PRODUCT MONOGRAPH

# [Pr] ACT ESCITALOPRAM ODT

Escitalopram Orodispersible Tablets

10 mg & 20 mg escitalopram

**Antidepressant**

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## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | All Nonmedicinal Ingredients |
|---|---|---|
| Oral | Orodispersible Tablets / 10 mg and 20 mg | Acesulfame potassium, croscarmellose sodium, hydrochloric acid, lactose monohydrate, magnesium stearate, microcrystalline cellulose, neohesperidin-dihydrochalcone, peppermint flavour, and polacrilin potassium. Residual potassium oxalate is present in the tablet (formed *in situ*). |

### INDICATIONS AND CLINICAL USE

**Adults**

- ACT ESCITALOPRAM ODT is indicated for the symptomatic relief of Major Depressive Disorder (MDD).

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

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

**Geriatrics (≥ 65 years of age):**

Elderly patients should be administered lower doses and a lower maximum dose (**see DOSAGE AND ADMINISTRATION, Geriatrics AND WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Geriatrics**).

**Pediatrics (< 18 years of age):**

ACT ESCITALOPRAM ODT is not indicated for use in patients below the age of 18 (see **WARNINGS AND PRECAUTIONS, GENERAL, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

## CONTRAINDICATIONS

- ACT ESCITALOPRAM ODT is contraindicated in patients with known hypersensitivity to escitalopram or any of the excipients of the drug product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- Escitalopram is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome. (see also sections **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS/POST-MARKET ADVERSE REACTIONS/CARDIAC DISORDERS, 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 discontinued an SSRI and have been started on a MAOI (see **DRUG INTERACTIONS**). With the co-administration of an SSRI with MAOI, there have been reports of serious, sometimes fatal reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible fluctuations of vital signs, and mental status changes, including extreme agitation progressing to delirium and coma. Some cases presented with features resembling serotonin syndrome.

  Therefore, ACT ESCITALOPRAM ODT 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 MAO inhibitor, and methylene blue, which is a MAOI). Similarly, at least 14 days should elapse after discontinuing ACT ESCITALOPRAM ODT treatment before starting a MAOI.

- **PIMOZIDE**
  ACT ESCITALOPRAM ODT should not be used in combination with the antipsychotic drug pimozide, as results from a controlled study with racemic citalopram indicate that concomitant use is associated with an increased risk of QTc prolongation compared to pimozide alone. This apparent pharmacodynamic interaction occurred in the absence of a clinically significant pharmacokinetic interaction; the mechanism is unknown (see **DRUG INTERACTIONS**).

## WARNINGS AND PRECAUTIONS

### GENERAL

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

**Pediatrics: Placebo-Controlled Clinical Trial Data**

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

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

**Adults and Pediatrics: Additional data**

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

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

  ***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 risk of suicidal behaviours with antidepressants compared to placebo.***

**Discontinuation Symptoms**

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

#### DISCONTINUATION OF TREATMENT WITH ACT ESCITALOPRAM ODT

When discontinuing treatment, patients should be monitored for symptoms that may be associated with discontinuation (e.g. dizziness, abnormal dreams, sensory disturbances [including paraesthesias and electric shock sensations], agitation, anxiety, emotional indifference, impaired concentration, headache, migraine, tremor, nausea, vomiting and sweating) or other symptoms that may be of clinical significance (see **ADVERSE REACTIONS**). A gradual reduction in the dosage over several weeks, rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a

decrease in the dose or upon discontinuation of treatment, dose titration should be managed on the basis of the patient's clinical response (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

**ESCITALOPRAM TREATMENT DURING PREGNANCY – EFFECTS ON NEWBORNS**
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 **TOXICOLOGY, REPRODUCTION TOXICITY**). There are no adequate and well-controlled studies in pregnant women; therefore, ACT ESCITALOPRAM ODT should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

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 ACT ESCITALOPRAM ODT during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant and Nursing Women**; and **DOSAGE AND ADMINISTRATION**).

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

**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 ACT ESCITALOPRAM ODT. Elderly patients and patients with important risk factors for bone fractures should be advised of possible 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 escitalopram, cannot be excluded, and may be a potential concern for patients with osteoporosis or major risk factors for bone fractures.

**The following additional PRECAUTIONS are listed alphabetically.**

**CARCINOGENESIS AND MUTAGENESIS**

For animal data, see **Part II: TOXICOLOGY** section.

## CARDIOVASCULAR

### PATIENTS WITH CARDIAC DISEASE

Neither escitalopram nor racemic citalopram has been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical trials during the drug's premarketing assessment. 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 ≥ 60 years old, the mean decrease was approximately 0.6 bpm (see **ADVERSE REACTIONS, ECG**). Consequently, caution should be observed when ACT ESCITALOPRAM ODT 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 sections **CONTRAINDICATIONS, ADVERSE REACTIONS/POST-MARKET ADVERSE REACTIONS, CARDIAC DISORDERS**, **DRUG INTERACTIONS/QT Interval Prolongation**)

## 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). ACT ESCITALOPRAM ODT should be used with caution in diabetic patients on insulin or oral hypoglycaemic drugs.

## HEMATOLOGIC

### ABNORMAL BLEEDING

SSRIs and SNRIs, including ACT ESCITALOPRAM ODT, 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.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of ACT ESCITALOPRAM ODT and NSAIDs, ASA, or other drugs that affect coagulation (see **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 ACT ESCITALOPRAM ODT in hepatically impaired patients should be approached with caution and a lower dosage is recommended (see **DOSAGE AND ADMINISTRATION**). No information is available about the pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). ACT ESCITALOPRAM ODT should be used with additional caution in patients with severe hepatic impairment.

