ESCITALOPRAM

Indications

Below are the therapeutic indications for escitalopram:

1) Escitalopram is indicated for the treatment of major depressive disorder in adult patients (Agenzia Italiana del Farmaco – AIFA; Food and Drug Administration – FDA);
2) Escitalopram is indicated for the treatment of panic disorder in adult patients, with or without agoraphobia (Agenzia Italiana del Farmaco – AIFA);
3) Escitalopram is indicated for the treatment of generalized anxiety disorder in adult patients (Agenzia Italiana del Farmaco – AIFA; Food and Drug Administration – FDA);
4) Escitalopram is indicated for the treatment of social anxiety disorder (social phobia) in adult patients (Agenzia Italiana del Farmaco – AIFA).

Dosage

Monotherapy

Depression

Oral administration.

Adults: 10 mg/day as a single dose, regardless of morning or evening; if necessary, the dosage can be increased to 20 mg/day after at least one week. Food intake does not affect drug absorption. After symptom resolution, continue therapy for at least six months to consolidate the response.

Panic disorder with or without agoraphobia

Oral administration.

Adults: 5 mg/day for the first week; then increase the dose to 10 mg/day. If necessary, the dose can be further increased to 20 mg/day. Maximum therapeutic efficacy is reached after about three months.

Generalized anxiety disorder

Oral administration.

Adults: recommended dose of 10 mg/day. Maximum dose is 20 mg/day. Long-term treatment has been studied for up to six months (recurrence prevention). Periodically reassess pharmacological therapy.

Social Anxiety Disorder

Oral administration.

Adults: recommended dose of 10 mg/day. Clinical benefits are usually observable after 2-4 weeks. After this period, dosage adjustments may be made by either reducing it (minimum effective dose: 5 mg/day) or increasing it (maximum dose: 20 mg/day). Duration of treatment: at least twelve weeks. Long-term treatment in responsive patients has been studied for up to six months (recurrence prevention). Reassess pharmacological therapy periodically.

Special Patient Populations

Elderly Patients

Oral administration.

Initiate therapy with doses halved from the recommended ones.

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment, the recommended initial dose is 5 mg/day for the first two weeks. Subsequently, the dosage can be increased based on therapeutic response and drug tolerability. Maximum dose: 10 mg/day.

Patients with renal impairment

No dosage adjustment is required for escitalopram in patients with renal impairment. Administer escitalopram cautiously in patients with severe renal failure (Clcr <30 ml/min).

Slow CYP2C19 metabolizers

Initiate therapy with 5 mg/day for the first two weeks. Subsequently, assess a possible dosage increase (maximum dose: 10 mg/day). CYP2C19 is involved in escitalopram metabolism, along with CYP3A4 and CYP2D6, but compared to the latter two enzymes, CYP2C19 exhibits high genetic polymorphism.

Contraindications

Contraindications for the use of escitalopram:

1) Escitalopram is contraindicated in cases of hypersensitivity;
2) Escitalopram is contraindicated when used in combination with MAO inhibitors (increased toxicity). Escitalopram should not be administered during therapy with monoamine oxidase inhibitors and within 14 days after discontinuation of MAO inhibitors. MAO inhibitors should not be administered within 14 days following the end of escitalopram therapy.
3) Escitalopram is also contraindicated when used in combination with drugs that reversibly inhibit monoamine oxidases, such as moclobemide or linezolid. Methylene blue administered parenterally is among the drugs contraindicated in combination with escitalopram (Food and Drug Administration – FDA, 2014);
4) Escitalopram is contraindicated when used in combination with drugs that can cause prolongation of the QT interval on the electrocardiogram, in patients with QT prolongation or congenital long QT syndrome (risk of severe cardiac rhythm disturbances).

Warnings

Discontinuation syndrome/withdrawal syndrome: discontinuation of escitalopram treatment should be done gradually to reduce the risk of withdrawal syndrome. In most patients, withdrawal symptoms resolve within 2-3 weeks, but in a limited number of patients, they have persisted for a longer period (2-3 months). Withdrawal symptoms can occur when ending the treatment, changing the dosage, switching from one antidepressant to another, or if the dose is missed. Never abruptly stop escitalopram therapy when withdrawal symptoms appear.

Suicide/suicidal ideation in pediatric patients: SSRIs are not approved for treating depression in pediatric patients. Depression is rare in children (prevalence 0.5%) but increases in adolescence (prevalence 3%) and is associated with significant suicide risk (Expertise Collective Inserm, 2003). Based on the analysis of 11 clinical trials in pediatric patients treated with SSRIs for major depressive disorder (MDD), the UK Committee on Safety of Medicines (CSM) and the US FDA have found clinical efficacy data for fluoxetine and probably for citalopram, but not for paroxetine, sertraline, and venlafaxine. Moreover, SSRI use in this patient population has been linked to an increased risk of suicidal behaviors (suicidal ideation, suicide attempts, self-harm) compared to placebo (especially for paroxetine and venlafaxine, but citalopram and its S-enantiomer, sertraline, and fluoxetine are also implicated; literature data on fluvoxamine are limited).

Suicide/suicidal ideation in adult patients: as suicidal ideation is inherent to major depressive disorder and other pathological behavioral disorders, the risk of suicide remains high until clear signs of improvement associated with pharmacological therapy are evident. Therefore, It is essential to monitor signs and symptoms related to suicidal ideation, especially in the early weeks of therapy when optimal disease control has not yet been achieved and whenever the drug dosage is adjusted. Clinical data have shown a higher incidence of suicidal behavior in adult patients, compared to placebo, in the age range of 18 to 30 years. No differences were found when comparing SSRIs and tricyclic antidepressants.

Serotonin syndrome: all SSRIs can induce serotonin syndrome, a rare but potentially life-threatening adverse event. The combination with drugs with serotonergic activity (sibutramine, triptans, serotonergic drugs, St. John's Wort) increases the risk of developing this syndrome, which may include altered mental state, fever, agitation, tremors, myoclonus, hyperreflexia, ataxia, incoordination, sweating, chills, and gastrointestinal symptoms. Rarely, increased white blood cell counts, creatine phosphokinase levels, hepatic transaminase levels, or decreased serum bicarbonate, disseminated intravascular coagulation, myoglobinemia, and renal failure have been observed. Clinical manifestations do not correlate with blood serotonin concentration because what matters is its concentration at the nerve ending. Treatment of serotonin syndrome involves reducing drug dosage or drug discontinuation, sedation, external cooling, and administration of antiepileptic and antihypertensive drugs.

