CEROPRAM *Citalopram 20 mg*

1. Name of the medicinal product: Ceropram 20 mg tablets

2. Qualitative and quantitative composition:

Each tablet contains :

Active ingredient : 20mg citalopram .

Inactive ingredients : lactose, croscarmellose sodium, Mg stearate.

3. Pharmaceutical form: Tablets.

4. Clinical particulars:

4.1 Therapeutic indications:Treatment of depressive illness in the initial phase and as maintenance against potential relapse/recurrence.

Ceropram/citalopram is also indicated in the treatment of panic disorder with or without agoraphobia.

4.2 Posology and method of administration; Posology:

Major depressive episodes: The recommended dose is 20 mg daily. In general, improvement in patients starts after one week, but may only become evident from the second week of therapy.

As with all antidepressant medicinal products, dosage should be reviewed and adjusted, if necessary, within 3 to 4 weeks of initiation of therapy and thereafter as judged clinically appropriate. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen, some patients may benefit from having their dose increased according to the patient's response (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose.

Patients with depression should be treated for a sufficient period of at least 6 months to ensure that they are free from symptoms.

Panic disorder: Patients should be started on 10 mg/day and the dose gradually increased in 10 mg steps according to the patient's response up to the recommended dose. The recommended dose is 20-30 mg daily. A low initial starting dose is recommended to minimize the potential worsening of panic symptoms, which is generally recognized to occur early in the treatment of this disorder. Although there may be an increased potential for undesirable effects at higher doses, if after some weeks on the recommended dose insufficient response is seen some patients may benefit from having their dose increased gradually (see section 5.1). Dosage adjustments should be made carefully on an individual patient basis, to maintain the patients at the lowest effective dose.Patients with panic disorder should be treated for a sufficient period to ensure that they are free from symptoms. This period may be several months or even longer.

Elderly patients (> 65 years of age): The recommended daily dose is 20 mg. Dependent on individual patient response this may be increased to a maximum of 40 mg daily.

Children and adolescents (< 18 years of age):Citalopram should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.4).

Reduced hepatic function: Dosage should be restricted to the lower end of the dose range.

Reduced renal function: Dosage adjustment is not necessary in cases of mild or moderate renal impairment. No information is available in cases of severe renal impairment (creatinine clearance <20 mL / min).

- Citalopram should not be prescribed at doses greater than 40 mg /day.
- 20 mg /day is the maximum recommended dose for patients with hepatic impairment, who are greater than 60 years of age, who are CYP 2 C19 poor metabolizers, or who are taking concomitant cimetidine (Tagamet), because these drugs factors lead to increased blood levels of citalopram, increasing risk of QT interval prolongation and Torsade de Pointes.

Withdrawal symptoms seen on discontinuation of citalopram: Abrupt discontinuation should be avoided. When stopping treatment with citalopram the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4 Special Warnings and Precautions for Use and section 4.8 Undesirable Effects). 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.

Method of administration: Ceropram tablets are administered as a single daily dose. Ceropram tablets can be taken at any time of the day without regard to food intake.

4.3 Contraindications: Hypersensitivity to the active substance or to any of the excipients .

Monoamine Oxidase Inhibitors (MAOIs): Some cases presented with features resembling serotonin syndrome.

Citalopram should not be given to patients receiving MAOIs, including selegiline, in daily doses exceeding 10 mg/day.

Citalopram should not be given for fourteen days after discontinuation of an irreversible MAOI or for the time specified after discontinuation of a reversible MAOI (RIMA) as stated in the prescribing text of the RIMA.

MAOIs should not be introduced for seven days after discontinuation of citalopram (see section 4.5).

Citalopram is contraindicated in combination with linezolid unless there are facilities for close observation and monitoring of blood pressure (see section 4.5).

Citalopram should not be used concomitantly with pimozide (see also section 4.5).

Do not use of citalopram with other medicinal products known to prolong the QT interval.

Citalopram is contraindicated in patients with congenital long QT syndrome.

4.4 Special warnings and precautions for use: Suicide/suicidal thoughts or clinical worsening

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

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

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

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Use in children and adolescents under 18 years of age.

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

Elderly patients: Caution should be used in the treatment of elderly patients (see section 4.2).

Reduced kidney and liver function: Caution should be used in the treatment of patients with reduced kidney and liver function (see section 4.2).

Paradoxical anxiety: Some patients with panic disorder may experience intensified anxiety symptoms at the start of treatment with antidepressants. This paradoxical reaction usually subsides within the first two weeks of starting treatment. A low starting dose is advised to reduce the likelihood of a paradoxical anxiogenic effect (see section 4.2).

Hyponatraemia: Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported as a rare adverse reaction with the use of SSRIs and generally reverses on discontinuation of therapy. Elderly female patients seem to be at particularly high risk.

Akathisia/psychomotor restlessness: The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Mania: In patients with manic-depressive illness a change towards the manic phase may occur. Should the patient enter a manic phase citalopram should be discontinued.