## NEUROLOGIC

### SEIZURES

Escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from the clinical studies. In clinical trials with escitalopram 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, ACT ESCITALOPRAM ODT should be used with caution in patients with a history of seizure disorder. ACT ESCITALOPRAM ODT 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 SYNDROME/NEUROLEPTIC MALIGNANT SYNDROME (NMS)- LIKE EVENTS

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

## OPHTALMOLOGIC

### ANGLE-CLOSURE GLAUCOMA

As with other antidepressants, ACT ESCITALOPRAM ODT 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 improvement may 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 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 to seek medical advice immediately if these symptoms present (see **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, ACT ESCITALOPRAM ODT 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 escitalopram or racemic citalopram and ECT have 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), ACT ESCITALOPRAM ODT should be used with caution in these patients (see **DOSAGE AND ADMINISTRATION**).

**SPECIAL POPULATIONS**

**Fertility, Pregnant Women and Newborns:**

**Male Fertility:** Animal data have shown that some SSRIs, may affect sperm quality (see TOXICOLOGY, Reproduction Toxicity). Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

**Pregnant Women and Newborns:**
ACT ESCITALOPRAM ODT 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 ACT ESCITALOPRAM ODT continues into the later stages of pregnancy, particularly in the third trimester. If ACT ESCITALOPRAM ODT 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 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 **WARNINGS AND PRECAUTIONS - SEROTONIN SYNDROME/NEUROLEPTIC MALIGNANT SYNDROME**). When treating a pregnant woman with ACT ESCITALOPRAM ODT during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

**Risk of PPHN and Exposure to SSRIs:**
Epidemiological studies on persistent pulmonary hypertension of the newborn (PPHN) have shown that the use of SSRIs (including escitalopram) in pregnancy, particularly use in late pregnancy, was associated with an increased risk of PPHN. PPHN occurs in 1-2 per 1,000 live births 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 20$^{th}$ 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).

**Nursing Women:**
Studies with escitalopram have not been performed in nursing mothers, but it is known that racemic citalopram is excreted in human milk and it is expected that escitalopram is also excreted into breast milk. ACT ESCITALOPRAM ODT 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.

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

**Geriatrics (≥ 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 as compared to young subjects. Consequently, elderly patients should be administered lower doses and a lower maximum dose (see **PHARMACOKINETICS** and **DOSAGE AND**

**ADMINISTRATION**).

## ADVERSE REACTIONS

### ADVERSE DRUG REACTION OVERVIEW

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

#### 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 events was 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 that of placebo were: nausea (1.5% vs. 0.2%) and ejaculation failure (1.8% vs. 0.0% of male patients).

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

### CLINICAL TRIAL ADVERSE DRUG REACTIONS

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

#### MAJOR DEPRESSIVE DISORDER

Table 1 enumerates the incidence of treatment emergent adverse events that occurred in 715 depressed patients who received escitalopram 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 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 Medical Dictionary for Regulatory Activities (MedDRA), version 9.1.

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

| Body System/Adverse Event | Percentage of Patients Reporting | |
|---|---|---|
| | Escitalopram 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 |
| 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 |

| TABLE 1<br>TREATMENT-EMERGENT ADVERSE EVENTS*<br>INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS<br>FOR MAJOR DEPRESSIVE DISORDER | | |
|---|---|---|
| **Body System/Adverse Event** | **Percentage of Patients Reporting** | |
| | **Escitalopram oxalate (n= 715)** | **Placebo (n= 592)** |
| 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 tract infection, 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 Major Depressive Disorder that compared fixed doses of escitalopram (10 mg/day and 20 mg/day) with placebo, the most common adverse events that occurred in patients treated with escitalopram are shown in Table 2.

| TABLE 2<br>INCIDENCE OF COMMON ADVERSE EVENTS[1]<br>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. This is a difficult area to study because patients may not spontaneously report symptoms of this nature, and therefore, it is thought that sexual side effects with SSRIs may be underestimated.

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

| TABLE 3<br>INCIDENCE OF SEXUAL SIDE EFFECTS IN<br>PLACEBO-CONTROLLED CLINICAL TRIALS<br>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 |

## 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.

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

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

**ADVERSE REACTIONS DURING TREATMENT FOR UP TO 44 WEEKS**

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

LESS COMMON CLINICAL TRIAL ADVERSE DRUG REACTIONS

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

The events listed below present treatment emergent adverse events reported during the clinical development program of escitalopram oxalate in depressed patients (n=896), which includes a long-term clinical trial. Excluded from this list are those already listed in Table 1.

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 that occurred in less than 1/100 patients but at least in 1/1000 patients; *rare:* adverse events that occurred in less than 1/1000 but at least in 1/10000 patients.

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

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

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

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

**Endocrine Disorders**
*Rare:* Goitre, hyperthyroidism, thyroiditis.

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

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

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

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

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

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

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

**Metabolism and Nutrition Disorders**
*Infrequent:* Food craving. *Rare:* Dehydration, gout, hypercholesterolaemia, hypermagnesaemia, hyperphagia, 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**
*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, testicular pain (gs). *Rare:* Breast discharge, breast pain, breast tenderness, genital pain, menopausal symptoms (gs), uterine spasm (gs), vaginal discharge (gs), vaginal haemorrhage (gs).

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

## POST-MARKET ADVERSE DRUG REACTIONS

During the 9.5 years of post marketing experience, it is estimated that more than 265 million patients have been treated with escitalopram, which corresponds to more than 66 million patient-years of treatment.

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

**Table 4**
**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 |

| Table 4<br>Spontaneous Adverse Events | |
|---|---|
| **System Organ Class** | **Adverse Event** |
| 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 | Galactorrhoea, Menometrorrhagia, Priapism |
| Respiratory, thoracic and mediastinal disorder | Hyperventilation, Pulmonary embolism, Rhinorrhoea |
| Skin and subcutaneous tissue disorders | Angioedema, Ecchymosis, Epidermal necrolysis, Stevens-Johnson syndrome |

### 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 have been 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 ms (90% CI: 2.2, 6.4) at the 10 mg/day dose and 10.7 ms (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 sections Contraindications, Warnings and Precautions/QT Interval Prolongation, Drug Interactions/QT Interval Prolongation).

