SUMMARY OF PRODUCT CHARACTERISTICS (SPCs)

SUICIDAL THOUGHTS AND BEHAVIORS
Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Escitalopram is not approved for use in pediatric patients less than 7 years of age.

1. NAME OF THE MEDICINAL PRODUCT

Citanew Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Citanew 10mg Tablet
Each tablet contains:
Escitalopram (as Oxalate) 10mg

Citanew 20mg Tablet
Each tablet contains:
Escitalopram Oxalate eq. to Escitalopram 20mg

3. PHARMACEUTICAL FORM

Film coated tablets.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Escitalopram is indicated for the treatment of:

- Major depressive disorder (MDD) in adults and pediatric patients 12 years of age and older.
- Generalized anxiety disorder (GAD) in adults and pediatric patients 7 years of age and older.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

4.2.1. Major Depressive Disorder

Adults

The recommended dosage of Escitalopram in adults is 10 mg once daily. A fixed-dose trial of Escitalopram demonstrated the effectiveness of both 10 mg and 20 mg of Escitalopram, but failed to demonstrate a greater benefit of 20 mg over 10 mg.

Depending on clinical response and tolerability, dosage may be increased to the maximum recommended dosage of 20 mg once daily at an interval of no less than 1 week.

Pediatric Patients 12 years of age and older

The recommended dosage of Escitalopram in pediatric patients 12 years of age and older is 10 mg once daily. Depending on clinical response and tolerability, dosage may be increased to the maximum recommended dosage of 20 mg once daily at an interval of no less than 3 weeks.

4.2.2. Generalized Anxiety Disorder

Adults

The recommended starting dosage of Escitalopram in adults is 10 mg once daily. Depending on clinical response and tolerability, dosage may be increased to the maximum recommended dosage of 20 mg once daily at an interval of no less than 1 week.

Pediatric Patients 7 years of age and older

The recommended starting dosage of Escitalopram for pediatric patients ages 7 years of age and older is 10 mg once daily. Depending on clinical response and tolerability, dosage may be increased to the maximum recommended dosage of 20 mg once daily at an interval of no less than 2 weeks.

4.2.3. Administration Information

Administer Escitalopram orally once daily, in the morning or evening, with or without food.

4.2.4. Screen for Bipolar Disorder Prior to Starting Escitalopram

Prior to initiating treatment with Escitalopram or another antidepressant, screen patients for a personal family history of bipolar disorder, mania, or hypomania.

4.2.5. Recommended Dosage for Specific Populations

The recommended dosage for most elderly patients and patients with hepatic impairment is 10 mg once daily. The recommended dosage for Escitalopram in adults with a creatinine clearance less than 20 mL/minute has not been determined. No dosage adjustment is necessary for patients with mild or moderate renal impairment.

4.2.6. Discontinuation of Treatment with Escitalopram

Symptoms associated with discontinuation of Escitalopram and other SSRIs and SNRIs have been reported. Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose

may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

4.2.7. Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with Escitalopram. Conversely, at least 14 days should be allowed after stopping Escitalopram before starting an MAOI intended to treat psychiatric disorders.

4.3. CONTRAINDICATIONS

Escitalopram is contraindicated in patients:

- Taking MAOIs with Escitalopram or within 14 days of stopping treatment with Escitalopram because of an increased risk of serotonin syndrome. The use of Escitalopram within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated. Starting Escitalopram in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome.
- Taking pimozide.
- With a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Escitalopram.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1. Suicidal Thoughts and Behaviors in Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in the antidepressant-treated patients aged 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts and Behaviors per 1000

	Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18 to 24 years old	5 additional patients
	Decreases Compared to Placebo
25 to 64 years old	1 fewer patient
≥65 years old	6 fewer patients

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing Escitalopram, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

4.4.2. Serotonin Syndrome

SSRIs, including Escitalopram, can precipitate serotonin syndrome, a potentially life-threatening condition. The risk is increased with concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, meperidine, methadone, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort) and with drugs that impair metabolism of serotonin, i.e., MAOIs.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination) seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

The concomitant use of Escitalopram with MAOIs is contraindicated. In addition, do not initiate Escitalopram in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection). If it is necessary to initiate treatment with an MAOI such as linezolid or intravenous methylene blue in a patient taking

Escitalopram, discontinue Escitalopram before initiating treatment with the MAOI.