Seizures: Seizures are a potential risk with antidepressant drugs. Citalopram should be discontinued in any patient who develops seizures. Citalopram should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Citalopram should be discontinued if there is an increase in seizure frequency.

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

Glaucoma: As with other SSRIs, citalopram can cause mydriasis and should be used with caution in patients with narrow angle glaucoma or history of glaucoma.

Serotonin syndrome: In rare cases, serotonin syndrome has been reported in patients using SSRIs. A combination of symptoms such as agitation, tremor, myoclonus and hyperthermia may indicate the development of this condition (see section 4.5). Treatment with citalopram should be discontinued immediately and symptomatic treatment initiated.

Serotonergic medicines: Citalopram should not be used concomitantly with medicinal products with serotonergic effects such as sumatriptan or other triptans, tramadol, oxitriptan and tryptophan.

*Haemorrhage.*There have been reports of prolonged bleeding time and /or bleeding abnormalities such as ecchymoses, gynaecological haemorrhages, gastrointestinal bleeding and other cutaneous or mucous bleedings with SSRIs (see section 4.8). Caution is advised in patients taking SSRIs, particularly with concomitant use of active substances known to affect platelet function or other active substances that can increase the risk of haemorrhage, as well as in patients with a history of bleeding disorders (see section 4.5).

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 citalopram with MAO-A inhibitors is generally not recommended due to the risk of onset of a serotonin syndrome (see section 4.5).

For information on concomitant treatment with non-selective, irreversible MAO-inhibitors see section 4.5.

St. John's wort: Undesirable effects may be more common during concomitant use of citalopram and herbal preparations containing St John's wort (Hypericum perforatum). Therefore citalopram and St John's wort preparations should not be taken concomitantly (see section 4.5).

Withdrawal symptoms seen on discontinuation of SSRI treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8 Undesirable effects).

In a recurrence prevention clinical trial with citalopram, adverse events after discontinuation of active treatment were seen in 40% patients versus 20% in patients continuing citalopram.

The risk of withdrawal symptoms may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, palpitations, emotional instability, irritability, and visual disturbances are the most commonly reported reactions. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that citalopram should be gradually tapered when discontinuing treatment over a period of several weeks or months, according to the patient's needs (see "Withdrawal symptoms seen on discontinuation of citalopram", Section 4.2)

*Psychosis:*Treatment of psychotic patients with depressive episodes may increase psychotic symptoms.

*QT prolongation:*Elevated levels of a side metabolite (didemethylcitalopram) can theoretically prolong the QT interval in patients predisposed, patients with congenitally prolonged QT syndrome or in patients with hypokalaemia/hypomagnesaemia. ECG monitoring may be advisable in case of overdose or conditions of altered metabolism with increased peak levels, e.g. liver impairment.

*Excipients:*The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp deficiency or glucose-galactose malabsorption should not receive this medicine.

Warnings:

- Patients with congestive heart failure, bradyarrhythmias, myocardial infarction or predisposition to hypokalemia or hypomagnesaemia because of concomitant illness or drugs, are at higher risk of developing Torsade de Pointes.
- Health care professionals should consider more frequent electrocardiogram (ECG) monitoring in patients with congestive heart failure, bradyarrythmias.
- Hypokalemia and hypomagnesaemia should be corrected before administering citalopram. Electrolytes should be monitored as clinically indicated.
- Patients should contact a healthcare professional immediately if they experience signs and symptoms of an abnormal heart rate or rhythm while taking citalopram.
- Patients should be advised not to stop taking citalopram or change or reduce the dose without first consulting their healthcare professional, as withdrawal symptoms may occur when citalopram treatment is discontinued, particularly if this is abrupt.

4.5 Interaction with other medicinal products and other forms of interaction:

Pharmacodynamic interactions: At the pharmacodynamic level cases of serotonin syndrome with citalopram and moclobemide and buspirone have been reported.

Contraindicated combinations: ***MAO-inhibitors:*** The simultaneous use of citalopram and MAO-inhibitors can result in severe undesirable effects, including serotonin syndrome (see section 4.3).Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), including the irreversible MAOI selegiline and the reversible MAOIs linezolid and moclobemide and in patients who have recently discontinued an SSRI and have been started on a MAOI. Some cases presented with features resembling serotonin syndrome. Symptoms of an active substance interaction with a MAOI include: agitation, tremor, myoclonus, and hyperthermia.

Pimozide:Due to the interaction noted at a low dose of pimozide, concomitant administration of citalopram and pimozide is contraindicated.

Combinations requiring precaution for use;*Selegiline (selective MAO-B inhibitor):* A pharmacokinetic / pharmacodynamic interaction study with concomitantly administered citalopram (20 mg daily) and selegiline (10 mg daily) (a selective MAO B inhibitor) demonstrated no clinically relevant interactions. The concomitant use of citalopram and selegiline (in doses above 10 mg daily) is not recommended.