Gastrointestinal bleeding: observational studies suggest that SSRI use is associated with a threefold increase risk of gastrointestinal bleeding compared to non-users. The absolute risk can be considered low (3 cases of gastrointestinal bleeding requiring hospitalization per 1000 patients per year of treatment), with a relative risk similar to that associated with NSAIDs or acetylsalycilic acid (ASA) use. The risk increases when SSRIs are combined with NSAIDs or ASA, in elderly patients (>80 years old), and in patients with a positive history of gastrointestinal bleeding.

Diabetes: in diabetic patients, SSRI administration may alter glycemic control. The increase in serotonergic tone induced by the antidepressant seems to increase insulin secretion and sensitivity (Gulseren et al., 2005). Therefore, dosage adjustments of oral hypoglycemic drugs and insulin may be necessary (Sansone, Sansone, 2003).

Prolongation of QT interval: prolongation of the QT interval on the electrocardiogram, corresponding to the ventricular repolarization phase, can lead to the development of severe ventricular arrhythmias, such as "torsade de pointes". Escitalopram has been associated with episodes of QT interval prolongation, especially in women, with low blood potassium levels (hypokalemia), pre-existing QT interval prolongation, or other heart conditions. Before starting escitalopram therapy, an electrocardiogram should be performed in patients with stable heart disease; correct any existing hypokalemia and/or hypomagnesemia (risk factors for ventricular arrhythmia). If cardiac arrhythmia occurs during escitalopram therapy, discontinue the drug.

Epilepsy/seizures: monitor patients with epilepsy; if an increase in seizure frequency, discontinue escitalopram. Escitalopram is not recommended in patients with uncontrolled epilepsy.

Hyponatremia: SSRIs can induce hyponatremia (plasma sodium concentration <135 mEq/L) with a 3.5-fold increased risk (Kirby et al., 2002). In most patients, this adverse effect occurs during the first month of therapy; the risk is higher in elderly women and in patients taking diuretics. Hyponatremia manifests with confusion, seizures, fatigue, delirium, syncope, drowsiness, agitation, dizziness, hallucinations; more rarely with aggression, personality disorders, and depersonalization. Therefore, the onset of neuropsychiatric symptoms during the first month of treatment should prompt measurement of serum electrolytes. The treatment of SSRI-induced hypotonic hyponatremia in the absence of circulatory volume imbalances includes fluid restriction and mild diuresis promotion with loop diuretics. Severe cases require high doses of loop diuretics and hypertonic saline solution.

Syndrome of inappropriate antidiuretic hormone secretion (SIADH): monitor baseline sodium and urea levels and perform additional checks two weeks after starting SSRI treatment, especially if patients exhibit symptoms such as weakness, lethargy, headache, anorexia, confusion, constipation, and weight gain.

Depression and heart disease: according to available clinical studies, SSRIs appear to have minimal adverse cardiac effects and thus represent a valid therapeutic

option in treating depression in cardiac patients. In these patients, an indirect risk due to SSRI use may arise from drug-induced hyponatremia.

Diaphoresis: diaphoresis or excessive sweating is a common adverse event with antidepressant drugs. Therapy involves reducing the antidepressant dosage or discontinuing the treatment. If these measures are not possible, the administration of one of the following drugs has been associated with clinical benefit: benztropine (anticholinergic), cyproheptadine (acetylcholine, serotonin, histamine antagonist), labetalol (beta agonist), or clonidine (hypothalamic sweating).

Mania/hypomania: administer escitalopram with caution in patients with a history of mania, as the drug could trigger a relapse.

Sedation/drowsiness: caution is required in activities that require constant attention and alertness.

Substance abuse: no dedicated studies on the potential misuse of escitalopram are available: carefully assess the use of this medication in patients with a history of substance abuse.

Osteoporosis: some studies have linked SSRI therapy to an increased risk of osteoporosis. However, depression itself could promote osteoporosis through alterations in the hypothalamic-pituitary-adrenal axis activity and an increase in corticosteroid and cytokine production (Mezuk et al., 2007). In the absence of definitive data, it is advisable to periodically monitor bone density values in patients undergoing SSRI therapy, especially those also taking drugs that could negatively affect bone homeostasis, such as corticosteroids, anticonvulsants, antipsychotics increasing prolactin levels, and anticoagulants.

Electroconvulsive therapy: limited data are available regarding the administration of escitalopram in combination with electroconvulsive therapy.

Serotonergic agents (dextromethorphan, tramadol, meperidine, venlafaxine, trazodone, nefazodone, paracetamol, doxylamine, pseudoephedrine, linezolid, tryptophan, oxitriptan, risperidone): when combined with citalopram, there is an increased risk of serotonin syndrome. Agitation and nausea can occur with tryptophan and citalopram. Dextromethorphan, tramadol, and meperidine inhibit serotonin reuptake.

MAO inhibitors: do not administer escitalopram and MAO inhibitors simultaneously due to the risk of severe adverse reactions such as hyperthermia, rigidity, myoclonus, rapid fluctuations in vital signs, agitation, delirium, and coma (serotonin syndrome). Allow at least 14 days between discontinuation of MAO inhibitors and initiation of citalopram and at least one week between discontinuation of citalopram and initiation of MAO inhibitors. The risk of serotonin syndrome is higher with non-selective MAO inhibitors (tranylcypromine, phenelzine) or those selective for form A of the monoamine oxidase enzyme (moclobemide) and lower for form B of the enzyme (selegiline).

NSAIDs/acetylsalicylic acid: since both SSRIs and NSAIDs, including acetylsalicylic acid, are associated with an increased risk of upper gastrointestinal

bleeding, any pharmacological combination requires caution. If avoiding the pharmacological combination is not possible, prefer an antidepressant with low serotonin reuptake inhibition, especially in high-risk individuals. In these patients (age >65 years, positive history of peptic ulcer or gastrointestinal bleeding, debilitated patients, patients on anticoagulants or corticosteroids), consider the possibility of gastroprotective treatment.

Atypical antipsychotics: atypical antipsychotic-induced hypertension is a known adverse event. When combined with SSRIs, the risk likely increases due to pharmacometabolic inhibition of SSRIs on antipsychotics. Because the onset of hypertension is early, carefully monitor blood pressure values, especially in the initial stages of combination therapy.

Barbiturates: co-administration of SSRIs and barbiturates might lower the seizure threshold. Possible antagonism of the anticonvulsant effect.

Lithium: lithium toxicity may occur when combined with SSRIs.

Sibutramine: co-administration with SSRIs is not recommended.

Pimozide, thioridazine: the combination with some SSRIs has been associated with severe ventricular arrhythmias, including "torsades de pointes."

Neuroleptics: co-administration with SSRIs requires caution because it may promote the onset of neuroleptic malignant syndrome.

Coumarin anticoagulants: combination with SSRIs may increase the risk of non-gastrointestinal bleeding leading to hospitalization.