## DRUG INTERACTIONS

**Serious Drug Interactions**

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

### OVERVIEW

Escitalopram is the active enantiomer of racemic citalopram. The pharmacokinetic studies described in the following sections, whether using escitalopram 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.

**DRUG-DRUG INTERACTIONS**

**Monoamine Oxidase Inhibitors (MAOIs)**

Combined use of ACT ESCITALOPRAM ODT and MAO inhibitors is contraindicated due to the potential for serious reactions with features resembling serotonin syndrome or neuroleptic malignant syndrome (see **CONTRAINDICATIONS**; **WARNINGS AND PRECAUTIONS, Serotonin Syndrome/Neuroleptic Malignant Syndrome)**. In patients receiving SSRIs in combination with a monoamine oxidase inhibitor (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. ACT ESCITALOPRAM ODT should not be used in combination with a MAOI, (including linezolid, an antibiotic which is a reversible non-selective MAO inhibitor, 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 ACT ESCITALOPRAM ODT treatment before starting a MAOI (see **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 **DOSAGE AND ADMINISTRATION, CYP2C19 Poor metabolizers**).

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

CYP2D6, and that have a narrow therapeutic index.

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

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

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

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

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

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

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

**Drugs Affecting Platelet Function (e.g. NSAIDs, ASA and other anticoagulants)**
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the 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 an NSAID, 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 ACT ESCITALOPRAM ODT is initiated or discontinued. (see **WARNINGS AND PRECAUTIONS, Hematologic, Abnormal Bleeding)**

**Racemic 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, the concomitant 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 of escitalopram 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 ACT ESCITALOPRAM ODT 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 also sections **CONTRAINDICATIONS, ADVERSE REACTIONS/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 **DOSAGE AND ADMINISTRATION, CYP2C19 Poor metabolizers**). Although no significant change in exposure was observed in poor metabolizers with respect to CYP2D6, caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolized by this enzyme, and that have a narrow therapeutic index.

## Interaction data which include studies conducted with escitalopram oxalate

| Table 5<br>Established or Predicted Drug-Drug Interactions with escitalopram | | | |
|---|---|---|---|
| **Escitalopram** | **Reference** | **Effect** | **Clinical Comment** |
| Cimetidine | CT | Co-administration of cimetidine (400 mg twice daily for 5 days), a moderately potent CYP2D6, 3A4 and 1A2 inhibitor, with escitalopram 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 6<br>Established or Predicted Drug-Drug Interactions with racemic citalopram | | | |
|---|---|---|---|
| **Racemic Citalopram** | **Reference** | **Effect** | **Clinical Comment** |
| Carbamazepine | CT | Carbamazepine, titrated to 400 mg/day, was given for 21 days alone and then in combination with racemic citalopram (40 mg/day) for an additional 14 days. Citalopram did not affect the plasma levels of carbamazepine, a CYP3A4 substrate, or its metabolite, carbamazepine-epoxide | Since carbamazepine is a microsomal enzyme inducer, the possibility that carbamazepine may increase the clearance of escitalopram should be considered if the two drugs are given concomitantly |
| Digoxin | CT | Administration of racemic citalopram (40 mg/day for 21 days) did not affect the pharmacokinetics of digoxin (single dose of 1 mg). The serum levels of citalopram were slightly lower in the presence of digoxin but with no clinical relevance | |
| Ketoconazole | CT | Combined administration of racemic citalopram (40 mg single dose) and the potent CYP3A4 inhibitor ketoconazole (200 mg single dose) decreased the $C_{max}$ of ketoconazole by 21% and did not affect the pharmacokinetics of racemic citalopram | |
| Levomepromazine | CT | Co-administration of racemic citalopram (40 mg/day for 10 days) and a CYP2D6 inhibitor, levomepromazine (single dose of 50 mg) did not affect the pharmacokinetics of either drug | |
| 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 | |

| Table 6<br>Established or Predicted Drug-Drug Interactions with racemic citalopram | | | |
|---|---|---|---|
| **Racemic Citalopram** | **Reference** | **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

### DRUG-FOOD INTERACTION

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

### DRUG-HERB INTERACTIONS

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

### DRUG-LABORATORY TEST INTERACTIONS

Interactions with laboratory test have not been established.

## DOSAGE AND ADMINISTRATION

### DOSING CONSIDERATION

- **General**: ACT ESCITALOPRAM ODT should be administered as a single oral daily dose, with or without food.

- **ACT ESCITALOPRAM ODT is not indicated for use in children under 18 years of age** (see **WARNINGS AND PRECAUTIONS, POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

- **ACT ESCITALOPRAM ODT orodispersible tablets:** The orodispersible tablet should be placed on the tongue, where it rapidly disintegrates and can be swallowed without water. The orodispersible tablet is fragile and should be handled carefully.

Since ACT ESCITALOPRAM ODT tablets are only available as 10 and 20 mg, they cannot be used when 5 mg or 15 mg doses are required.

## RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

### ADULTS

#### MAJOR DEPRESSIVE DISORDER

ACT ESCITALOPRAM ODT should be administered as a single oral dose of 10 mg daily. Depending on individual patient response, an increase in the dose to a maximum of 20 mg daily should be considered. Where initial sensitivity to adverse events may be a concern, escitalopram could be started at 5 mg daily and titrated upwards as tolerated. Since ACT ESCITALOPRAM ODT is only available as 10 mg and 20 mg tablets, they cannot be used when 5 mg or 15 mg doses are required.

#### TREATMENT OF PREGNANT WOMEN

The safety of escitalopram during pregnancy has not been established. Therefore, ACT ESCITALOPRAM ODT should not be used during pregnancy, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible risk to the foetus.