Serotonergic medicinal products; Lithium and tryptophan: No pharmacodynamic interactions have been found in clinical studies in which citalopram has been given concomitantly with lithium. However there have been reports of enhanced effects when SSRIs have been given with lithium or tryptophan and therefore the concomitant use of citalopram with these medicinal products should be undertaken with caution. Routine monitoring of lithium levels should be continued as usual.

Co-administration with serotonergic medicinal products (e.g. tramadol, sumatriptan) may lead to enhancement of 5-HT associated effects.Until further information is available, the simultaneous use of citalopram and 5-HT agonists, such as sumatriptan and other triptans, is not recommended (see section 4.4).

St. John's wort: Dynamic interactions between SSRIs and the herbal remedy St John's wort (Hypericum perforatum) can occur, resulting in an increase in undesirable effects (see section 4.4). Pharmacokinetic interactions have not been investigated.

Haemorrhage: Caution is warranted for patients who are being treated simultaneously with anticoagulants, medicinal products that affect the platelet function, such as non steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, dipyridamole, and ticlopidine or other medicines (e.g.atypical antipsychotics, phenothiazines, tricyclic antidepressants) that can increase the risk of haemorrhage (see section 4.4).

ECT (electroconvusive therapy): There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and citalopram (see section 4.4).

Alcohol: No pharmacodynamic or pharmacokinetic interactions have been demonstrated between citalopram and alcohol. However, the combination of citalopram and alcohol is not advisable.

Medicinal products inducing QT prolongation or hypokalaemia/hypomagnesaemia

Caution is warranted for concomitant use of other QT interval prolonging medicines or hypokalaemia- / hypomagnesaemia-inducing drugs as they, like citalopram, potentially prolong the QT interval.

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).

Desipramine, imipramine: In a pharmacokinetic study no effect was demonstrated on either citalopram or imipramine levels, although the level of desipramine, the primary metabolite of imipramine was increased. When desipramine is combined with citalopram, an increase of the desipramine plasma concentration has been observed. A reduction of the desipramine dose may be needed.

Neuroleptics: Experience with citalopram has not revealed any clinically relevant interactions with neuroleptics. However, as with other SSRIs, the possibility of a pharmacodynamic interaction cannot be excluded.

Pharmacokinetic interactions: Biotransformation of citalopram to demethylcitalopram is mediated by CYP2C19 (approx. 38%), CYP3A4 (approx. 31%) and CYP2D6 (approx. 31%) isozymes of the cytochrome P450 system. The fact that citalopram is metabolised by more than one CYP means that inhibition of its biotransformation is less likely as inhibition of one enzyme may be compensated by another. Therefore co-administration of citalopram with other medicinal products in clinical practice has very low likelihood of producing pharmacokinetic medicinal product interactions.

Food: The absorption and other pharmacokinetic properties of citalopram have not been reported to be affected by food.

Influence of other medicinal products on the pharmacokinetics of citalopram:

- Co-administration with ketoconazole (potent CYP3A4 inhibitor) did not change the pharmacokinetics of citalopram.
- A pharmacokinetic interaction study of lithium and citalopram did not reveal any pharmacokinetic interactions (see also above).
- Cimetidine; Cimetidine, a known enzyme-inhibitor, caused a slight rise in the average steady-state citalopram levels. Caution is therefore recommended when administering high doses of citalopram in combination with high doses of cimetidine. Co-administration of escitalopram (the active enantiomer of citalopram) with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50%) increase in the plasma concentrations of escitalopram. Thus, caution should be exercised when used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine) or cimetidine. A reduction inthe dose of citalopram may be necessary based on monitoring of undesirable effects during concomitant treatment.
- Metoprolol; Escitalopram (the active enantiomer of citalopram) is an inhibitor of the enzyme CYP2D6. Caution is recommended when citalopram 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 nortriptyline or antipsychotics like risperidone, thioridazine and haloperidol. Dosage adjustment may be warranted. Co-administration with metoprolol resulted in a twofold increase in the plasma levels of metoprolol, but did not statistically significant increase the effect of metoprolol on the blood pressure and cardiac rhythm.

Effects of citalopram on other medicinal products: A pharmacokinetic / pharmacodynamic interaction study with concomitant administration of citalopram and metoprolol (a CYP2D6 substrate) showed a twofold increase in metoprolol concentrations, but no statistically significant increase in the effect of metoprolol onblood pressure and heart rate in healthy volunteers.

Citalopram and demethylcitalopram are negligible inhibitors of CYP2C9, CYP2E1 and CYP3A4, and only weak inhibitors of CYP1A2, CYP2C19 and CYP2D6 as compared to other SSRIs established as significant inhibitors.

Levomepromazine, digoxin, carbamazepine;Thus no change or only very small changes of no clinical importance were observed when citalopram was given with CYP1A2 substrates (clozapine and theophylline), CYP2C9 (warfarin), CYP2C19 (imipramine and mephenytoin), CYP2D6 (sparteine, imipramine, amitriptyline, risperidone) and CYP3A4 (warfarin, carbamazepine (and its metabolite carbamazepine epoxid) and triazolam).