Monitor all patients taking Escitalopram for the emergence of serotonin syndrome. Discontinue treatment with Escitalopram and any concomitant serotonergic agents immediately if the above symptoms occur and initiate supportive symptomatic treatment. If concomitant use of Escitalopram with other serotonergic drugs is clinically warranted, inform patients of the increased risk for serotonin syndrome and monitor for symptoms.

4.4.3. Discontinuation Syndrome

During marketing of Escitalopram and other SSRIs, there have been spontaneous reports of adverse reactions occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.

Monitor for these symptoms when discontinuing treatment with Escitalopram. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

4.4.4. Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Escitalopram has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Escitalopram, cases of convulsion have been reported in association with Escitalopram treatment. Like other drugs effective in the treatment of major depressive disorder, Escitalopram should be introduced with care in patients with a history of seizure disorder.

4.4.5. Activation of Mania or Hypomania

In patients with bipolar disorder, treating a depressive episode with Escitalopram or another antidepressant may precipitate a mixed/manic episode. In placebo-controlled trials of Escitalopram in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Escitalopram and in none of the 592 patients treated

with placebo. One additional case of hypomania has been reported in association with Escitalopram treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. Prior to initiating treatment with Escitalopram, screen patients for any personal or family history of bipolar disorder, mania, or hypomania.

4.4.6. Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs, including Escitalopram. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and was reversible when Escitalopram was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk. Consider discontinuation of Escitalopram in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

4.4.7. Increased Risk of Bleeding

Drugs that interfere with serotonin reuptake inhibition, including Escitalopram, increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), other antiplatelet drugs, 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. Based on data from the published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage. Bleeding events related to drugs that interfere with serotonin reuptake have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Inform patients about the increased risk of bleeding associated with the concomitant use of Escitalopram and antiplatelet agents or anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.

4.4.8. Interference with Cognitive and Motor Performance

In a study in normal volunteers, Escitalopram 10 mg daily did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Escitalopram therapy does not affect their ability to engage in such activities.

4.4.9. Angle Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs, including Escitalopram, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

4.4.10. Use in Patients with Concomitant Illness

Clinical experience with Escitalopram in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Escitalopram in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Escitalopram has not 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 studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased, and plasma concentrations were increased. The recommended dose of Escitalopram in hepatically impaired patients is 10 mg daily.

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment

have been evaluated during chronic treatment with Escitalopram, however, it should be used with caution in such patients.

4.4.11. Sexual Dysfunction

Use of SSRIs, including Escitalopram, may cause symptoms of sexual dysfunction. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Escitalopram and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying

psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Clinically important drug interactions with Escitalopram.

Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	Concomitant use of SSRIs, including Escitalopram, and MAOIs increases the risk of serotonin syndrome.
Intervention:	Escitalopram is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue.
Pimozide	
Clinical Impact:	Concomitant use of racemic citalopram with pimozide increases plasma concentrations of pimozide, a drug with a narrow therapeutic index, and may increase the risk of QT prolongation and/or ventricular arrhythmias compared to use of racemic citalopram alone.
Intervention:	Escitalopram is contraindicated in patients taking pimozide.
Other Serotonergic Drugs	
Clinical Impact:	Concomitant use of Escitalopram and other serotonergic drugs (including other SSRIs, SNRIs, triptans, tricyclic antidepressants, opioids, lithium, buspirone, amphetamines, tryptophan, and St. John's Wort) increases the risk of serotonin syndrome.
Intervention:	Monitor patients for signs and symptoms of serotonin syndrome, particularly during Escitalopram initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of Escitalopram and/or concomitant serotonergic drugs.
Drugs That Interfere with Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)	
Clinical Impact:	Concomitant use of Escitalopram and an antiplatelet or anticoagulant may potentiate the risk of bleeding.

Intervention:	Inform patients of the increased risk of bleeding associated with the concomitant use of Escitalopram and antiplatelet agents and anticoagulants. For patients taking warfarin, carefully monitor the international normalized ratio.
Sumatriptan	
Clinical Impact:	There have been post-marketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan.
Intervention:	If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.
Carbamazepine	
Clinical Impact:	Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate.
Intervention:	Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are co-administered.
Drugs Metabolized by CYP2D6	
Clinical Impact:	Coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in Cmax and a 100% increase in AUC of desipramine.
Intervention:	The clinical significance of this finding is unknown. Exercise caution during coadministration of escitalopram and drugs metabolized by CYP2D6.

