of 18 years. Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

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.

After prolonged administration abrupt cessation of SSRIs may produce withdrawal reactions in some patients. Although withdrawal reactions may occur on stopping therapy, the available preclinical and clinical evidence does not suggest that SSRIs cause dependence.

Withdrawal symptoms (dizziness, headache and nausea) have been observed in some patients after abrupt discontinuation of escitalopram treatment. Most symptoms were mild and self-limiting. In order to avoid withdrawal reactions, tapered discontinuation over 1-2 weeks is recommended.

The following adverse reactions have occurred more frequently with escitalopram than with placebo in double-blind placebo-controlled studies. The frequencies listed are not placebo-corrected.

Metabolism and nutrition disorders	appetite decreased
Psychiatric disorders	female and male: libido decreased
	female: anorgasmia
Nervous system disorders	insomnia, somnolence, dizziness
	taste disturbance, sleep disorder
Respiratory, thoracic and mediastinal disorders	sinusitis, yawning
Gastrointestinal disorders	nausea
	diarrhoea, constipation
Skin and subcutaneous tissue disorders	sweating increased
Reproductive system and breast disorders	male: ejaculation disorder, impotence
General disorders and administration site conditions	fatigue, pyrexia

The following adverse reactions apply to the therapeutic class of SSRIs.

Metabolism and nutrition disorders	Hyponatraemia, inappropriate ADH secretion
Psychiatric disorders	Hallucinations, mania, confusion, agitation, anxiety, depersonalisation, panic attacks, nervousness
Nervous system disorders serotonin syndrome	Seizures, tremor, movement disorders,
Eye disorders	Abnormal vision
Vascular disorders	Postural hypotension
Gastrointestinal disorders anorexia	Nausea, vomiting, dry mouth, diarrhoea,
Hepatobiliary disorders	Abnormal liver function tests
Skin and subcutaneous tissue disorders	Rash, ecchymoses, pruritus, angioedema, sweating
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia
Renal and urinary disorders	Urinary retention
Reproductive system and breast disorders anorgasmia	Galactorrhoea, sexual dysfunction terms including impotence, ejaculation disorder,
General disorders and administration site conditions	Insomnia, dizziness, fatigue, drowsiness, anaphylactic reactions

OVERDOSE

Toxicity

Clinical data on escitalopram overdose are limited. However, it has been observed that doses of 190 mg of escitalopram have been taken without any serious symptoms being reported.

Symptoms

Symptoms of overdose with racemic citalopram (>600 mg): Dizziness, tremor, agitation, somnolence, unconsciousness, seizures, tachycardia, changes in the ECG with ST-T changes, broadening of the QRS complex, prolonged QT interval, arrhythmias, respiratory depression, vomiting, rhabdomyolosis, metabolic acidosis, hypokalaemia. It is anticipated that overdoses with escitalopram would result in similar symptoms.

Treatment

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

STORAGE : Store below 25°C.Protect from light

Presentation : Blister pack of 10 tablets

Cipla

881 ZC

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only (as applicable)

Escitalopram Oxalate tablets

CITADEP E 10

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Escitalopram or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Escitalopram is not approved for use in pediatric patients.

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

COMPOSITION

Each film-coated tablet contains

Escitalopram oxalate

Equivalent to Escitalopram.....10 mg

PHARMACOLOGY

Pharmacodynamics

Escitalopram is a selective inhibitor of serotonin (5-HT) re-uptake. The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram. Escitalopram has no or low affinity for a number of receptors including 5-HT_{1A}, 5-HT_2, DA D_1 and D_2 receptors, $á_1$-, $á_2$-, â-adrenoceptors, histamine H_1, muscarine cholinergic, benzodiazepine, and opioid receptors**.**

Pharmcokinetics

Absorption is almost complete and independent of food intake. (Mean time to maximum concentration (mean T_{max}) is 4 hours after multiple dosing). As with racemic citalopram, the absolute bio-availability of escitalopram is expected to be about 80%.

The apparent volume of distribution ($V_{d,ß}$/F) after oral administration is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites.

Escitalopram is metabolised in the liver to the demethylated and didemethylated metabolites. Both of these are pharmacologically active. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent and metabolites are partly excreted as glucuronides. After multiple dosing the mean concentrations of the demethyl and didemethyl metabolites are usually 28-31% and <5%, respectively, of the escitalopram concentration. Biotransformation of escitalopram to the demethylated metabolite is mediated primarily by CYP2C19. Some contribution by the enzymes CYP3A4 andCYP2D6 is possible.