No pharmacokinetic interaction was observed between citalopram and levomepromazine, or digoxin, (indicating that citalopram neither induces nor inhibits P-glycoprotein).

4.6 Pregnancy and lactation:

Pregnancy;Citalopram can be used during pregnancy if clinically needed, taking into account the aspects mentioned below.

Neonates should be observed if maternal use of citalopram continues into the later stages of pregnancy, particular in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonates after maternal SSRI/SNRI use in later stages of pregnancy: respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (<24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

Lactation;Citalopram is excreted into breast milk. It is estimated that the suckling infant will receive about 5% of the weight related maternal daily dose (in mg/kg). No or only minor events have been observed in the infants. However, the existing information is insufficient for assessment of the risk to the child.Caution is recommended. If treatment with citalopram is considered necessary, discontinuation of breast feeding should be considered.

4.7 Effects on ability to drive and use machines: Citalopram has minor or moderate influence on the ability to drive and use machines.Patients who are prescribed psychotropic medication may be expected to have some impairment of general attention and concentration due to the illness itself and psychoactive medicinal products can reduce the ability to make judgements and to react to emergencies. Patients should be informed of these effects and be warned that their ability to drive a car or operate machinery could be affected.

4.8 Undesirable effects: Adverse effects observed with citalopram are in general mild and transient. They are most frequent during the first one or two weeks of treatment and usually attenuate subsequently. The adverse reactions are presented at the MedDRA Preferred Term Level.For the following reactions a dose-response was discovered: Sweating increased, dry mouth, insomnia, somnolence, diarrhoea, nausea and fatigue.The table shows the percentage of adverse drug reactions associated with SSRIs and/or citalopram seen in either ≥1% of patients in double-blind placebo-controlled trials or in the post-marketing period. Frequencies are defined as: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥ 1/10000, <1/1000); very rare (<1/10000), not known (cannot be estimated from available data).

MedDRA SOC	Frequency	Preferred term
Blood and lymphatic disorders	Not Known	Thrombocytopenia
Immune system disorders	Not Known	Hypersensitivity, anaphylactic reaction
Endocrine disorders	Not Known	Inappropriate ADH secretion
Metabolism and nutrition disorders	Common	Appetite decreased, weight decreased
	Uncommon	Increased appetite, weight increased
	Rare	Hyponatraemia
	Not Known	Hypokalaemia
Psychiatric disorders	Common	Agitation, libido decreased, anxiety, nervousness, confusional state, abnormal orgasm (female), abnormal dreams
	Uncommon	Aggression, depersonalization, hallucination, mania
	Not Known	Panic attack, bruxism, restlessness, suicidal ideation, suicidal behaviour[2]
Nervous system disorders	Very common	Somnolence, insomnia
	Common	Tremor, paraesthesia, dizziness, disturbance in attention
	Uncommon	Syncope
	Rare	Convulsion grand mal, dyskinesia, taste disturbance
	Not Known	Convulsions, serotonin syndrome, extrapyramidal disorder, akathisia, movement disorder.

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Eye disorders	Uncommon	Mydriasis (which may lead to acute narrow angle glaucoma), see section 4.4 Special warnings and precautions for use)
	Not Known	Visual disturbance
Ear and labyrinth disorders	Common	Tinnitus
Cardiac disorders	Uncommon	Bradycardia, tachycardia
	Not Known	QT-prolongation[1]
Vascular disorders	Rare	Haemorrhage
	Not Known	Orthostatic hypotension
Respiratory thoracic and mediastinal disorders	Common	Yawning
	Not Known	Epistaxis
Gastrointestinal disorders	Very common	Dry mouth, nausea
	Common	Diarrhoea, vomiting, constipation
	Not Known	Gastrointestinal haemorrhage (including rectal haemorrhage)
Hepatobiliary disorders	Rare	Hepatitis
	Not Known	Liver function test abnormal
Skin and subcutaneous tissue disorders	Very common	Sweating increased
	Common	Pruritus
	Uncommon	Urticaria, alopecia, rash, purpura, photosensitivity reaction
	Not Known	Ecchymosis, angioedemas
Musculoskeletal, connective tissue and bone disorders	Common	Myalgia, arthralgia
Renal and urinary disorders	Uncommon	Urinary retention
Reproductive system and breast disorders	Common	Impotence, ejaculation disorder, ejaculation failure,
	Uncommon	Female: Menorrhagia
	Not Known	Female: Metrorrhagia, Male: Priapism, Galactorrhoea
General disorders and administration site conditions	Common	Fatigue,
	Uncommon	Oedema
	Rare	Pyrexia

Number of patients: citalopram / placebo = 1346 / 545

Cases of QT-prolongation have been reported during the post-marketing period, predominantly in patients with pre-existing cardiac disease

Cases of suicidal ideation and suicidal behaviours have been reported during citalopram therapy or early after treatment discontinuation (see section 4.4).