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

#### ELDERLY PATIENTS

A longer half-life and decreased clearance have been demonstrated in the elderly. Initial dosage is 5 mg once daily. Since ACT ESCITALOPRAM ODT is only available as 10 mg and 20 mg tablets, they cannot be used when 5 mg doses are required. Depending on individual patient 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), ACT ESCITALOPRAM ODT 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. Since ACT ESCITALOPRAM ODT is only available as 10 mg and 20 mg tablets, they cannot be used when 5 mg doses are required. Subsequently, the dose may be increased based on the patient's response and clinical judgement. A daily dose of 10 mg is the recommended maximum dose for most patients with hepatic impairment. No information is available about the

pharmacokinetics of escitalopram in patients with severe hepatic impairment (Child-Pugh Criteria C). ACT ESCITALOPRAM ODT 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. Since ACT ESCITALOPRAM ODT is only available as 10 mg and 20 mg tablets, they cannot be used when 5 mg doses are required. Depending on the individual response, the dose may be increased to a maximum of 10 mg.

**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 ACT ESCITALOPRAM ODT. Similarly, at least 14 days should be allowed after stopping ACT ESCITALOPRAM ODT before starting a MAOI (see **CONTRAINDICATIONS**).

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

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

**CHILDREN**
See **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM** under **WARNINGS AND PRECAUTIONS**.

**MISSED DOSE**

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

## OVERDOSAGE

Clinical data on escitalopram overdose are limited and many cases involve concomitant overdoses of other drugs. In the majority of cases mild or no symptoms have been reported. Fatal cases of escitalopram overdose have rarely been reported with escitalopram alone (doses unknown); the majority of cases have involved multiple drug overdose. Doses up to 800 mg of

escitalopram alone have been taken without any severe symptoms.

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

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

Fatal cases of serotonin syndrome have been reported in patients who took overdoses of moclobemide (Manerix®) and racemic citalopram. The plasma concentrations of moclobemide were between 16 and 90 mg/L (therapeutic range: 1 to 3 mg/L) and those of racemic citalopram between 0.3 and 1.7 mg/mL (therapeutic concentration: 0.3 mg/L). This indicates that a relatively low dose of citalopram, given with an overdose of moclobemide represents a serious risk for the patient.

Symptoms most often accompanying overdose of racemic citalopram included dizziness, sweating, nausea, vomiting, tremor, 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 immediately.

## ACTION AND CLINICAL PHARMACOLOGY

Escitalopram (S-citalopram) is the active enantiomer of the racemic drug citalopram. *In vitro*

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

Escitalopram has no or very low affinity for a series of receptors including 5-$HT_{1A}$, 5-$HT_2$, dopamine $D_1$ and $D_2$ receptors, $\alpha_1$, $\alpha_2$, 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.

**PHARMACOKINETICS**

The single and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic with a mean terminal half-life of about 27-32 hours. With once daily dosing, steady-state plasma levels are achieved within approximately 1 week. At steady state, the plasma concentration of escitalopram in young healthy subjects was approximately 2.6 times that observed after a single dose.

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

**METABOLISM AND ELIMINATION:** The plasma clearance following oral administration is about 0.6 L/min with approximately 7% due to renal clearance. Escitalopram is metabolized in the liver to S-demethylcitalopram (S-DCT) and to S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. After multiple-dose administration of escitalopram, the mean plasma concentrations of the metabolites S-DCT and S-DDCT are usually 28-31% and <5% of the parent compound concentration, respectively. Results from *in vitro* studies suggest that the metabolites (S-DCT and S-DDCT) do not contribute significantly to the clinical actions of escitalopram.

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

**CARDIAC SAFETY:** See section **POST-MARKET ADVERSE DRUG REACTIONS, Cardiac Disorders**.

**SPECIAL POPULATIONS**

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

**Gender:** In a multiple dose study of escitalopram 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 area under the curve (AUC), $C_{max}$, and half-life between the male and the female subjects. No adjustment in dosage is recommended on the basis of gender difference.

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

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

## STORAGE AND STABILITY

ACT ESCITALOPRAM ODT (escitalopram) orodispersible tablets should be stored in a dry place in the original package in order to protect from light. Store between 15ºC to 30ºC.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Dosage Forms:

ACT ESCITALOPRAM ODT is available in 10 mg and 20 mg tablets.

| | |
|---|---|
| 10 mg: | White to off-white round, flat tablets with beveled edges and engraved with "10" on one side |
| 20 mg: | White to off-white round, flat tablets with beveled edges and engraved with "20" on one side |

### Composition:

ACT ESCITALOPRAM ODT tablets contain 10 mg or 20 mg escitalopram, and the following non medicinal ingredients: acesulfame potassium, croscarmellose sodium, hydrochloric acid, lactose monohydrate, magnesium stearate, microcrystalline cellulose, neohesperidin-dihydrochalcone, peppermint flavour, and polacrilin potassium. Residual potassium oxalate is present in the tablet (formed *in situ*).

### Packaging:

ACT ESCITALOPRAM ODT is available in blister packs of 30 tablets (2 blister strips, 15 tablets per strip).