Pregnancy: carefully evaluate the risk/benefit ratio before administering escitalopram to pregnant women. Depression can affect up to 20% of pregnant women and has been associated with delayed fetal growth and low birth weight. Untreated maternal depression can also disrupt the mother-infant relationship (impaired parenting capacity). Clinical studies on the use of SSRIs (as a therapeutic class) have shown a low risk of congenital abnormalities (Alwan et al., 2007); individual drug analysis has revealed a correlation with septal cardiac defects and omphalocele for sertraline and paroxetine (Louik et al., 2007). Exposure to SSRIs during the third trimester of pregnancy can lead to neonatal SSRI withdrawal syndrome and persistent pulmonary hypertension (Malm et al., 2005; Chambers et al., 2006). Common withdrawal symptoms include agitation, irritability, hypo/hypertonia, hyperreflexia, drowsiness, feeding difficulties, and persistent crying. Rarely, hypoglycemia, respiratory distress, thermoregulation abnormalities, and seizures have been reported. Persistent pulmonary hypertension is a severe condition requiring intensive therapy and can result in neurological developmental abnormalities and death. The incidence is 1/100 neonates exposed to SSRIs in the second half of pregnancy compared to an incidence of 1/1000 live births in the general population. Probably, this condition is related to serotonin effects on cardiovascular development (Mills, 2006). Transplacental passage of SSRIs can cause bleeding in the newborn (Serebruany, 2006). The effects of SSRI exposure during pregnancy on children's neurobehavioral development are unknown. Pregnant

women undergoing SSRI therapy should undergo fetal ultrasound monitoring at 20 weeks to detect possible fetal malformations and monitoring for signs and/or symptoms suggestive of neonatal toxicity (respiratory distress, jaundice, seizures, PPHN).

Interactions

In vitro, escitalopram does not inhibit the enzymatic activity of CYP3A4, 1A2, 2C9, 2C19, and 2E1 and is, in turn, metabolized by multiple enzymatic systems. The potential for clinically significant pharmacokinetic interactions is therefore considered low (von Moltke et al., 2001).

Inhibitors of CYP3A4 and 2C19: although these two enzymes are involved in the metabolism of escitalopram, the administration of ritonavir, a potent CYP3A4 inhibitor, did not result in significant changes in the pharmacokinetic parameters of escitalopram (a 10% reduction in Vd) and its primary metabolite (partly obtained through CYP3A4) (a slight increase in peak plasma time) (Gutierrez et al., 2003).

CYP2D6 Metabolized drugs: in vitro, escitalopram showed no inhibitory activity on the cytochrome enzyme 2D6. In vivo, a weak inhibitory effect on CYP2D6 was observed, as demonstrated by co-administration with desipramine, a CYP2D6 substrate, resulting in a 40% increase in its peak plasma level and a 100% increase in AUC (area under the curve time-concentration). The clinical significance of this interaction is not known.

Alcohol: in clinical trials, the administration of citalopram to patients who consumed alcohol did not potentiate its effects on the nervous system. However, alcohol consumption is not recommended in depressed patients.

Anticoagulants, platelet aggregators (NSAIDs, ASA, ticlopidine): when combined with citalopram, these drugs may increase the risk of bleeding due to the gastrolesive effects of SSRIs. The combination of SSRIs and NSAIDs is associated with an absolute risk of gastrointestinal bleeding of 1 in every 80 patients treated per year; the combination of SSRIs and ASA is associated with an absolute risk of 1 in every 200 patients treated per year, compared to 1 in 300 patients treated per year for SSRIs in monotherapy and 1 in 200 patients treated per year for NSAIDs in monotherapy (Patron, Ferrier, 2005).

Antiepileptics: SSRIs antagonize the anticonvulsant effects of antiepileptic drugs, lowering the seizure threshold.

Atypical antipsychotics: Atypical antipsychotic-induced hypertension is a known adverse event. When combined with SSRIs, the risk may increase due to pharmacometabolic inhibition of SSRIs on antipsychotics. Since the onset of hypertension is early, blood pressure values should be carefully monitored, especially in the early stages of therapeutic combination.

Antivirals (darunavir, efavirenz, ritonavir): ritonavir, a potent CYP3A4 inhibitor, does not significantly alter the pharmacokinetic parameters of escitalopram (a 10% reduction in Vd) and its primary metabolite (partly obtained through CYP3A4) (a slight increase in peak plasma time) (Gutierrez et al., 2003).

Atomoxetine: when combined with SSRIs, an increased risk of seizures may occur.

Barbiturates: SSRIs antagonize the anticonvulsant effects of barbiturates, reducing the seizure threshold.

Methylene Blue: it has been hypothesized that this dye may be a weak monoamine oxidase inhibitor since its infusion for parathyroid gland localization has been associated with serotonergic neurological symptoms.

Bupropion: SSRIs can increase the plasma concentration of bupropion.

Buspirone: when combined with SSRIs, symptoms of serotonin toxicity have been observed. Buspirone is a 5-HT1A serotonin receptor antagonist used as an anxiolytic (Spigset, Adielsson, 1997).

Carbamazepine (CYP3A4 inducer): it may reduce plasma concentrations of escitalopram (Steinacher et al., 2002).

Ciproheptadine: it can antagonize the antidepressant effect of SSRIs.

Cimetidine: co-administration of escitalopram (20 mg) and cimetidine (steady-state concentrations) has been associated with a 72% increase in exposure to the antidepressant. This change is not considered to have clinical relevance (Rao, 2007).

Chlorphenamine: it inhibits serotonin reuptake and acts as a 5-HT1A receptor agonist. It can cause serotonin syndrome, especially when administered intravenously (Alisky, 2006).

Dextroamphetamine: combined use with citalopram increases the risk of serotonin syndrome due to pharmacodynamic interaction (increased synaptic serotonin concentration by both increasing neurotransmitter release and inhibiting reuptake). Since escitalopram is the D-enantiomer of citalopram, a pharmacological interaction cannot be ruled out.

Dextromethorphan: potential increase in the risk of serotonin syndrome (both drugs inhibit serotonin reuptake). The interaction has been observed with citalopram and dextromethorphan-based cough suppressant (Chris, 2006).

Duloxetine: combined use with SSRIs can increase serotoninergic effects. Co-administration require caution.

Entacapone: the manufacturer of entacapone recommends caution when co-administered with SSRIs.

Fluvoxamine: it may increase plasma concentration of escitalopram by inhibiting CYP2C19-mediated metabolism. This pharmacokinetic interaction has not been shown to affect QT interval values (Yasui-Furukori et al., 2016).

St. John's Wort: nausea, vomiting, lethargy, confusion, and anxiety, up to serotonin syndrome (enhancement of SSRIs' effects), may occur when combined with escitalopram. The combination is contraindicated.