The following additional adverse events have also been reported in clinical trials:

Very common: Headache, asthenia, sleep disorder.

Common: Migraine, , palpitation, taste perversion, impaired concentration, amnesia, anorexia, apathy, dyspepsia, abdominal pain, flatulence, increased salivations, rhinitis.

Rare: Increased libido, coughing, malaise.

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.

Withdrawal symptoms seen on discontinuation of SSRI treatment :

Discontinuation of citalopram (particularly when abrupt) commonly leads to withdrawal symptoms.

Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, confusion, sweating, headache, diarrhoea, 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 citalopram treatment is no longer required, gradual discontinuation by dose tapering should be carried out.

(see section 4.2 and section 4.4).

4.9 Overdose:

Toxicity:

Comprehensive clinical data on citalopram overdose are limited and many cases involve concomitant overdoses of other drugs/alcohol. Fatal cases of citalopram overdose have been reported with citalopram alone; however, the majority of fatal cases have involved overdose with concomitant medications.

Fatal dose is not known. Patients have survived ingestion of more than 2 g citalopram.

The effects may be potentiated by alcohol taken at the same time.

Potential interaction with TCAs, MAOIs and other SSRIs.

Symptoms:

The following symptoms have been seen in reported overdose of citalopram: convulsion, tachycardia, somnolence, QT prolongation, coma, vomiting, tremor, hypotension, cardiac arrest, nausea, serotonin syndrome, agitation, bradycardia, dizziness, bundle branch block, QRS prolongation, hypertension, mydriasis, torsade de pointes, stupor, sweating, cyanosis, hyperventilation, hyperpyrexia, and atrial and ventricular arrhythmia.

ECG changes including nodal rhythm, prolonged QT intervals and wide QRS complexes may occur. Fatalities have been reported.

Prolonged bradycardia with severe hypotension and syncope has also been reported.

Rarely, features of the "serotonin syndrome" may occur in severe poisoning. This includes alteration of mental status, neuromuscular hyperactivity and autonomic instability. There may be hyperpyrexia and elevation of serum creatine kinase. Rhabdomyolysis is rare.

Treatment: There is no known specific antidote to citalopram.

Treatment should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of ECG and vital signs until stable.

Consider oral activated charcoal in adults and children who have ingested more than 5 mg/kg body weight within 1 hour. Activated charcoal given ½ hour after ingestion of citalopram has been shown to reduce absorption by 50%.

Osmotically working laxative (such as sodium sulphate) and stomach evacuation should be considered.

If consciousness is impaired the patient should be intubated.

Control convulsions with intravenous diazepam if they are frequent or prolonged.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

ATC-code: N 06 AB 04.

Biochemical and behavioural studies have shown that citalopram is a potent inhibitor of the serotonin (5-HT)-uptake. Tolerance to the inhibition of 5-HT-uptake is not induced by long-term treatment with citalopram. Citalopram is the most Selective Serotonin Reuptake Inhibitor (SSRI) yet described, with no, or minimal, effect on noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA) uptake.

In contrast to many tricyclic antidepressants and some of the newer SSRIs, citalopram has no or very low affinity for a series of receptors including 5-HT $_{1A}$, 5-HT$_2$, D_A D_1 and D_2 receptors, α1-, α2-, β-adrenoceptors, histamine H1, muscarine cholinergic, benzodiazepine, and opioid receptors. A series of functional in vitro tests have confirmed the lack of receptor affinity. This absence of effects on receptors could explain why citalopram produces fewer of the traditional side effects such as dry mouth, bladder and gut disturbance, blurred vision, sedation, cardiotoxicity and orthostatic hypotension.

Suppression of rapid eye movement (REM) sleep is considered a predictor of antidepressant activity. Like tricyclic antidepressants, other SSRIs and MAO inhibitors, citalopram suppresses REM-sleep and increases deep slow-wave sleep.

Although citalopram does not bind to opioid receptors it potentiates the anti-nociceptive effect of commonly used opioid analgesics. There was potentiation of d-amphetamine-induced hyperactivity following administration of citalopram.

The main metabolites of citalopram are all SSRIs although their potency and selectivity ratios are lower than those of citalopram. However, the selectivity ratios of the metabolites are higher than those of many of the newer SSRIs. The metabolites do not contribute to the overall antidepressant effect.

In humans citalopram does not impair cognitive (intellectual function) and psychomotor performance and has no or minimal sedative properties, either alone or in combination with alcohol.

Citalopram did not reduce saliva flow in a single dose study in human volunteers and in none of the studies in healthy volunteers did citalopram have significant influence on cardiovascular parameters. Citalopram has no effect on the serum levels of prolactin and growth hormone.

*Dose response:*In the fixed dose studies there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that up-titrating the dose might be beneficial for some patients.

5.2 Pharmacokinetic properties:

Absorption: Absorption is almost complete and independent of food intake (T_{max} average/mean 3.8 hours). Oral bioavailability is about 80%.

Distribution: The apparent volume of distribution (V_d) β is about 12.3 L/kg. The plasma protein binding is below 80% for citalopram and its main metabolites.