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

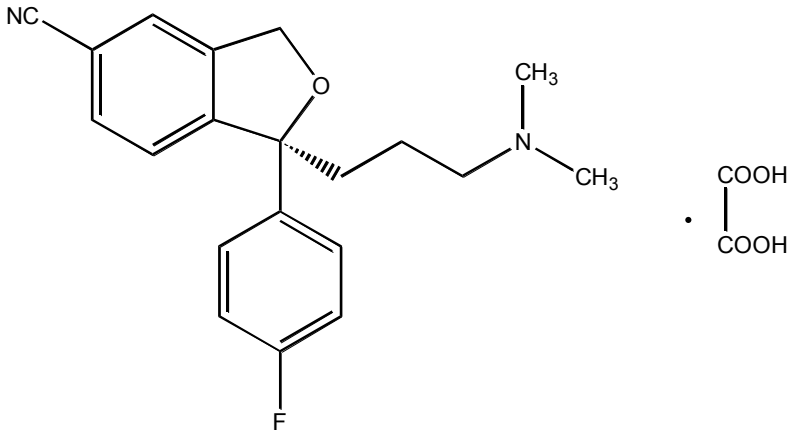
Common Name: Escitalopram Oxalate

Chemical Name: - (+)-1(S)[3-(dimethylamino)propyl]-1-(4–fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile oxalate

Molecular Formula: $C_{20}H_{21}FN_2O \cdot C_2O_4H_2$

Molecular Mass: 414.43 g/mol

Structural Formula:




Physical Form: Fine, white to slightly yellow powder
Melting Point: 149°C - 155°C
Solubility: Water (sparingly soluble)
Ethanol (sparingly soluble)
Ethyl acetate (slightly soluble)
Methanol (freely soluble)
Dimethyl sulfoxide (freely soluble)
Isopropyl alcohol (slightly soluble)
Heptane (insoluble)
Partition Coefficient: Log P (octanol/phosphate buffer pH 7.4) – 1.34

## CLINICAL TRIALS

### COMPARATIVE BIOAVIALABILITY TRIALS

A double-blinded, randomized, single dose, two way crossover comparative bioavailability study of ACT ESCITALOPRAM ODT 20 mg tablets and the Canadian Reference Product, Cipralex MELTZ® 20 mg tablets (Lundbeck Canada Inc.), was performed in 30 healthy adult subjects under fasting conditions. The study products were administered as 1 x 20 mg doses without water. A summary of the bioavailability data is presented in the table below.

| **Escitalopram ( 1 x 20 mg) From measured data Geometric Mean Arithmetic Mean (CV %)** | | | | |
|---|---|---|---|---|
| **Parameter** | **Test*** | **Reference†** | **% Ratio of Geometric Means** | **90% Confidence Interval** |
| $AUC_{0-72}$ (ng·hr/mL) | 783.14<br>796.316 (23.20%) ‡ | 790.31<br>804.78 (19.40%) | 99.09 | 95.49 – 102.83 |
| $C_{max}$ (ng /mL) | 23.46<br>24.06 (23.35%) | 23.03<br>23.36 (17.65%) | 101.84 | 98.03 – 105.80 |
| $T_{max}$ § (h) | 4.50 (2.00 – 8.00) | 4.50 (2.50 – 8.00) | | |

* ACT Escitalopram ODT 20 mg Tablets, Manufactured by Actavis Pharma Company, Canada

† Cipralex MELTZ® 20 mg Tablets, Lundbeck Canada Inc., Montreal, QC, H2Y 1N9

‡ N = 29

§ Expressed as the median (range) only

Due to the reported long terminal half-life of escitalopram, the terminal elimination constant, $K_{el}$, could not be reliably estimated in this study and therefore, parameters derived from $K_{el}$ such as $T_{1/2}$ and $AUC_I$ are not provided in the summary table.

### SAFETY AND EFFICACY TRIALS

#### MAJOR DEPRESSIVE DISORDER (MDD)

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

**ESCITALOPRAM FIXED-DOSE STUDIES**

**Study 1**
A total of 377 primary care patients with major depressive disorder were treated with 10 mg/day escitalopram 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 change from baseline to 8-week end-point (-16.3 vs. -13.6, respectively).

**Study 2**
In another study, a total of 485 outpatients with major depressive disorder were treated with 10 mg escitalopram 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 major depressive disorder 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 LONGER TERM RELAPSE OBSERVATION STUDY**

The efficacy of escitalopram oxalate in maintaining an antidepressant response in patients with major depressive disorder was demonstrated in a longer term study consisting of a 36-week placebo controlled relapse observation phase in responders of a preceding 8-week acute treatment phase. In a longer term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week, open-label treatment phase with escitalopram 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 $\leq 12$. Relapse during the double-blind phase was defined as an increase of the MADRS total score to $\geq 22$, or discontinuation due to insufficient clinical response. Patients receiving continued escitalopram oxalate experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

## DETAILED PHARMACOLOGY

Escitalopram is the S (+) enantiomer of citalopram. At clinically relevant doses, the pharmacological activity of the racemic citalopram is mediated through the S (+) enantiomer. Tolerance to the inhibition of serotonin reuptake is not induced by long-term (up to 5 weeks)

treatment of rats with escitalopram. No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted on rats with escitalopram and racemic citalopram showed a similar profile. The pharmacodynamic and pharmacokinetic properties of escitalopram are shown to parallel those of the racemate citalopram.

## ANIMAL DATA

### *IN VITRO* EXPERIMENTS

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

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

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

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

**Effect of neurotransmitter receptors**
Escitalopram has no or very low affinity for a series of receptors including 5-$HT_{1A}$, 5-$HT_2$, dopamine $D_1$ and $D_2$ receptors, $\alpha_1$-, $\alpha_2$-, β-adrenoreceptors, histamine $H_1$, muscarinic cholinergic, benzodiazepine, and opioid receptors; nor has it an action on MAO except at extremely high concentrations achievable only *in vitro*.

### BEHAVIOURAL EFFECTS

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

The 5-HT precursors tryptophan, *d,l*-5-HTP and *l*-5HTP induce in mice a characteristic 5-HT

syndrome (tremor, hyperactivity and abduction of the hind limbs). Individual behavioural changes are scored for each animal resulting in a total score that corresponds to a complete 5-HT syndrome. Concomitant acute treatment with a 5-HT reuptake inhibitor potentiates the behavioural response to the precursors. Table 7 below shows relative potencies ($ED_{50}$) of escitalopram, racemic citalopram and corresponding metabolites.