The elimination half-life ($t_{1/ß}$) after multiple dosing is about 30 hours and the oral plasma clearance (Cl_{oral}) is about 0.6 L/min. The major metabolites have a significantly longer half-life.

Escitalopram and major metabolites are assumed to be eliminated by both the hepatic (metabolic) and the renal routes, with the major part of the dose excreted as metabolites in the urine.

There is linear pharmacokinetics. Steady-state plasma levels are achieved in about 1 week. Average steady-state concentrations of 50 nmol/L (range 20 to 125 nmol/L) are achieved at a daily dose of 10 mg.

Elderly patients (>65 years)

Escitalopram appears to be eliminated more slowly in elderly patients compared to younger patients. Systemic exposure (AUC) is about 50 % higher in elderly compared to young healthy volunteers.

Reduced hepatic function

In patients with mild or moderate hepatic impairment (Child-Pugh Criteria A and B), the half-life of escitalopram was about twice as long and the exposure was about 60% higher than in subjects with normal liver function.

Reduced renal function

With racemic citalopram, a longer half-life and a minor increase in exposure have been observed in patients with reduced kidney function (CL_{cr} 10-53 ml/min). Plasma concentrations of the metabolites have not been studied, but they may be elevated.

Polymorphism

It has been observed that poor metabolisers with respect to CYP2C19 have twice as high a plasma concentration of escitalopram as extensive metabolisers. No significant change in exposure was observed in poor metabolisers with respect to CYP2D6.

INDICATIONS

Escitalopram is indicated for:

- The treatment of major depressive disorder.

DOSAGE AND METHOD OF ADMINISTRATION

Major Depressive Disorder

Initial Treatment

The recommended dose of Escitalopram is 10 mg once daily. If the dose is increased to 20

PACKAGING DEVELOPMENT

Product Name : Citadep Pack Insert	Item Code : 881ZC	Date : 29-1-08
Cordinator : Sandeep	Artist : Amol	Software : PageMaker 6.5
Fonts : -------		
Colours: Black BLUE WOOL TEST VALUE 5-8 (LIGHT FASTENING DATA)		
Supersedes / Reference	Screen : NA	Unwinding Direction: NA
Tuck Flap : NA	Side / Collar flap overlap :NA	
Links :		
Pharmacode: 104 Mini	Design : Unfolded	
Material : 54 GSM Maplitho Paper	Varnish : NA	
Actual Size : 180 x 200 mm	Size after Folding : NA	
Print repeat length : NA		
Grain Direction : Perpendicular to Crease / Perpendicular to Pasting Flap / Parallel to Length		
Reference / Instructions / Remark / Braille Text Embosing :		
Path : PC : Amol t / E / Amol / Citadep Pack Insert/ 881 ZC Citadep Pack Insert		

mg, this should occur after a minimum of one week. Escitalopram should be administered once daily, in the morning or evening, with or without food.

Special Populations

10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment. No dosage adjustment is necessary for patients with mild or moderate renal impairment. Escitalopram should be used with caution in patients with severe renal impairment.

Maintenance Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing Escitalopram 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking Escitalopram during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment.Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

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.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of Escitalopram therapy. Similarly, at least 14 days should be allowed after stopping Escitalopram before starting an MAOI.

CONTRAINDICATIONS

Hypersensitivity to escitalopram or to any of the excipients.

Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors (MAO-inhibitors)

WARNINGS AND PRECAUTIONS

Paradoxical anxiety

Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect.

Seizures

The medicinal product should be discontinued in any patient who develops seizures. SSRIs should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. SSRIs should be discontinued if there is an increase in seizure frequency.

Mania

SSRIs should be used with caution in patients with a history of mania/hypomania. SSRIs should be discontinued in any patient entering a manic phase.

Diabetes

In patients with diabetes, treatment with an SSRI may alter glycaemic control (hypoglycaemia or hyperglycaemia). Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Suicide/suicidal ideation

Depression is associated with an increased risk of suicidal thoughts, self harm and suicide. This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience with all antidepressant therapies that the risk of suicide may increase in the early stages of recovery.

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

Patients with a history of suicidal behaviour or thoughts, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment, are at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

There are insufficient data concerning the risk of suicide related behaviour in treatment naïve patients, but careful monitoring might be warranted.