MAO inhibitors: co-administration with escitalopram increases the risk of serotonin syndrome. The risk is higher with non-selective (tranilcipromine, phenelzine) and A-selective (moclobemide) MAO inhibitors; it is less frequent with B-selective MAO

inhibitors (selegiline, rasagiline). Serotonin toxicity symptoms occur in up to 50% of cases with moclobemide and serotoninergic drugs, with severe toxicity in 30%. Co-administration is contraindicated. Allow at least 2 weeks between the end of MAO inhibitor therapy and the start of escitalopram therapy, and at least one week between the end of escitalopram therapy and the start of MAO inhibitors.

Linezolid: in combination with SSRIs, it increases the risk of serotonin syndrome. Linezolid is an antibiotic with weak MAO-inhibitor activity. Literature reports 8 cases of serotonin syndrome attributed to linezolid combined with SSRIs or venlafaxine since market release (Bergeron et al., 2005).

Lithium: It may increase the serotoninergic effects of escitalopram and facilitate the onset of serotonin syndrome. Lithium increases the sensitivity of postsynaptic 5-HT receptors, causing a nonspecific increase in the pharmacodynamic response to serotonin.

Methylphenidate: it may inhibit SSRI metabolism.

Metoprolol: the co-administration of escitalopram (20 mg/day for 21 days) with metoprolol (a single dose of 100 mg) led to a 50% increase in peak plasma concentration and 82% increase in AUC of metoprolol. The increase in blood metoprolol concentration is associated with a reduction in cardioselectivity. However, the combination of the two drugs did not result in clinically significant changes in heart rate and blood pressure.

Pimozide: the combination with some SSRIs has been associated with severe ventricular arrhythmias, including "torsades de pointes".

Omeprazole: co-administration with escitalopram (20 mg) and omeprazole (steady state concentrations) resulted in a 51% increase in escitalopram exposure. This change was not considered clinically relevant (Rao, 2007).

Opioids: phenylpiperidine-derived opioids (meperidine, tramadol, methadone, fentanyl) weakly inhibit serotonin reuptake. Combined with SSRIs, they increase the risk of neurological toxicity (serotonin syndrome).

Sibutramine: increased risk of central nervous system toxicity when combined with SSRIs (increased risk of serotonin syndrome). Co-administration is not recommended.

Thioridazine: Combining with some SSRIs can cause severe ventricular arrhythmias, including "torsades de pointes".

Triptans (almotriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan): co-administration with escitalopram may increase the risk of hypertension and coronary vasoconstriction due to the summation of serotoninergic effects. The combination of triptans and escitalopram may increase the risk of serotonin syndrome: caution is advised. A 2018 study assessing the quantitative risk of serotonin syndrome when prescribing SSRIs and triptans found a low incidence of serotonin syndrome, ranging from 0 to 4 cases per 10,000 person-years of exposure to both drugs (Orlova et al., 2018).

Warfarin: possible increased anticoagulant effect with a higher risk of non-gastrointestinal bleeding. An analysis including citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline showed an increased risk of hospitalization for non-gastrointestinal bleeding in antidepressant users (OR: 1.7; 95% CI 1.1-2.5), but not for gastrointestinal bleeding (OR 0.8; 95% CI: 0-4-1.5). The risk of non-gastrointestinal bleeding was similar to that seen in NSAID users (OR 1.7; 95% CI: 1.3-2.2). Specific evaluation for individual SSRIs did not identify significant differences in the risk of both gastrointestinal and non-gastrointestinal bleeding (Kurdyak et al., 2005).

Side Effects

The most frequent side effects associated with the use of selective serotonin reuptake inhibitors (SSRIs) in the early stages of therapy include nausea, headache, diarrhea, irritability, insomnia, and asthenia. These dose-dependent effects tend to diminish within a few weeks. In long-term treatments, the most common adverse event is sexual dysfunction (reduced libido, delayed ejaculation, anorgasmia). The restlessness and insomnia characterizing the initial phase of treatment can be managed with the administration of benzodiazepines.

SSRIs have a lower incidence of anticholinergic effects (xerostomia, constipation) compared to tricyclic antidepressants.

In pediatric and adolescent patients, the administration of SSRIs has been significantly associated with a higher percentage of adverse drug reactions (ADRs) compared to the placebo, and these adverse effects have been more frequently deemed "severe." According to some authors, the clinical benefit associated with the use of SSRIs in children may not outweigh the risk of serious adverse effects (Jureidini et al., 2004). In some clinical studies, the fraction of pediatric patients discontinuing treatment due to ADRs was statistically higher than the placebo group (9% vs. 3%) (Wagner et al., 2003). Side effects in clinical trials with an incidence ≥2% and at least twice that of the placebo group included decreased appetite, tremor, sweating, hyperkinesia, hostile attitude, agitation, emotional lability, including crying, mood swings, self-harm, suicidal ideation, especially in patients with major depression.

Discontinuation of SSRIs, especially if not done gradually, can be associated with withdrawal syndrome characterized by gastrointestinal symptoms (nausea, vomiting, intestinal motility disorders), neurological symptoms (paresthesia, feeling of instability, dizziness, headache, tremors, dystonia, sensation of decreased strength, muscle pain), and psychiatric symptoms (anxiety, sleep disturbances, aggression and irritability, sadness, mood swings, fatigue, hot flashes). These symptoms often occur within the first 10 days after discontinuation (sleep disturbances, sensory disturbances, and dizziness have an incidence of 7%), but in most patients, these events are mild to moderate and self-limiting. Paroxetine is associated with a higher incidence of withdrawal syndrome among SSRIs.

The tolerability profile of escitalopram is similar to that of citalopram.

Adverse Reaction

Cardiovascular: postural hypotension. Sinus tachycardia, ventricular fibrillation, palpitations, and QTc interval prolongation have been reported with the racemic compound.

Central nervous system: insomnia, drowsiness, dizziness, altered sleep patterns, taste disturbances, mania, confusion, agitation, anxiety, depersonalization, panic attacks, irritability, seizures, tremors, movement disorders; rarely, serotonin syndrome, sensory hallucinations.

SSRIs have been associated with the emergence of akathisia, an extrapyramidal symptom characterized by restlessness and a constant urge to move (Lane, 1998).

Endocrine system: sexual dysfunctions, decreased libido, anorgasmia (in women), ejaculation disorders, impotence.

A case report in the literature described iatrogenic sexual dysfunction (10 mg/day of escitalopram) in a female patient, presenting with increased libido, spontaneous orgasms, and sexual behavior during sleep (Luìz-Lazaro et al., 2007).

The WHO Adverse Drug Reactions database has associated escitalopram with altered sexual function (12 reports) and abnormal orgasms (7 reports).

Eye: abnormal vision.