**Table 7**
**Potentiation of 5-HTP-induced behavioural changes in mice.**
**Effects of racemic citalopram and S- and R-enantiomers and the corresponding demethylated metabolites.**

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

NT = not tested

**CARDIOVASCULAR STUDIES**

Patch clamp experiments showed that escitalopram and racemic citalopram had some inhibitory effect on $I_{kr}$ and $I_{Na}$ channels, and on cardiac L-type calcium currents, but only at concentrations in the micromolar range.

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

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

**RESPIRATORY STUDIES**

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

**PHARMACOKINETICS AND METABOLISM IN ANIMAL MODELS**

Animal models have shown that the pharmacokinetics and metabolism of escitalopram does not depend on whether it is given on its own or together with the R-enantiomer in the racemate. In

addition, results of studies carried out *in vitro* and *in vivo* show lack of inter-conversion between the two enantiomers. It is considered appropriate, therefore, to combine the kinetics and other information about escitalopram when given on its own with the other knowledge available of the body's handling and responses to the racemic citalopram.

**ABSORPTION**

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

**DISTRIBUTION**

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

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

**METABOLISM**

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

**ELIMINATION**

Following the administration of $^{14}C$-labelled citalopram by oral gavage to rats, maximum excretion in urine occurred at 2-8 hours and in faeces at 8-24 hours. At a dose of 20 mg/kg,

approximately equal amounts of the dose were excreted in the urine and feces, with total recovery being about 80% of the dose. In the 4- and 13- week toxicity studies the apparent serum elimination half-life of escitalopram was generally short: about 0.8-5.5 hours in rats and about 4-8 hours in dogs. The apparent increase of the elimination half-life in the dog with increasing doses is presumably due to the saturation of the first-pass metabolism. This is consistent with the results obtained with racemic citalopram. Of the three compounds (escitalopram, S-DCT, S-DDCT), S-DDCT appears to have the longest elimination half-life (about 8-36 hours) in animals.

**TOXICOKINETICS**

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

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

[1] The 120 mg/kg/day dose was reduced to 100 mg/kg/day for males on day 13 and further for both genders to 80 mg/kg/day during Week 6.

[2] n=17 (10 mg) or n=16 (30 mg)

| Study/ Species | Dose ESC (mg/kg/day) Oral Route | Gender | $C_{max}$ (nmol/l) | $AUC_{0-t}$ (h•nmol/l) | Ratio of AUC values animal/human | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 10 mg/day | | 20 mg/day[3] | |
| | | | | | $C_{max}$ | $AUC_{0-t}$ | $C_{max}$ | $AUC_{0-t}$ |

[3] The 20 mg/day dose is estimated from the mean of the 10 and 30 mg/day results.
Numbers in *italics* refer to the NOEL (40 mg/kg/day) with respect to cardiac effects.
n.d.: not determined

Exposure margins of approximately up to 10 times the maximum therapeutic dose for the parent drug and up to about 30-140 times for the metabolites have been produced in the various toxicity tests of escitalopram. The data indicate that the rat resembles man most closely in its metabolism. The R/S ratio in rats for citalopram and the metabolites, DCT and DDCT, is comparable to that found in humans. However, there are some quantitative differences in the pharmacokinetics and metabolism of citalopram and escitalopram in man and animals. The most important is the lesser degree of first pass metabolism in humans relative to animals, which results in proportionately lower circulating levels of S-DCT and S-DDCT in humans.

## TOXICOLOGY

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

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

### ACUTE TOXICITY

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

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

### SUBCHRONIC AND REPEATED DOSE TOXICITY

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

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

In the 13-week toxicity experiments in the rat, it was demonstrated that the pattern of toxic actions of escitalopram was similar to that of citalopram. Toxic actions mainly comprised

hepatic enlargement and inflammation of the myocardium at high dose levels, plus typical phospholipidosis seen with many cationic amphophilic medicines. There were also clinical signs including reduced weight gain, sedation and trembling. The NOEL was about 5-10 mg/kg/day for both compounds.

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

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

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

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

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

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

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

presence of diazepam in order to prevent convulsions), 5 out of 9 dogs died due to ventricular fibrillation. At these doses, the plasma levels of citalopram and didemethylcitalopram were 1950 ng/mL and 300 ng/mL, respectively.

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

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

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

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

**REPRODUCTION TOXICITY**

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

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 at doses ≥ 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 incidence of 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 NOAEL 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 of human 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 sperm DNA strand breaks, aberrant primary spermatocytes and oxidative DNA damage. No animal data related to this aspect are available for escitalopram.

### MUTAGENIC POTENTIAL

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 *in vitro* Chinese hamster lung cell assay, in the presence and absence of metabolic activation.

### CARCINOGENICITY

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

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## PART III: CONSUMER INFORMATION

**PrACT ESCITALOPRAM ODT**
Escitalopram Orodispersible Tablets

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

## ABOUT THIS MEDICATION

**What the medication is used for:**
ACT ESCITALOPRAM ODT has been prescribed to you by your doctor to relieve your symptoms of depression. **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

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

ACT ESCITALOPRAM ODT is thought to work by increasing the levels of a chemical in the brain called serotonin (5-hydroxytryptamine). Disturbances in the serotonin-system are considered an important factor in the development of depression and related diseases.

**When it should not be used:**
- Do not use ACT ESCITALOPRAM ODT at the same time as pimozide.
- Do not use ACT ESCITALOPRAM ODT if you are currently or have recently taken monoamine oxidase anti-depressants (e.g. phenelzine sulphate, moclobemide).
- Do not take ACT ESCITALOPRAM ODT if you are allergic to it, or to any of the components of its formulation (for list of components see the section on "What the nonmedicinal ingredients are").
- Stop taking ACT ESCITALOPRAM ODT and contact your doctor immediately if you experience an allergic reaction or any severe side effect.
- Do not use ACT ESCITALOPRAM ODT if you have been diagnosed with a congenital long QT syndrome.