Biotransformation: Citalopram is metabolized to the active demethylcitalopram, didemethylcitalopram, citalopram-N-oxide and an inactive deaminated propionic acid derivative. All the active metabolites are also SSRIs, although weaker than the parent compound. Unchanged citalopram is the predominant compound in plasma.

Elimination: The elimination half-life (T½β) is about 1.5 days and the systemic citalopram plasma clearance (Cls) is about 0.33 L/min, and oral plasma clearance (Cl oral) is about 0.41 L/min.

Citalopram is excreted mainly via the liver (85%) and the remainder (15%) via the kidneys. About 12% of the daily dose is excreted in urine as unchanged citalopram. Hepatic (residual) clearance is about 0.35 L/min and renal clearance about 0.068 L/min.

The kinetics are linear. Steady state plasma levels are achieved in 1-2 weeks. Average concentrations of 250 nmol/L (100-500 nmol/L) are achieved at a daily dose of 40 mg. There is no clear relationship between citalopram plasma levels and therapeutic response or side effects.

Elderly patients (≥65 years): Longer half-lives and decreased clearance values due to a reduced rate of metabolism have been demonstrated in elderly patients.

Reduced hepatic function: Citalopram is eliminated more slowly in patients with reduced hepatic function. The half-life of citalopram is about twice as long and steady state citalopram concentrations at a given dose will be about twice as high as in patients with normal liver function.

Reduced renal function: Citalopram is eliminated more slowly in patients with mild to moderate reduction of renal function, without any major impact on the pharmacokinetics of citalopram. At present no information is available for treatment of patients with severely reduced renal function (creatinine clearance <20 mL/min).

6. Storage: Store at temperature not exceeding 30°C

7. Manufactured by: Egyptian group for pharmaceutical industries (EGPI)

Manufactured by:

Egyptian Group for Pharmaceutical Industries.

EGPI

سيروبـــرام

أقراص مغلفة

سيتالوبرام ٢٠ مجم

بيان التركيب: سيروبرام ٢٠مجم: كل قرص مغلف يحتوى على:

المواد الفعالة: سيتالوبرام ٢٠مجم.

المواد الغير فعالة: لاكتوز، كروسكارميلوز، ستيرات الماغنيزيوم.

١- ماهو سيروبرام أقراص:

سيروبرام أقراص يحتوي على سيتالوبرام ٢٠مجم.

سيتالوبرام ينتمى إلى مجموعة مضادات الإكتئاب المعروفة باسم المثبطات الإنتقائية لإعادة إمتصاص السيروتونين .

وهى تزيد من تأثير السيروتونين على الجسم بمنع إمتصاصه من الخلايا العصبية.

سيروبرام يستخدم لعلاج نوبات الإكتئاب الكبرى.

٢- قبل تناول سيروبرام أقراص:

لا تتناول سيروبرام أقراص: في الحالات التالية:

• الحساسية لسيتالوبرام أو أحد مكونات المستحضر.

• تناول أو إستخدام خلال آخر اسبوعين مثبطات أوكسيديز أحادى الأمين يستخدم للإكتئاب أو مرض برکنسون (مثل سيلجيلين أو موكلوبيمید).

• تناول بيموزايد (مضاد للذهان) أو لينزولید (مضاد حيوى).

موانع استخدام سيروبرام أقراص:

• لا تستخدم سيتالوبرام مع أى دواء معروف إنه يطيل فترة QT .

• سيتالوبرام ممنوع إستخدامه مع مرضى متلازمة فترة QT الطويلة الخلقية.

يرجى مراجعة الطبيب قبل تناول سيتالوبرام: في الحالات التالية :

• تعانى من هوس (هوسة، إثارة، صعوبة في التركيز).

• تعانى من أمراض عقلية مثل الإكتئاب أو نوبات هلع.

• مريض الداء السكرى.

• تعانى من صرع.

• تعانى من أمراض الكبد أو تليف الكبد.

• تعانى من أمراض الكلى الشديدة.

• تعانى من مشاكل بالقلب، أو عدم إنتظام ضربات القلب.

• المعالجة بالصدمة الكهربائية.

• إضطرابات النزف.

• تناول أعشاب طبية تحتوى على نبات سان جون المستخدمة لعلاج الاكتئاب.

• تناول سوماتريبتان أو أى تريبتان آخر (لعلاج الصداع النصفى)،أوكسترپتان أو ترپتوفان أو ترامادول.

تناول أدوية أخرى:

برجاء إبلاغ الطبيب في حالة تناول الأدوية التالية:

- مضادات الاكتئاب ثلاثية الحلقات مثل ديسيبرامين أو كلوميرامين.

- مضادات التخثر مثل وارفارين. الأدوية التي تسبب النزيف مثل مضادات الإلتهاب الغير إستيرويدية (مثل إيبروفين)، أسبرين، داييريمادول أو تيكلوبيدين.