Patients (and caregivers of patients) should be alerted about the need to monitor for the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as elderly, cirrhotic patients or patients concomitantly treated with medications known to cause hyponatraemia.

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal anti-inflammatory medicinal products (NSAIDs), ticlopidine and dipyridamole) and in patients with known bleeding tendencies.

ECT (electroconvulsive therapy)

There is limited clinical experience of concurrent administration of SSRIs and ECT, therefore caution is advisable.

Reversible, selective MAO-A inhibitors

The combination of escitalopram with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome.

Concomitant treatment with non-selective, irreversible MAO-inhibitors.

Serotonin syndrome

Caution is advisable if escitalopram is used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol and tryptophan. In rare cases, serotonin syndrome has been reported in patients using SSRIs concomitantly with serotonergic medicinal products. A combination of symptoms, such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition. If this occurs treatment with the SSRI and the serotonergic medicinal product should be discontinued immediately and symptomatic treatment initiated.

St. John's Wort

Concomitant use of SSRIs and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Withdrawal reactions

When stopping therapy with Escitalopram, the dose should be gradually reduced over a period of one or two weeks in order to avoid possible withdrawal reactions.

Coronary heart disease

Due to limited clinical experience, caution is advised in patients with coronary heart disease.

Drug Interactions

Non-selective MAOIs

Cases of serious reactions have been reported in patients receiving an SSRI in combination with a non-selective monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued SSRI treatment and have been started on MAOI treatment. In some cases, the patient developed serotonin syndrome.

Escitalopram is contra-indicated in combination with non-selective MAOIs. Escitalopram may be started 14 days after discontinuing treatment with an irreversible MAOI and at least one day after discontinuing treatment with the reversible MAOI (RIMA), moclobemide. At least 7 days should elapse after discontinuing escitalopram treatment, before starting a non-selective MAOI.

Reversible, selective MAO-A inhibitor (moclobemide)

Due to the risk of serotonin syndrome, the combination of escitalopram with a MAO-A inhibitor is not recommended . If the combination proves necessary, it should be started at the minimum recommended dosage and clinical monitoring should be reinforced.

Selegiline

In combination with selegiline (irreversible MAO-B inhibitor), caution is required due to the risk of developing serotonin syndrome. Selegiline doses up to 10 mg/day have been safely co-administered with racemic citalopram.

Serotonergic medicinal products

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan and other triptans) may lead to serotonin syndrome.

Medicinal products lowering the seizure threshold

SSRIs can lower the seizure threshold. Caution is advised when concomitantly using other medicinal products capable of lowering the seizure threshold (e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol).

Lithium, tryptophan

There have been reports of enhanced effects when SSRIs have been given together with lithium or tryptophan, therefore concomitant use of SSRIs with these medicinal products should be undertaken with caution.

St. John's Wort

Concomitant use of SSRIs and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Haemorrhage

Altered anti-coagulant effects may occur when escitalopram is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when escitalopram is started or stopped.

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram and alcohol. However, as with other psychotropic medicinal products, the combination with alcohol is not advisable.

Others

Caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction in the dose of escitalopram may be necessary based on monitoring of side-effects during concomitant treatment.

Escitalopram is an inhibitor of the enzyme CYP2D6. Caution is recommended when escitalopram is co-administered with medicinal products that are mainly metabolised by this enzyme, and that have a narrow therapeutic index, e.g. flecainide, propafenone and metoprolol (when used in cardiac failure), or some CNS acting medicinal products that are mainly metabolised by CYP2D6, e.g. antidepressants such as desipramine, clomipramine and nortryptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted.

Pregnancy

For escitalopram only limited clinical data are available regarding exposed pregnancies. Escitalopram should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.

Using SSRIs in the third trimester may result in a withdrawal state, including neurobehavioral disturbances, in the newborn infant. The following effects were reported in neonates with SSRIs administered to pregnant women until birth: irritability, tremor, hypertonia, increased muscle tone, constant crying, difficulty in suckling or in sleeping. They may either indicate serotonergic effects or withdrawal syndrome. The neonate should be observed if the mother has used escitalopram during late pregnancy. If used during pregnancy SSRIs should never be stopped abruptly.

Lactation

It is expected that escitalopram will be excreted into human milk. Consequently, breast-feeding is not recommended during treatment.

Paediatric use

Escitalopram should not be used in the treatment of children and adolescents under the age