4.6. FERTILITY, PREGNANCY AND LACTATION

4.6.1. Pregnancy

Risk Summary

Based on data from published observational studies, exposure to SSRIs, particularly in the month before delivery, has been associated with a less than 2-fold increase in the risk of postpartum hemorrhage.

Available data from published epidemiologic studies and post-marketing reports have not established an increased risk of major birth defects or miscarriage. There are risks of persistent pulmonary hypertension of the newborn (PPHN) and poor neonatal adaptation with exposure to selective

serotonin reuptake inhibitors (SSRIs), including escitalopram, during pregnancy. There are risks associated with untreated depression in pregnancy.
In animal reproduction studies, both escitalopram and racemic citalopram have been shown to have adverse effects on embryo/fetal and postnatal development, including fetal structural abnormalities, when administered at doses greater than human therapeutic doses.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other

adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal risk and/or embryo/fetal risk

Women who discontinue antidepressants are more likely to experience a relapse of major depression than women who continue antidepressants. This finding is from a prospective longitudinal study of 201 pregnant women with a history of major depression, who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Maternal Adverse Reactions

Use of Escitalopram in the month before delivery may be associated with an increased risk of postpartum hemorrhage.

Fetal/Neonatal adverse reactions

Neonates exposed to SSRIs or SNRIs, including Escitalopram, late in 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, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome.

Human Data

Exposure to SSRIs, particularly later in pregnancy, may increase the risk for PPHN. PPHN occurs in 1-2 per 1000 live births in the general populations and is associated with substantial neonatal morbidity and mortality.

Animal Data

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses [approximately ≥ 55 times the maximum recommended human dose (MRHD) of 20 mg/day on a mg/m2 basis]. Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 27 times the MRHD of 20 mg on a mg/m2 basis. No malformations were observed at any of the doses tested (as high as 73 times the MRHD on a mg/m2 basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 23 times the MRHD of 20 mg on a mg/m2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD of 20 mg on a mg/m2 basis.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the MRHD of 60 mg/day on a mg/m2 basis. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain).

The developmental no-effect dose was 56 mg/kg/day is approximately 9 times the MRHD on a mg/m2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day, or approximately 5 times the MRHD on a mg/m2 basis. Thus, developmental effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD of 60 mg on a mg/m2 basis. The no-effect dose was 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day, approximately 4 times the MRHD on a mg/m2 basis. A no-effect dose was not determined in that study.

4.6.2. Lactation

Risk Summary

Data from the published literature report the presence of escitalopram and desmethylescitalopram in human milk. There are reports of excessive sedation, restlessness, agitation, poor feeding and poor weight gain in infants exposed to escitalopram, through breast milk. There are no data on the effects of escitalopram or its metabolites on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for escitalopram and any potential adverse effects on the breastfed child from escitalopram or from the underlying maternal condition.

Clinical Considerations

Infants exposed to escitalopram should be monitored for excess sedation, restlessness, agitation, poor feeding and poor weight gain.

A study of 8 nursing mothers on escitalopram with daily doses of 10-20 mg/day showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram.

Pediatric Use

Major Depressive Disorder

The safety and effectiveness of Escitalopram for the treatment of major depressive disorder have been established in pediatric patients 12 years of age and older. Use of Escitalopram for this indication is supported by evidence from adequate and well-controlled studies in adults with additional evidence from an 8-week, flexible-dose, placebo-controlled study that compared Escitalopram 10 mg to 20 mg once daily to placebo in pediatric patients 12 to 17 years of age with major depressive disorder. The safety of Escitalopram was similar to adult patients with MDD.

The safety and effectiveness of Escitalopram for the treatment of major depressive disorder have not been established in pediatric patients younger than 12 years of age. In a 24-week, open- label safety study in 118 pediatric patients aged 7 to 11 years who had major depressive disorder, the safety findings were consistent with the known safety and tolerability profile for Escitalopram.

Generalized Anxiety Disorder

The safety and effectiveness of Escitalopram for the treatment of generalized anxiety disorder have been established in pediatric patients 7 years of age and older. Use of Escitalopram for this indication is supported by evidence from adequate and well-controlled studies in adults with additional evidence from an 8-week, flexible-dose, placebo-controlled study that compared Escitalopram 10 mg to 20 mg once daily to placebo in pediatric patients 7 to 17 years of age with GAD. The safety of Escitalopram was similar to adult patients with GAD.