Gastrointestinal: nausea, vomiting, diarrhea, constipation, xerostomia, upper gastrointestinal bleeding.

SSRI administration is linked to gastrointestinal symptoms (nausea and diarrhea) due to serotonin presence in the enteric nervous system. About 95% of the body's serotonin is released by enterochromaffin cells in response to intestinal stimuli such as pressure, acidity, and chemicals. Serotonin promotes peristalsis and secretion by stimulating intrinsic sensory nerves (5-HT1P receptors); it induces nausea, vomiting, and cramps by stimulating extrinsic sensory nerves (5-HT3 receptors). Locally, serotonin action is terminated by uptake into intestinal lining cells via the serotonin transporter protein (Sert). Continuous SSRI administration leads to receptor desensitization due to prolonged serotonin stimulation (inhibition of serotonin transporter). Intestinal desensitization causes a shift from diarrhea (excessive peristalsis stimulation) to constipation (peristalsis blockade).

SSRIs have been associated with upper gastrointestinal bleeding. It has been observed that the risk of bleeding increases about threefold and is similar for all SSRIs (class effect).

General: reduced appetite, fatigue, fever, anorexia, anaphylactic reactions, pancreatitis.

Hematological: ecchymosis, purpura, epistaxis, gingival bleeding, thrombocytopenia with citalopram.

Liver/biliary: abnormal liver function tests.

Metabolic disorder: hyponatremia, inappropriate ADH secretion, hyperglycemia.

Hyponatremia is more frequent in patients over 70 years old, receiving diuretics or dehydrated. Onset varies from 3 days to 4 months after therapy initiation. Predictors for hyponatremia development include low baseline plasma sodium concentration (<138 mEq/L) and low body mass index.

Musculoskeletal: myalgia, arthralgia.

Renal: urinary retention, urinary incontinence.

Urinary incontinence risk associated with SSRIs is nearly double that of non-users; among SSRIs, sertraline carries the highest risk.

Respiratory System: sinusitis, yawning.

Skin: sweating. With citalopram, alopecia, itching, rash, and urticaria have been reported.

Major depression (escitalopram vs placebo)

In depressed patients, side effects led to therapy discontinuation in 6% of patients (vs 2% in the placebo group); 10% vs 4% vs 3%, respectively, with escitalopram 20 and 10 mg/day and placebo.

Side effects leading to treatment discontinuation at a rate double that of placebo were nausea (2%) and ejaculation disorders (2%).

Side effects occurring at an incidence ≥5% or approximately double that of placebo included insomnia, ejaculation disorders, nausea, fatigue, increased sweating, and drowsiness.

Central nervous system: insomnia (9% vs 4%), dizziness (5% vs. 3%), hyperhidrosis (5% vs 2%), drowsiness (6% vs 2%).

Endocrine: ejaculation disorders (9% vs <1%), decreased libido (3% vs 1%), impotence (3% vs <1%, male), anorgasmia (2% vs <1%, female).

Gastrointestinal: nausea (1%5 vs 7%), diarrhea (8% vs 5%), xerostomia (6% vs 5%), constipation (3% vs 1%), indigestion (3% vs 1%), abdominal pain (2% vs 1%), anorexia (3% vs 1%).

Respiratory: rhinitis (5% vs 4%), sinusitis (3% vs 2%).

Systemic: influenza-like syndrome (5% vs 4%), fatigue (5% vs 2%).

Generalized anxiety disorder (escitalopram vs placebo)

In generalized anxiety, treatment discontinuation due to adverse effects occurred in 8% of patients vs 4% in the placebo group. Side effects leading to treatment discontinuation at a rate double that of placebo were nausea (2%), insomnia (1%), and fatigue (1%).

Side effects occurring at an incidence ≥5% and approximately double that of placebo included nausea, ejaculation disorders, insomnia, fatigue, decreased libido, and anorgasmia.

Central nervous system: headache (24% vs 17%), paresthesia (2% vs 1%), drowsiness (13% vs 7%), insomnia (12% vs 6%), altered dream activity (3% vs 2%), lethargy (3% vs 1%).

Gastrointestinal: nausea (18% vs 8%), diarrhea (8% vs 6%), constipation (5% vs 4%), indigestion (3% vs 2%), vomiting (3% vs 1%), abdominal pain (2% vs 1%), flatulence (2% vs 1%), toothache (2% vs 0%), anorexia (3% vs 1%).

Endocrine: reduced libido (7% vs 2%).

Musculoskeletal: neck and shoulder pain (3% vs 1%).

Systemic: influenza-like syndrome (5% vs 4%, respectively, with escitalopram and placebo), fatigue (8% vs 2%).

Urogenital: ejaculation disorders (14% vs 2%, respectively, with escitalopram and placebo), anorgasmia (6% vs <1%), menstrual disorders (2% vs 1%).

Toxicity

Overdose: in cases of overdose (130 mg), tachycardia, dizziness, hypertension, and vomiting have been frequently reported. The incidence of seizures and tremors is lower compared to citalopram. Prolongation of the QTc interval has also been observed in fewer cases with escitalopram compared to the racemic compound (7 cases vs 14 cases respectively, out of 421 overdose episodes with escitalopram and 374 with citalopram) (Hayes et al., 2008). In case of overdose, symptomatic therapy should be initiated; consider gastric lavage or activated charcoal if possible. Due to escitalopram's high volume of distribution (Vd), forced diuresis, dialysis, or hemoperfusion are likely ineffective.

Serotonin syndrome: escitalopram can induce serotonin syndrome. This sudden-onset syndrome is caused by increased serotonin concentration in nerve endings (independent of plasma neurotransmitter concentration), and seems to primarily involve 5-HT1A receptors. The most common cause of serotonin syndrome is the cumulative effect resulting from the co-administration of drugs both directly or indirectly affecting serotonin. The most severe cases occur with the combination of MAO inhibitors and SSRIs, leading to significantly elevated brain serotonin levels due to both neurotransmitter reuptake inhibition and degradation blockade.

Serotonin syndrome can also occur with a single drug if the dosage is too high or during a switch from one active ingredient to another, especially if the first has a long half-life or pharmacologically active metabolites. A "washout" period is necessary before administering the second drug in such cases. Mild serotonin syndrome is usually self-limiting, especially if promptly recognized and managed through dosage reduction or discontinuation of the responsible medication. Resolution occurs within approximately 24 hours (70% of cases). In cases of mild to moderate serotonin syndrome, supportive therapy (sedation, external cooling, antiepileptics, antihypertensives) allows symptoms resolution within 24-36 hours. Complication-free forms rarely persist beyond 72-96 hours. Severe serotonin syndrome requires hospitalization and presents with neuromuscular effects, hyperthermia, hypoxia, rhabdomyolysis, metabolic acidosis, disseminated intravascular coagulation, and renal failure. Hyperthermia exceeding 40.5°C is associated with severe morbidity and mortality rates that can reach 12%.