- أدوية الأمراض العقلية مثل كلوزبروميزين، هالوبيريدول، ثاوريدازين.

- ليثيوم لعلاج الهوس.

- سيميتيدين، أوميرازول، زوميرازول، لانزوبرازول لعلاج قرح المعدة.

- ميثيروبولول لعلاج أمراض القلب.

- أدوية الفصام.

- ميفلوكين لعلاج الملاريا.

- فلیكينايد أو بروبوفينون لعلاج إضطرابات القلب.

الإستخدام لأقل من ١٨ سنة:

سيتالوبرام لا يستخدم لأقل من ١٨ سنة. إستخدام سيتالوبرام لأقل من ١٨ سنة يزيد الآثار الجانبية.

أفكار الانتحار و تدهور الاكتئاب و القلق:

في حالات الاكتئاب أو القلق أحيانا يكون هناك أفكار الإضرار أو قتل النفس. هذه الأفكار تزيد في بداية العلاج وقد تكون أكثر عرضه لهذه الأفكار إذا حدثت من قبل أو لو سنك أقل من ٢٥ عاما. إذا حدث ذلك ابلغ الطبيب فورا أو توجه لأقرب مستشفى.

الحمل و الرضاعة الطبيعية:

أبلغ الطبيب في حالة الحمل أو الرضاعة قبل تناول الدواء. في حالة تناول سيتالوبرام في أخر ٣ أشهر من الحمل سيتالوبرام قد يزيد من حدوث ارتفاع مستمر لضغط الدم الرئوي عند الرضيع الذي يؤدي إلي التنفس بشكل سريع و يبدو مزرق. هذه الأعراض تحدث عادة في أول ٢٤ ساعة بعد الولادة. إذا حدثت ابلغ الطبيب فورا.

القيادة واستخدام الآلات:

سيتالوبرام يمكن أن يؤثر على رد فعلك للطوارىء. إذا حدث ذلك لا تقم بالقيادة او استخدام الآلات.

٣- كيفية تناول سيروبرام:

• يجب تناول سيروبرام أقراص كما وصف الطبيب.

• لا تشرب الكحوليات أثناء تناول سيتالوبرام.

• أبلع الأقراص مع الماء جرعة واحدة مع أو بدون طعام سواء صباحاً أو مساءاً.

الجرعة:

البالغين:

تبدأ الجرعة ب ٢٠ مجم و حسب استجابة المريض قد تزيد إلى ٤٠ مجم يومياً وهى الجرعة القصوى.

المسنين (فوق ٦٥ سنة):

يأخذ المسن نصف جرعة البالغين وهى ١٠مجم - ٢٠ مجم و ٢٠ مجم يومياً وهى الجرعة القصوى.

الأطفال والمراهقين:

لا ينصح بتناوله لأقل من ١٨ سنة.

مرضى الكلى:

لا ينصح باستخدامه لمرضى الإعتلال الكلوى الشديد .

مرضى الكبد:

تبدأ الجرعة ب ١٠ مجم يومياً لمدة أسبوعين و قد تزيد إلى ٢٠ مجم يومياً وهى الجرعة القصوى.

□ الجرعة القصوى لسيتالوبرام ينبغي الا تزيد عن ٤٠ مجم يوميا

□ مرضى الكبد أو كبار السن فوق ٦٠ سنة أو الذين يتناولون سيميتدين أو الذين يتناولون الأدوية التي ايضها ضعيف عن طريق CYP 2C19.

الجرعة القصوى هي ٢٠ مجم يوميا وذلك لان هذه الأدوية ترفع من مستوى سيتالوبرام في الدم مما يؤدي الي زيادة مخاطر إطالة فترة QT و مرض (Torsade de Pointes).

- مع بدء العلاج قد لا تظهر نتائج للعلاج في أول اسبوعين. هذا الدواء يجب أن يستمر تناوله لفترات طويلة. يجب على الطبيب إستمرار العلاج حتي تكون خالى من الأعراض لمدة ٤-٦ أشهر.

في حالة تناول جرعة عالية من سيروبرام أقراص :

يجب إبلاغ الطبيب فوراً أو اذهب إلى أقرب مستشفى. زيادة الجرعة تسبب شعور بالنعاس، تشنجات، لون أزرق حول الشفتين، الأظافر، عرق، غيبوبة، سرعة ضربات القلب، سرعة التنفس و تغير في رسم القلب.

في حالة نسيان جرعة من سيروبرام أقراص :

في حالة نسيان جرعة تناول الجرعة عند التذكر. لا تتناول ضعف الجرعة لتعويض الجرعة المنسية.

□ لا توقف استعمال سيروبرام أقراص. أبلغ الطبيب قبل وقف الإستخدام. يجب سحب إستخدام أقراص سيتالوبرام بصورة بطيئة وتدريجية على مدار أسبوع أو اسبوعين.