The safety and effectiveness of Escitalopram for the treatment of generalized anxiety disorder have not been established in pediatric patients younger than 7 years of age.

Antidepressants increase the risk of suicidal thoughts and behaviors in pediatric patients.

Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as Escitalopram.

Juvenile Animal Toxicity Data

In a juvenile animal study, male and female rats were administered escitalopram at 5, 40, or 80 mg/kg/day by oral gavage from postnatal day (PND) 21 to PND 69. A delay in sexual maturation was observed in both males and females at ≥ 40 mg/kg/day with a No Observed Adverse Effect Level (NOAEL) of 5 mg/kg/day. This NOAEL was associated with plasma AUC levels less than those measured at the maximum recommended dose (MRHD) in pediatrics (20 mg). However, there was no effect on reproductive function. Increased motor activity (both ambulatory and fine movements) was observed in females prior to daily dosing at ≥ 40 mg/kg/day (3.5 times the MRHD based on AUC levels). A reversible disruption of learning and memory function was observed in males at 80 mg/kg/day with a NOAEL of 40 mg/kg/day, which was associated with an AUC level 3.5 times those measured at the MRHD in pediatrics. There was no effect on learning and memory function in treated female rats.

Geriatric Use

Approximately 69 patients (6%) of the 1,144 patients receiving escitalopram in controlled trials of Escitalopram in major depressive disorder and GAD were 60 years of age or older. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Escitalopram cannot be ruled out.

In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in subjects 65 years and older as compared to young subjects and Cmax was unchanged. The recommended dosage of escitalopram for elderly patients is 10 mg. SSRIs, including Escitalopram, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse reaction.

Of 4,422 patients in clinical studies of racemic citalopram, 1,357 were 60 and over, 1,034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the geriatric and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

Hepatic Impairment

Increased citalopram exposure occurs in patients with hepatic impairment. The recommended dosage of escitalopram in patients with hepatic impairment is 10 mg daily.

Renal Impairment

Pharmacokinetics of Escitalopram in patients with a creatinine clearance less than 20 mL/minute has not been evaluated. No dosage adjustment is necessary for patients with mild or moderate renal impairment.

Physical and Psychological Dependence

Consequently, physicians should carefully evaluate Escitalopram patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Although escitalopram has been shown not to affect intellectual function or psychomotor performance, any psychoactive medicinal product may impair judgement or skills. Patients should be cautioned about the potential risk of an influence on their ability to drive a car and operate machinery.

4.8. UNDESIRABLE EFFECTS

Adverse reactions are most frequent during the first or second week of treatment and usually decrease in intensity and frequency with continued treatment.

Tabulated list of adverse reactions

Adverse reactions known for SSRIs and also reported for escitalopram in either placebo-controlled clinical studies or as spontaneous post-marketing events are listed below by system organ class and frequency.

Frequencies are taken from clinical studies; they are not placebo corrected. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data).

System organ class	Frequency	Undesirable Effect

Blood and lymphatic system disorders	Not known	Thrombocytopenia
Immune system disorders	Rare	Anaphylactic reaction
Endocrine disorders	Not known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Decreased appetite, increased appetite, weight increased
	Uncommon	Weight decreased
	Not known	Hyponatremia, anorexia[1]
Psychiatric disorders	Common	Anxiety, restlessness, abnormal dreams, libido decreased. Female: anorgasmia
	Uncommon	Bruxism, agitation, nervousness, panic attack, confusional state
	Rare	Aggression, depersonalization, hallucination
	Not known	Mania, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Very common	Headache
	Common	Insomnia, somnolence, dizziness, paraesthesia, tremor
	Uncommon	Taste disturbance, sleep disorder, syncope
	Rare	Serotonin syndrome
	Not known	Dyskinesia, movement disorder, convulsion, psychomotor restlessness/akathisia[1]
Eye disorders	Uncommon	Mydriasis, visual disturbance
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Tachycardia
	Rare	Bradycardia
	Not known	Electrocardiogram QT prolonged Ventricular arrhythmia including torsade de pointes
Vascular disorders	Not known	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Sinusitis, yawning
	Uncommon	Epistaxis
Gastrointestinal	Very common	Nausea