Positive outcomes in serotonin syndrome treatment have been reported with cyproheptadine (antihistamine with 5-HT1A and 5-HT2 receptor antagonist activity), methysergide (specific 5-HT receptor antagonist), and chlorpromazine (antagonist activity on 5-HT1A, 5-HT2, and D2 receptors). Mixed outcomes (therapeutic success and failure) have been reported with benzodiazepines, dantrolene, and dopamine antagonists (bromocriptine and haloperidol are not recommended due to worsened serotonin syndrome). SSRIs are responsible for serotonin syndrome more frequently (33.5%) than other antidepressant classes. Among SSRIs, fluoxetine, sertraline, and paroxetine are most frequently associated with the syndrome.

Reproductive toxicity: in vivo, the administration of escitalopram during organogenesis is associated with reduced fetal weight and delayed ossification (doses

≥56 times the recommended maximum human dose); maternal toxicity, manifested as reduced body weight and decreased food consumption, is also observed. No teratogenicity was noted for escitalopram at doses up to 72 times the recommended maximum human dose. In vivo escitalopram administration during pregnancy and lactation resulted in a slight increase in perinatal mortality and delayed postnatal growth (doses equivalent to 24 times the recommended maximum human dose).

Neonatal toxicity: exposure to escitalopram in the last trimester of pregnancy is associated with complications in neonates, requiring prolonged hospitalization, intubation, and respiratory support: respiratory distress, cyanosis, apnea, seizures, thermal instability, difficulty in breastfeeding, vomiting, hypoglycemia, hypo/hypertonia, hyperreflexia, tremor, irritability, inconsolable crying. These effects can be attributed to both direct SSRI toxicity and a form of withdrawal syndrome due to discontinuation of drug intake by the mother.

Late exposure (exclusively after the 20th week of gestation) to SSRIs has been associated with the onset of persistent pulmonary hypertension of the newborn (PPHN). Fluoxetine seems to be the most implicated drug. PPHN occurs in 1-2 out of 1000 neonates and has high morbidity and mortality rates (20-30%). The proposed mechanism involves fetal pulmonary serotonin accumulation, causing proliferation of smooth muscle cells, characteristic of PPHN (besides vasoconstriction effects, serotonin also possesses mitogenic effects on pulmonary smooth muscle cells). Another mechanism considers the inhibitory effect of SSRIs on the synthesis of nitric oxide, a potent physiological vasodilator, which seems to regulate vascular tone and reactivity in both the fetus and the neonate (Chambers et al., 2006; Abman, 1999).

Serotonin is present in the very early fetal development and, besides its role as a neurotransmitter, seems to act as a growth factor and regulator toward both serotoninergic and non-serotoninergic neurons. Therefore, exposure to SSRIs during gestation might have adverse effects on fetal brain development, leading to neurological and behavioral effects in the neonate. The few available clinical data, although not uniform, suggest a lower psychomotor development index in children between 6 and 40 months of age exposed to SSRIs during pregnancy compared to non-exposed children (Oberlander et al., 2002; Morag et al., 2004; Laine et al., 2003; Zeskind, Stephens, 2004; Zeskind et al., 2005; Nulman et al., 2002; Casper et al., 2003).

Pharmacology

Escitalopram is the S-enantiomer of the racemic compound citalopram, a selective serotonin reuptake inhibitor (SSRI) employed in the treatment of depression. Among the two enantiomers of citalopram, the R-isomer is pharmacologically inactive (lacks activity at the serotonin transporter). Therefore, at equivalent dosages, escitalopram exhibits double the serotonin reuptake inhibition activity compared to the racemic compound. Escitalopram's binding affinity to the human serotonin transporter is 1.1 nmol, which is 6,000 and 25,000 times higher than its affinity for the human norepinephrine and dopamine transporters, respectively. In vitro, the serotonin reuptake inhibition induced by escitalopram is two times greater than citalopram and 100 times greater than the R-enantiomer.

Escitalopram stands out as the most selective SSRI for the serotonin system. Unlike citalopram, it lacks the weak antihistaminic activity due to the R-enantiomer's low affinity for the H1 receptor (Owens et al., 2001).

In vitro and in vivo settings, escitalopram demonstrates selectivity in inhibiting serotonin reuptake, with minimal effects on norepinephrine and dopamine reuptake. It exhibits little or no affinity for serotonin receptors (5HT1-7), alpha and beta adrenergic receptors, dopamine receptors (D1-5), histamine receptors (H1-3), muscarinic receptors (M1-5), and benzodiazepine receptors; it does not affect ion channel activity (Na+, K+, Cl-, Ca++).

Escitalopram is fully soluble in methanol and dimethyl sulfoxide, soluble in isotonic saline solution, slightly soluble in water and ethanol, poorly soluble in ethyl acetate, and insoluble in heptane.

In clinical settings, the onset of the antidepressant effects of escitalopram typically takes about 2-4 weeks. In vivo, the antidepressant action (reversal of anhedonic behavior in animal models) of escitalopram occurs more rapidly than citalopram (1 week vs 2 weeks) (Sanchez et al., 2003). It has also been observed that the R-enantiomer not only lacks pharmacological activity but also tends to attenuate the effects of the active enantiomer. Co-administration of R-citalopram reduces the increase in serotonin levels in the synaptic cleft and completely prevents the antidepressant effect of escitalopram in animal models.

The serotonin transporter, a protein responsible for neurotransmitter reuptake in nerve endings and the target of SSRI action, possesses two binding sites: a primary site responsible for pharmacodynamic action and an allosteric modulation site. Escitalopram binds to both the primary site, responsible for inhibiting serotonin transport, and the allosteric site, altering the conformation of the transport protein and stabilizing the binding between the primary site and the drug (complete blockade of the transporter). Conversely, the R-enantiomer binds only to the allosteric site, disturbing the binding between the primary site and the S-enantiomer, thereby interfering with the inhibitory activity of escitalopram (incomplete blockade of transporter activity).

Serotonin has vasoconstrictive and antiplatelet activities. Platelets, unable to synthesize serotonin, absorb it from a protein acting as a serotonin transporter. Inside platelets, serotonin accumulates in granules to be released back into the bloodstream when platelets are activated during hemostasis. Inhibition of serotonin reuptake induced by SSRIs also blocks the platelet serotonin transporter. It has been observed that SSRI treatment increases the risk of uterine bleeding, bleeding associated with orthopedic surgery in elderly patients, and upper gastrointestinal bleeding (Movig et al., 2003; van Walraven et al., 2001).