□ إيقاف العلاج بسيتالوبرام فجاءه قد يحدث دوخة، نخز، صداع، شعور بالإعياء، اضطراب النوم، شعور بالهياج أو القلق، تشنجات ، ارتباك، عرق، إسهال، خفقان، عدم استقرار المشاعر، هياج و اضطرابات في الرؤية.

٤- الآثار الجانبية: مثل جميع الأدوية يمكن حدوث بعض الآثار الجانبية مع سيروبرام أقراص وان لم تحدث للجميع.

إذا عانيت من أي من الآثار الجانبية التالية أثناء العلاج أوقف استخدام الأقراص و ابلغ الطبيب فورا:

• حدوث متلازمة السيروتونين (حالة خطيرة قد تؤدي الي حمى، ارتباك، حركات غير طبيعية، رعشة، تشنج بالعضلات، هياج ، قد تتطور إلي غيبوبة، أو فقدان الوعي، تعلمل، عرق، هوسة، مبالغة في رد الفعل، تقلصات بالعضلات و سرعة ضربات القلب.

• فرط حساسية شديد يمكن أن يؤدي إلي انخفاض شديد بضغط الدم، شحوب، قلق، ضربات قلب سريعة وضعيفة، عرق، انخفاض الوعي، تشنجات، صعوبة في التنفس و تورم مفاجيء في الشفاه، اللعن و اللسان.

إذا عانيت من أي من الآثار الجانبية التالية أثناء العلاج ابلغ الطبيب:

الآثار الجانبية الأكثر شيوعا: وتشمل:

• شعور بالغثيان.

• جفاف بالفم.

• نعاس، صعوبة في النوم، مشاكل في النوم.

• إعياء.

• زيادة العرق.

أثار الجانبية شائعة: وتشمل:

• نخز.

• قلق.

• هياج.

• عصبية.

• مشاكل في الوعي.

• ارتباك.

• طنين بالأذن.

• أحلام غير طبيعية.

• تثاؤب.

• رجرجة اليدين والقدمين.

• دوخة.

• ضعف.

• فقدان شهية.

• نقص الوزن.

• قيء.

• إسهال، إمساك.

• عجز جنسي ومشاكل مع القذف، انخفاض الرغبة الجنسية .

• طفح جلدى.

• ألم بالمفاصل و العضلات.

أثار الجانبية غير شائعة: وتشمل:

• عدوانية.

• شعور زائف بالتحمس.

• عدم إنتظام ضربات القلب ، بطء فى ضربات القلب، سرعة فى ضربات القلب.

• هلوسة.

• هوس.

• شعور بحساسية غير واقعية لأشعة الشمس.

• إغماء.

• إضطرابات في الرؤية.

• زيادة الشهية، زيادة الوزن.

• مشاكل في التبول.

• ألم بالدورة الشهرية.

• فقدان الشعر.

• حكة.

أثار جانبية نادرة: وتشمل:

• نزيف من الجلد، المعدة، المهبل و الكدمات.

• تغير في مستويات الأملاح في الجسم.

• تغير في التذوق.

• حركات تشنجية.

• تشنجات.

• حمى.

أثار جانبية غير معروفة: وتشمل:

• كسور بالعظام.

• اضطرابات في الرؤية.

• شعور بالدوخة بعد الوقوف.

• تغير في وظائف الكبد.

• تكوين لبن في الثدى عند الرجال.

• ارق نفسي، نوبات هلع، أفكار إنتحار.

• متلازمة إفراز هرمون المضاد لإدرار البول بصورة غير ملائمة.

أبلغ الطبيب في حالة ظهور الأعراض الجانبية أو ظهور أثار أخرى غير مذرجة.

٥- الاحتياطات و التحذيرات :

- مرضى قصور القلب الإحتقاني،بطء ضربات القلب الغير منتظمة، إحتشاء عضلى قلبى أو استعداد لنقص البوتاسيوم بالدم أو الماغنسيوم بالدم لأنهم أكثر عرضة لحدوث مرض تورسادد بو بوانت .

- يجب عمل رسم قلب بصورة منتظمة مع مرضى قصور القلب الإحتقانى و بطء ضربات القلب الغير منتظمة.

- يجب ضبط نقص البوتاسيوم بالدم أو الماغنسيوم بالدم قبل البدء في إستخدام سيتالوبرام. يجب قياس الإلكتروليات.

- يجب إبلاغ الطبيب فورا في حالة ظهور أعراض أو علامات تغير أو عدم إنتظم ضربات القلب أثناء إستخدام سيتالوبرام.

- لا توقف أو تقلل جرعة سيتالوبرام بدون إستشارة الطبيب لتفادى أعراض سحب الدواء المفاجيء.

٦- العبوة وظروف التخزين :

يحفظ بعيدا عن متناول الأطفال.

يحفظ في درجة حرارة لا تتعدى ٣٠ درجة مئوية في مكان جاف.

علبة كرتون تحتوى على شريطين (الوانى فى سى) بكل شريط ٧ أقراص مغلفة و نشرة مرفقة.

إنتاج:

المجموعة المصرية للصناعات الدوائية

EGPI

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