disorders	Common	Diarrhea, constipation, vomiting, dry mouth
	Uncommon	Gastrointestinal hemorrhages (including rectal hemorrhage)
Hepatobiliary disorders	Not known	Hepatitis, liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Sweating increased
	Uncommon	Urticaria, alopecia, rash, pruritus
	Not known	Ecchymosis, angioedemas
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia
Renal and urinary disorders	Not known	Urinary retention
Reproductive system and breast disorders	Common	Male: ejaculation disorder, impotence
	Uncommon	Female: metrorrhagia, menorrhagia
	Not known	Galactorrhe a Male: priapism Postpartum haemorrhage[3]
General disorders and administration site conditions	Common	Fatigue, pyrexia
	Uncommon	Oedema

[1] These events have been reported for the therapeutic class of SSRIs.

[2] Cases of suicidal ideation and suicidal behaviors have been reported during escitalopram therapy or early after treatment discontinuation.

[3] This event has been reported for the therapeutic class of SSRIs/SNRIs. QT interval prolongation
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 hypokalemia, or with pre-existing QT interval prolongation or other cardiac diseases.

Class effects

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Discontinuation symptoms seen when stopping treatment.

Discontinuation of SSRIs/SNRIs (particularly when abrupt) commonly leads to discontinuation symptoms. Dizziness, sensory disturbances (including paraesthesia and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremors, confusion, sweating, headache, diarrhea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions.

Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when escitalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org '

4.9. OVERDOSE

Toxicity

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; the majority of cases have involved overdose with concomitant medications. Doses between 400 and 800mg of escitalopram alone have been taken without any severe symptoms.

Symptoms

Symptoms seen in reported overdose of escitalopram include symptoms mainly related to the central nervous system (ranging from dizziness, tremor, and agitation to rare cases of serotonin syndrome, convulsion, and coma), the gastrointestinal system (nausea/vomiting), and the cardiovascular system (hypotension, tachycardia, QT interval prolongation, and arrhythmia) and electrolyte/fluid balance conditions (hypokalemia, hyponatremia).

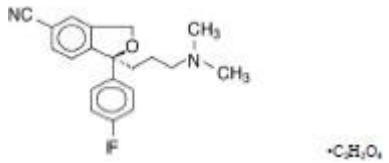
Management

There is no specific antidote. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Gastric lavage should be carried out as soon as possible after oral ingestion. Cardiac and vital signs monitoring are recommended along with general symptomatic supportive measures.

ECG monitoring is advised in case of overdose in patients with congestive heart failure/bradyarrhythmias, in patients using concomitant medications that prolong the QT interval, or in patients with altered metabolism, e.g. liver impairment.

5. PHARMACOLOGICAL PROPERTIES

Escitalopram contains escitalopram a selective serotonin reuptake inhibitor (SSRI), present as escitalopram oxalate salt. Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3(dimethyl-amino) propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414.40.

Escitalopram oxalate occurs as a fine, white to slightly yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane. Escitalopram tablets, for oral use, are film-coated, round tablets containing 6.38 mg, 12.75 mg,
25.5 mg escitalopram oxalate in strengths equivalent to 5 mg, 10 mg, and 20 mg, respectively, of escitalopram base. The 10 and 20 mg tablets are scored.

The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.

Escitalopram oral solution contains 1.29 mg/ml escitalopram oxalate equivalent to 1 mg/mL escitalopram base. It also contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor. The oral solution is not currently marketed.

Mechanism of Action

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT).

5.1. PHARMACODYNAMIC PROPERTIES

In vitro and in vivo studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least

100-fold more potent than the Renantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic (5-HT1-7) or other receptors including alpha- and beta-adrenergic, dopamine (D1-5), histamine (H1-3), muscarinic (M1-5), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na+, K+, Cl-, and Ca++ channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

5.2. PHARMACOKINETIC PROPERTIES

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

With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose.

Absorption

The absolute bioavailability of citalopram is about 80% relative to an intravenous dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.

Distribution

The binding of escitalopram to human plasma proteins is approximately 56%. The volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.

Elimination

Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.

Metabolism

Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the

antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic (5-HT1-7) or other receptors including alpha- and beta-adrenergic, dopamine (D1-5), histamine (H1-3), muscarinic (M1-5), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na+, K+, Cl-, and Ca++ channels. *In vitro* studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Excretion

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively.