In a cohort study of patients treated for 3 months with antidepressants, the hospitalization rate for upper gastrointestinal bleeding was 3.1 episodes per 1000 treatments per year for patients treated with serotonin reuptake inhibiting antidepressants compared to non-inhibitors (Dalton et al., 2003). The addition of NSAIDs or acetylsalicylic acid (ASA) further increased the risk, respectively, by 12.2 times and 5.2 times with ASA (the risk of bleeding with low-dose ASA monotherapy was estimated to be 2.5 times higher, and with NSAIDs, 4.5 times higher, compared to non-users). The risk also increases with non-selective antidepressants (amitriptyline, dosulepin, doxepin, imipramine, lofepramine) but to a lesser extent (2.3 times) compared to SSRIs. Antidepressants without action on serotonin receptors (amoxapine, desipramine, maprotiline, mianserin, nortriptyline, and trimipramine) increase the risk by 1.8 times. Furthermore, the risk of bleeding did not seem to depend on the duration of therapy (no difference after 1 month, 2 or 6 months) (Layton et al., 2001).

In case of outpatient with major depression, escitalopram (10 or 20 mg/day) has proven superior to placebo in inducing improvements in antidepressant effect assessment scales: MADRS (Montgomery-Asberg Depression Rating Scale), CGI-I and CGI-S (Clinical Global Impression Improvement and Severity Scale), and HAM-D (Hamilton Rating Scale for Depression) (Waugh, Goa, 2003).

In the treatment of major depressive disorder, escitalopram has demonstrated a faster and more significant deviation from placebo in therapeutic efficacy evaluations compared to citalopram. In a subgroup of patients with mild depression, escitalopram exhibited greater therapeutic efficacy than citalopram after 24 weeks. It has been associated with a more enduring clinical response and rapid remission compared to venlafaxine in patients with major depression (Waugh, Goa, 2003).

Administration of escitalopram (10 mg/day) was superior to placebo in reducing depression assessment scores after 4 weeks of therapy and superior to citalopram 20 mg/day (Montgomery et al., 2001).

In patients with moderate to severe depression treated for 8 weeks with escitalopram (10-20 mg/day) and citalopram (20-40 mg/day), the S-enantiomer was more effective than citalopram in improving the "inner tension" item of the MADRS scale from the first week, an item related to anxiety associated with depression (Gorman et al., 2002). Moreover, after 8 weeks, the remission rate (MADRS ≤12) was above 50% compared to the approximately 43% achieved with citalopram (Lepola et al., 2003).

No differences in therapeutic efficacy were found between escitalopram at 10 mg/day and the racemic compound citalopram at 40 mg/day after 8 weeks of therapy; escitalopram at 20 mg/day was superior to citalopram 40 mg/day (the superiority had borderline statistical significance, P=0.06). Both drugs showed therapeutic superiority over placebo (Burke et al., 2002).

The effectiveness of long-term escitalopram treatment (36 weeks) was evaluated in a trial vs placebo, where the relapse-free period was significantly longer in the treated group compared to the placebo group, as was the relapse percentage (cumulative relapse rate: 26% vs 40% for patients with escitalopram and placebo, respectively). Additionally, 7% of patients in the placebo group discontinued treatment due to adverse events compared to 4% in the treated group (Rapaport et al., 2004).

In another study, escitalopram and citalopram, both at low doses (10 mg/day and 20 mg/day, respectively), were compared for 24 weeks. At the end of the study, no differences were found in the average change in MADRS score between the two treatments. However, at the end of the first 8 weeks, the response rate was statistically higher with escitalopram (63% vs. 55%, P<0.05). After 24 weeks, approximately 80% vs 76% of patients, respectively, with escitalopram and citalopram had responded to pharmacological treatment, and the remission rate was 76% vs 71% (not statistically significant) (Colonna et al., 2005). As the dosage selected for this study was more suitable for patients with moderate depression (i.e., MADRS score <30), a post-hoc analysis was conducted on the subgroup of patients with moderate depression. It was found that the total MADRS score significantly decreased in favor of escitalopram after both 8 and 24 weeks (for both values, P <0.05). After 8 weeks, the percentage of responsive patients was 75% vs 58% (P <0.01), and the percentage of patients in remission was 75% vs 53% (P<0.001). After 24 weeks, the differences between the two groups did not reach statistical significance (Colonna et al., 2005).

In a study designed to assess the superiority of escitalopram over citalopram, patients with severe depression (MADRS ≥30) were treated with the S-enantiomer or the racemic compound at maximum doses (20 mg/day and 40 mg/day respectively) for 8 weeks. The primary clinical outcome was represented by the change in MADRS score, which was -22.4 vs -20.3 (P <0.05) with escitalopram and citalopram respectively. Adverse events occurred in 14.8% of patients in the escitalopram group and 16.4% in the citalopram group; among these patients, 19% and 36% respectively discontinued therapy prematurely (Moore et al., 2005).

In patients with depression and heart disease, the number of deaths from heart diseases doubles, and in the 2 years following a myocardial infarction, the incidence of total mortality and cardiovascular mortality increases by 2-2.5 times (Nicholson et al., 2006; van Melle et al., 2004). SSRIs have limited effects on blood pressure and heart rate, although postural hypotension has been reported. Furthermore, their use can lead to hyponatremia and, more rarely, QTc interval prolongation. In patients with coronary artery disease, SSRIs also appear to reduce platelet function (Serebruany et al., 2001).

In patients with heart failure, depression often occurs, which is associated with unfavorable clinical outcomes. In a double-blind, placebo-controlled, randomized clinical trial, the administration of escitalopram (10-20 mg) to patients with class II-IV heart failure (New York Heart Association class) and reduced left ventricular ejection fraction (<45%), who were diagnosed with depression, did not lead to clinical benefits in terms of reducing all-cause mortality or hospitalization (primary composite clinical outcome) and improving depression (secondary clinical outcome). The incidence of all-cause mortality or hospitalization was 63% in the escitalopram-treated group and 64% in the placebo group (p=0.92). The reduction in MADRS score, used to assess depression, was 9 points (from 20.2 to 11.2) with escitalopram and 8.9 points (from 21.4 to 12.5) with placebo after 12 weeks of therapy (p=0.26). The 24 month clinical trial was terminated prematurely after 18 months (Angermann et al., 2016).

In the case of panic disorders, with or without agoraphobia (defined according to DSM-IV diagnostic criteria), the administration of escitalopram (5 mg/day for 10 weeks) was more effective than placebo in reducing symptoms, the severity of panic attacks (the average number of attacks per week pre-treatment was 5), and quality of life (Stahl et al., 2003).

In patients treated with escitalopram, the percentage of patients free from panic attacks was higher (approximately 50% vs 39%, respectively, with escitalopram and placebo). Escitalopram was also more effective in reducing the sense of anticipatory anxiety. The most frequent side effects were nausea, headache, and insomnia, with a comparable incidence in both treatment groups and resulting in therapy discontinuation in a smaller percentage of patients in the escitalopram group (6 vs 8%).