**What the medicinal ingredient is:**
Escitalopram

**What the nonmedicinal ingredients are:**
Acesulfame potassium, croscarmellose sodium, hydrochloric acid, lactose monohydrate, magnesium stearate, microcrystalline cellulose, neohesperidin-dihydrochalcone, peppermint flavour, and polacrilin potassium. Residual potassium oxalate is present in the tablet (formed *in situ*).

**What dosage forms it comes in:**
10 mg or 20 mg orodispersible tablets in blister packs.

## WARNINGS AND PRECAUTIONS

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

ACT ESCITALOPRAM ODT is not for use in children under 18 years of age.

**New or Worsened Emotional or Behavioural Problems**
Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type may feel worse instead of better, they may experience new or worsened feelings of agitation, hostility, anxiety, or thoughts about suicide, or harm to others. Suicidal thoughts and actions can occur in any age group but may be more likely in patients 18 to 24 years old. Should this happen to you, or to those in your care, **consult your doctor immediately**. Close observation by a doctor is necessary in this situation. **Do not discontinue your medication on your own.**

You may be more likely to think like this if you have previously had thoughts about harming yourself.

You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read this leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.

**Effects on Pregnancy and Newborns**
**If you are already taking/using ACT ESCITALOPRAM ODT and have just found out that you are pregnant, you should talk to your doctor immediately. You should also talk to your doctor if you are planning to become pregnant.**

**Possible complications at birth (from taking any newer antidepressant, including ACT ESCITALOPRAM ODT):**
Post-marketing reports indicate that some newborns whose mothers took an SSRI (Selective Serotonin Reuptake Inhibitor) such as escitalopram or other newer antidepressant during pregnancy have developed complications at birth requiring prolonged hospitalisation, breathing support and tube feeding. Reported symptoms include: feeding and/or breathing difficulties, bluish skin, seizures, body temperature changes, vomiting, low blood sugar, tense or overly relaxed muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, sleepiness, sleeping difficulties and constant crying.

In most cases, the newer antidepressant was taken during the third trimester of pregnancy. These symptoms are consistent with either a direct adverse effect of the antidepressant on the baby, or possibly a discontinuation syndrome caused by sudden withdrawal from the drug. These symptoms normally resolve over time. However, if your baby experiences any of these symptoms, contact your doctor as soon as you can.

**Persistent Pulmonary Hypertension (PPHN) and newer antidepressants:**
When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like ACT ESCITALOPRAM ODT may increase the risk of a serious lung condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), that causes breathing difficulties in newborns soon after birth, making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your doctor immediately.

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

**Risk of Bone Fractures:**
Taking ACT ESCITALOPRAM ODT may increase your risk of breaking a bone if you are elderly or have osteoporosis or have 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:**
ACT ESCITALOPRAM ODT can cause dilation of the pupil which may trigger an acute glaucoma attack in an individual with narrow ocular angles. Having your eyes examined before you take ACT ESCITALOPRAM ODT could help identify if you are at risk of having angle-closure glaucoma. Seek immediate medical attention if you experience:

- eye pain
- changes in vision
- swelling or redness in or around the eye.

**Before you use ACT ESCITALOPRAM ODT, tell your doctor:**

- All your medical conditions, including heart problems, history of seizures, manic-depressive illness, liver or kidney disease, or diabetes
- You have a bleeding disorder or have been told that you have low platelets
- If you have QT/QTc prolongation or a family history of QT/QTc prolongation
- If you have a personal history of fainting spells
- If you have a family history of sudden cardiac death at < 50 years
- If you have electrolyte disturbances (e.g., low blood potassium, magnesium, or calcium levels) or conditions that could lead to electrolyte disturbances (e.g., vomiting, diarrhea, dehydration)
- If you have an eating disorder or are following a strict diet.
- If you had a recent bone fracture or were told you have osteoporosis or risk factors for osteoporosis
- If you are pregnant or thinking of becoming pregnant, or if you are breastfeeding
- If you are receiving electroconvulsive treatment
- Any medications (prescription or non-prescription) which you are taking or have taken within the last 14 days, especially monoamine oxidase inhibitors, pimozide, any other antidepressants, triptans used to treat migraines, lithium, tramadol or drugs containing tryptophan.
- If you ever had an allergic reaction to any medication or any of the ingredients mentioned in this leaflet.
- Your habits of alcohol and/or street drug consumption.
- Any natural or herbal products you are taking (e.g. St. John's Wort).
- If you drive a vehicle or perform hazardous tasks during your work.

## INTERACTIONS WITH THIS MEDICATION

**Serious Drug Interactions**

**Do not use ACT ESCITALOPRAM ODT if you are taking or have recently taken:**

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

The following list includes some, but not all, of the drugs that may increase the risk of side-effects while receiving ACT ESCITALOPRAM ODT. You should check with your doctor or pharmacist before taking any other medication (prescription, non-prescription or natural/herbal) with ACT ESCITALOPRAM ODT.

Other drugs that may interact with ACT ESCITALOPRAM ODT include:

- Drugs to treat heart rhythm disturbances (antiarrhythmics)
- Antipsychotics
- Opioid painkillers
- Drugs to treat infections
- Diuretics (water pills)
- Laxatives (including enemas)
- Other SSRIs (citalopram) or any other antidepressant (e.g., imipramine, desipramine)
- Lithium
- Tryptophan
- Cimetidine
- Triptans (e.g., sumatriptan, zolmitriptan, naratriptan)

- Fluconazole
- Ketoconazole
- Itraconazole
- Racemic Citalopram (Celexa)
- Warfarin
- Omeprazole
- 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 pain, such as fentanyl (used in anaesthesia or to treat chronic pain), tramadol, tapentadol, meperidine, methadone, pentazocine.
- Certain medicines used to treat cough, such as dextromethorphan.