Specific Populations

Pediatric Patients

Pediatric patients 7 to 11 years of age: Based on population PK simulations, following multiple dosing of 20 mg/day escitalopram, steady-state Cmax and AUCtau of escitalopram were increased by 93% and 86%, respectively in pediatric patients with GAD 7 to 11 years of age compared to adults.

Pediatric patients 12 to 17 years of age: In a single dose study of 10 mg escitalopram, AUC of escitalopram decreased by 19%, and Cmax increased by 26% in healthy pediatric subjects 12 to 17 years of age compared to adults. Following multiple dosing of 40 mg/day citalopram, escitalopram elimination half-life, steady-state Cmax and AUC were similar in pediatric patients 12 to 17 years of age with MDD compared to adults.

Geriatric Patients

Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to adults in a single-dose and a multiple-dose study.

Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and Cmax was unchanged.

Male and Female Patients

Based on data from single- and multiple-dose studies measuring escitalopram in elderly, young adults, and adolescents, no dosage adjustment on the basis of gender is needed.

Patients with Hepatic Impairment

Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects.

Patients with Renal Impairment

In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug Interaction Studies

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on

CYP3A4,
-1A2, -2C9, -2C19, and -2E1.

Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect.

CYP3A4 and CYP2C19 Inhibitors

In vitro studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Cimetidine

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg twice a day cimetidine for 8 days resulted in an increase in citalopram AUC and Cmax of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin

In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium

Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Escitalopram and lithium are co-administered.

Theophylline

Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Ketoconazole

Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the Cmax and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

Ritonavir

Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not

affect the pharmacokinetics of either ritonavir or escitalopram.

Triazolam

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 citalopram or triazolam.

Metoprolol

Administration of 20 mg/day Escitalopram for 21 days in healthy volunteers resulted in a 50% increase in Cmax and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Escitalopram and metoprolol had no clinically significant effects on blood pressure or heart rate.

Alcohol

Escitalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial. As with other psychotropic medications, the use of alcohol by patients taking Escitalopram is not recommended.

Warfarin

Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate.

Prothrombin time was increased by 5%. The clinical significance of these findings is unknown.

5.3. PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

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. It was clastogenic in the in vitro Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the in vitro mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled in vitro/in vivo unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the in vitro chromosomal aberration assay in human lymphocytes or in two in vivo mouse micronucleus assays.

Impairment of Fertility.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipient (s)

Citanew 10mg Tablet

1.1 Inactive Ingredients (Core Materials)	
Lactose 80 mesh (Tablettose 80)	USP
Microcrystalline Cellulose pH 102	USP
Povidone PVP K-30	USP
Croscarmellose Sodium	USP
Magnesium Stearate	USP
Silicon Dioxide 200	BP
1.2 Inactive Ingredients (Coating Materials)	
Opadry Pink - II # 85G54333	In-House
Deionized Water***	BP

Citanew 10mg Tablet

1.3 Inactive Ingredients (Core Materials)	
Lactose 80 mesh (Tablettose 80)	USP
Microcrystalline Cellulose pH 102	USP
Povidone PVP K-30	USP
Croscarmellose Sodium	USP
Magnesium Stearate	USP
Silicon Dioxide 200	BP
1.4 Inactive Ingredients (Coating Materials)	
Hydroxy Propyl Methyl Cellulose 606	USP
Hydroxy Propyl Cellulose	USP
Talcum Powder	BP
Titanium Dioxide	USP
Polyethylene Glycol-6000	USP
Food Color Blue No. 1 Lake	In-house
Deionized Water***	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf - Life

2 years

6.4 Special precautions for storage

Store below 30°C. Protect from sunlight & moisture. Keep out of reach of children.

6.5 Nature and contents of container

Blister pack of printed aluminium foil with PVC foil packed in printed carton along with leaflet. Pack size: 14's (1 x 14's)

7. MARKETING AUTHORIZATION HOLDER

Hilton Pharma (Pvt) Ltd.
8th & 9th Floor, Progressive Plaza,
Beaumont Road
Karachi, Pakistan.

Manufacturer:
Hilton Pharma (Pvt) Ltd. Plot. No. 13-14, Sector 15,
Korangi Industrial Area,
Karachi, Pakistan.

8. MARKETING AUTHORISATION NUMBER(S)

CTD1404

9. DATE OF THE REVISION OF THE TEXT

23/02/2026