The tolerability profile of escitalopram can be considered comparable to that of citalopram. The most frequent adverse effect is nausea, which affects approximately 15% of patients. In clinical trials in elderly patients, nausea occurred at an incidence of 5.1%. There were no observed effects on weight in both short-term and long-term trials (Wade et al., 2002; Colonna et al., 2002).

Escitalopram has demonstrated therapeutic efficacy comparable to sertraline. In an 8-week study, patients with depression were treated with fixed-dose escitalopram (10 mg/day) or variable-dose sertraline (50-200 mg/day). Both clinical response and clinical remission at the end of the study were comparable, but the percentage of patients was statistically higher with escitalopram at the second, third, and sixth weeks for clinical response; at the second, third, fourth, and sixth weeks for clinical remission. While in the escitalopram-treated group, the initial dose was sufficient to treat most patients (recommended dose), in the sertraline-treated group, 65% required an upward dose adjustment (150-200 mg/day). The percentage of patients who discontinued treatment prematurely due to adverse events was 2% with escitalopram and 4% with sertraline (Alexopoulos et al., 2003).

Escitalopram was compared to venlafaxine in patients with depression in two controlled studies, one where both drugs were administered at variable doses and the other where they were given at fixed doses (20 mg/day for escitalopram and 225

mg/day for venlafaxine). In the first study, patients were treated with initial doses of 10 mg/day for the SSRI and 75 mg/day for venlafaxine. If necessary, the dose was doubled in the second and fourth weeks. Based on MADRS scores (primary clinical outcome), the two drugs showed equivalent therapeutic efficacy. Escitalopram was associated with significantly higher percentages of clinical responses to venlafaxine after the second, third, and sixth weeks. Also, regarding the percentage of patients in remission, statistically superior results were obtained with escitalopram after the second, third, fourth, and sixth weeks. The percentage of patients who discontinued pharmacological treatment early was 11% vs 8% with venlafaxine and escitalopram respectively. Nausea, constipation, and increased sweating occurred more frequently in the venlafaxine-treated group. No adverse event had a higher incidence with escitalopram (Montgomery et al., 2003).

In the fixed-dose study, patients were treated with escitalopram or venlafaxine for 8 weeks. Based on the MADRS score (primary clinical outcome), the two antidepressants showed equivalent efficacy. In the subgroup of patients with severe depression (MADRS score ≥30), the reduction in MADRS score was statistically higher in the escitalopram-treated group compared to the venlafaxine-treated group. Patients who discontinued treatment due to adverse events were 16% vs 4.1% respectively with venlafaxine and escitalopram (Bielski et al., 2003).

Escitalopram was compared to duloxetine in the treatment of major depression, both acutely and as long-term therapy, especially concerning the treatment's impact on sexual dysfunction, a common side effect associated with SSRI use. The study lasted 8 months. The drugs were administered at an initial dose of 10 mg/day for escitalopram and 60 mg/day for duloxetine; after 8 weeks, dosage increments could be made to optimize therapy. After the first 8 weeks, 33.3% of patients treated with duloxetine vs 48.7% of the escitalopram group vs 16.7% of the placebo group exhibited sexual dysfunction; this difference between active drugs was no longer observable after 12 weeks. At 8 months, the incidence of treatment-associated sexual dysfunction was 33.3% vs 43.6% vs 25% respectively with duloxetine, escitalopram, and placebo. Regardless of treatment, patients who achieved remission of depressive illness showed improvement in overall sexual function, and vice versa; worsening was observed in the group of patients who did not achieve remission of depressive symptoms (Clayton et al., 2007).

In a study considering 12 systematic reviews related to the use of SSRIs, mirtazapine, venlafaxine, duloxetine, milnacipran, bupropion, and reboxetine in the acute treatment of major depression, it emerged that, in terms of acceptability (one of the parameters considered, along with therapeutic efficacy), escitalopram ranked first in acceptability and second in efficacy, after mirtazapine (Lancet, 2009).

Pharmacokinetics

The pharmacokinetic profile of escitalopram, both after single and repeated administration, is linear and proportional to the dose in the range of 10-30 mg/day.

Following oral administration, escitalopram absorption is rapid and not influenced by food intake.

Time to peak plasma concentration: 3-4 hours (single and repeated dose).

Steady state is achieved within 7-10 days.

Serum protein binding: 56%.

The low serum protein binding value excludes the possibility of pharmacological interactions with drugs characterized by high binding to plasma proteins.

Apparent oral volume of distribution (Vd): 1100 L (extensive tissue distribution).

Escitalopram undergoes hepatic metabolism by CYP2C19, 2D6, and 3A4 isoenzymes. The metabolites do not possess significant pharmacological activity. The main metabolites are represented by S-demethyl-citalopram (S-DCT) (contributing to intrinsic clearance: 37% by CYP2C19; 28% by CYP2D6; 35% by CYP3A4) and S-didemethyl-citalopram (CYP2D6 plus non-CYP pathway) (von Moltke et al., 2001).

At steady state, the blood concentration of S-demethyl-citalopram is about one-third of that of escitalopram, which is the most abundant compound in the blood; the concentration of S-didemethyl-citalopram is not detectable in most patients (Rao, 2007).

Escitalopram is primarily excreted in the urine, both as metabolites and, to a small extent, as unchanged drug.

Oral clearance: 600 ml/min, with 7% attributed to renal clearance.

Half-life: 27-32 hours.

Special Patient Populations

Elderly patients

In patients aged ≥65 years, the AUC and half-life of escitalopram increase by approximately 50%, while the peak plasma concentration remains unchanged. In this patient population, the recommended dose of the drug is 10 mg/day.

Pediatric patients

No significant differences in the pharmacokinetic profile have been observed in adolescent patients compared to adults (Rao, 2007).

Gender

No variations related to peak plasma concentration, AUC, and half-life correlating with gender differences have been identified.

Hepatic impairment

Since escitalopram undergoes hepatic metabolism and citalopram has a reduced total clearance by about 37% and a doubled half-life in this patient population, a dosage adjustment of the S-enantiomer might be required, based on the clinical relevance of hepatic impairment.

Renal impairment

Attributing a behavior similar to citalopram, whose oral clearance is reduced by about 17% in cases of mild/moderate renal failure, a dosage adjustment of escitalopram does not seem necessary in this patient population. There are no literature data available on the use of escitalopram in patients with a creatinine clearance (CLcr) less than 20 ml/min.

Classification

Chemical formula

$C_{20}H_{21}FN_2O$

Molecular weight

324.40

ATC Code

N06AB10

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