Avoid drinking alcohol while taking ACT ESCITALOPRAM ODT.

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

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

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

## PROPER USE OF THIS MEDICATION

Since ACT ESCITALOPRAM ODT is only available as 10 mg and 20 mg tablets, they cannot be used when 5 mg or 15 mg doses are required.

**Usual dose:**

- It is important that you take ACT ESCITALOPRAM ODT exactly as your doctor has instructed.

- Usually your doctor will prescribe 10 mg per day, which you will take once daily preferably at the same time each day. If you are elderly, your doctor may prescribe a lower dose. This dose may be increased. Never change the dose of ACT ESCITALOPRAM ODT you are taking, or that someone in your care is taking unless your doctor tells you to.

- You should continue to take ACT ESCITALOPRAM ODT even if you do not feel better, as it may take several weeks for your medication to work. Improvement may be gradual.

- Continue to take ACT ESCITALOPRAM ODT for as long as your doctor recommends it. Do not stop taking your tablets abruptly even if you begin to feel better, unless you are told to do so by your doctor. Your doctor may tell you to continue to take ACT ESCITALOPRAM ODT for several months. Continue to follow your doctor's instructions.

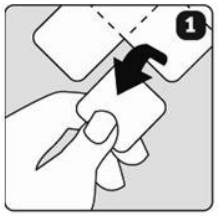
***Proper Handling Instructions***

ACT ESCITALOPRAM ODT orodispersible tablets:

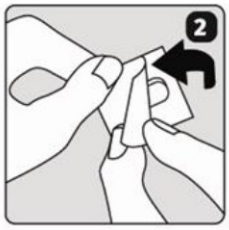
- Take everyday, as a single daily dose.
- ACT ESCITALOPRAM ODT can be taken with or without food.
- ACT ESCITALOPRAM ODT break easily, so you should handle the tablets carefully. Do not handle ACT ESCITALOPRAM ODT with wet hands as the tablets may break up.

Follow the instructions below, following the numbered diagrams:

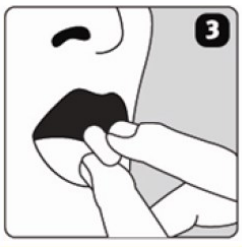
1. Hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it.




2. Carefully peel off the backing.




3. Place the tablet on your tongue. The tablet will rapidly disintegrate and can be swallowed without water.




**Overdose:**

If you have accidentally taken too much ACT

ESCITALOPRAM ODT contact your doctor, the Regional Poison Control Centre or nearest hospital emergency department immediately, even if you do not feel sick. If you go to the doctor or the hospital, take the ACT ESCITALOPRAM ODT container with you. Some of the signs of an overdose could be dizziness, tremor, agitation, convulsion, coma, nausea, vomiting, change in heart rhythm, decreased blood pressure and seizure.

If you think you have taken too much ACT ESCITALOPRAM ODT, contact your 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.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

- ACT ESCITALOPRAM ODT may cause unwanted effects (side-effects). These may include nausea, increased sweating, diarrhoea, fatigue, fever, constipation, clogged or runny nose, sleep disturbance, loss of appetite, 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.

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

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

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

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

| Symptom / effect | | Talk with your doctor or pharmacist right away | | Seek immediate emergency medical assistance |
|---|---|---|---|---|
| | | 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:** Low blood sugar (symptoms of dizziness, lack of energy, drowsiness, headache, trembling, sweating) or High blood sugar (symptoms of increased thirst, increased urination, weakness, confusion, fruity breath odour) | | √ | |
| | **Low platelets:** Bruising or unusual bleeding from the skin or other areas | | √ | |
| | **Hallucinations:** Strange visions or sounds | | √ | |
| | **Mania**: Overactive behaviour and thoughts | | √ | |
| | **Uncontrollable movements of the body or face** | | √ | |
| | **Inability to urinate** | | √ | |

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

| Symptom / effect | | Talk with your doctor or pharmacist right away | | Seek immediate emergency medical assistance |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Rare | **Serotonin syndrome:** A combination of symptoms, possibly including: agitation, confusion, tremor, sudden jerking of muscles, high fever | | | √ |
| | **Low sodium level in blood:** Symptoms of tiredness, weakness, confusion combined with achy, stiff or uncoordinated muscles | | √ | |
| | **Glaucoma:** Eye pain, change in vision, swelling or redness in or around the eye | | √ | |
| Very Rare | **Seizures:** Loss of consciousness with uncontrollable shaking ("fit") | | | √ |
| | **Liver disorder:** Symptoms include nausea, vomiting, loss of appetite combined with itching, yellowing of the skin or eyes, dark urine | | | √ |
| | **Gastrointestinal bleeding:** Vomiting blood or passing blood in stools | | | √ |
| See Warnings & Precautions | **New or Worsened Emotional or Behavioural Problems** | | | |
| | **Akathisia:** Feeling restless and unable to sit or stand still | | √ | |
| Unknown | **Abnormal heart rate or rhythm, palpitations, fainting** | | √ | |

*This list is not a complete list of side effects. If you have any unexpected effects while taking ACT ESCITALOPRAM ODT, contact your doctor or pharmacist.*

## HOW TO STORE IT

- As with all medicines, keep ACT ESCITALOPRAM ODT out of the reach and sight of children.
- Store your ACT ESCITALOPRAM ODT orodispersible tablets in a dry place, in the original package in order to protect from light and store between 15ºC and 30ºC.
- There is an expiry date on the label. Do not use the medicine after this date.
- If your doctor tells you to stop taking your medicine you should return any leftover tablets to the pharmacist, unless the doctor tells you to keep them at home.

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

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    **Health Canada, Postal Locator 0701E**
    **Ottawa, ON**
    **K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form are available at MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects contact your health professional. The Canada Vigilance Program does not provide medical advice***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Actavis Pharma Company, at: 1-866-254-6111.

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