.		✓	
Hallucinations: Strange visions or sounds.		✓	

Mania: Excessive physical activity, overactive behaviour or thoughts, increased energy, trouble sleeping, racing thoughts, reckless behaviour, excessive happiness or irritability, talking more or faster than usual.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Uncontrollable movements of the body or face		✓	
Inability to urinate		✓	
RARE			
Serotonin Toxicity and Neuroleptic Malignant Syndrome (various symptoms due to high level of serotonin level in the body) **:** a combination of most or all of the following: confusion, restlessness, sweating, shaking, shivering, high fever, hallucinations, sudden jerking of the muscles, muscle stiffness, feeling very agitated or irritable, fast heartbeat. The severity can increase, leading to loss of consciousness.			✓
Low sodium level in blood: tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles.		✓	
Angle-closure Glaucoma (Increased pressure in eyes, change in vision such as hazy or blurred vision)**:** Eye pain, change in vision, swelling or redness in or around the eye.			✓
VERY RARE			
Seizures (fits)**:** Loss of consciousness with uncontrollable shaking.			✓

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.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
New or Worsened Emotional or Behavioural Problems: Anxiety, hostility or impulsivity **Akathisia:** Feeling restless and unable to sit or stand still.		✓	
Self-harm and suicide: Have thoughts of harming or killing yourself.			✓
UNKNOWN			
Heart rhythm disturbance (Abnormal heart rate or rhythm): dizziness, palpitations (sensation of rapid, pounding or irregular heart beat), fainting.		✓	
Postpartum haemorrhage (Heavy vaginal bleeding shortly after birth): Excessive vaginal bleeding after child birth.		✓	
Symptoms after discontinuation or dose reduction: Dizziness, abnormal dreams, sensory disturbance like electric shock sensations, agitation, anxiety, emotional indifference, difficulty concentrating, headache, migraine, tremor (shakiness), nausea, vomiting, sweating.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Keep Bio-ESCITALOPRAM out of the reach and sight of children.
- Store Bio-ESCITALOPRAM at room temperature (15°C -30°C) in a dry place and keep the container tightly closed.

If you want more information about Bio-ESCITALOPRAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by contacting the manufacturer, Biomed Pharma: info@biomed-pharma.ca / +1 (888) 731-6703

This leaflet was prepared by Biomed Pharma.

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