SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Escitalopram Tablets USP 20 mg (ESCITAPRAM-20)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg Escitalopram (As Oxalate)

For full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated Tablets.

Distribution category POM

White coloured, round shaped, biconvex, film coated tablets having plain on both sides.

4. CLINICAL PARTICULARS

1. Therapeutic Indications

- Treatment of major depressive episodes.
- Treatment of panic disorder with or without agoraphobia.
- Treatment of social anxiety disorder (social phobia).
- Treatment of generalised anxiety disorder.
- Treatment of obsessive-compulsive disorder.

2. Posology and Method of Administration

Route of administration: It is administered orally single daily dose with or without regard to food intake. When stopping escitalopram treatments, gradual dose reduction should be considered. The safety of daily doses above 20 mg have not been established.

Adults:
Major depressive episodes: 10 mg single dose daily in adults. Depending on individual patient response, the dose may be increased to a maximum of 20 mg daily. Usually, 2-4 weeks are necessary for an antidepressant response.

Panic disorder with or without agoraphobia: An initial dose of 5 mg for the first week before increasing the dose to 10 mg daily. The dose may be further increased, up to a maximum of 20 mg daily, dependent on individual patient response. Maximum effectiveness is reached after about 3 months. The treatment lasts several months.

Social anxiety disorder: 10 mg once daily. Usually, 2-4 weeks are necessary to obtain symptom relief. The dose may subsequently, depend on individual patient response, be decreased to 5 mg or increased to a maximum of 20 mg daily. Chronic course: for 12 weeks and long-term course: for 6 months is recommend to consolidate response. It can be considered on an individual basis to prevent relapse; treatment benefits should be re-evaluated at regular intervals.

Generalized anxiety disorder and obsessive-compulsive disorder: Initial dosage is 10 mg once daily. Depending on the individual patient response, the dose may be increased to a maximum of 20 mg daily. Long-term course: at least 6 months in patients receiving 20 mg/ day.

Elderly patients (above 65 years of age): A lower (5 mg once daily) initial dose should be recommended.

Children and adolescents (<18 years): Not recommend.
Reduced kidney function: Not necessary to adjustment dose in patients with mild or moderate renal impairment. Caution is advice in patients with severely reduced renal function (CLCR less than 30 ml/min.)

Reduced liver function: Patients with liver complaints should not receive more than 10 mg/ day. Patients known to be poor metabolizers of the enzyme CYP2C19 Patients with this known genotype should not receive more than 10 mg per day. Take dose as prescribed by physician.

3. Contraindications

It is contraindicated hypersensitivity to escitalopram or to any of the excipients. Patients with known QT-interval prolongation or congenital long QT syndrome. Together with medicinal products that are known to prolong the QT-interval. Concomitant treatment with non-selective, irreversible monoamine oxidase inhibitors is contraindicated due to the risk of serotonin syndrome with agitation, tremor, hyperthermia etc. The combination of Escitalopram with reversible MAO-A inhibitors (e.g. moclobemide) or the reversible non-selective MAO-inhibitor linezolid is contraindicated due to the risk of onset of a serotonin syndrome.

4. Special warnings and precautions for use

Patients should be monitored for these symptoms when stopping treatment with Escitalopram. Sudden discontinuation should be avoided. When stopping treatment, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of discontinuation symptoms. The physician may continue decreasing the dose, but at a more gradual rate.

Paradoxical anxiety: Some patients may experience increased anxiety symptoms with treatment, subsides within two weeks. A low starting dose advised to reduce the likelihood of an anxiogenic effect.

Seizures: epilepsy patient’s treatment with escitalopram should be stopped if seizures occur for the first time or if there is an increase in the seizure frequency. Some patients with manic-depressive illness may enter into a manic phase. This is described by unusual and rapidly changing ideas, inappropriate happiness and excessive physical activity. Symptoms such as restlessness or difficulty in sitting or standing still can also occur during the first weeks of the treatment.
Diabetes: treatment with Escitalopram may alter glycaemic control. Insulin or oral hypoglycaemic dosage may need to be adjusted.
Suicide / suicidal thoughts or clinical worsening: Patients previously had thoughts about killing or harming yourself. Consult to physician or go to a hospital straight away. Increased

risk of suicidal behaviour with psychiatric conditions who were treated with an antidepressant.

The use of SSRIs / SNRIs has been associated with the development of akathisia and psychomotor restlessness.
Hyponatraemia: probably due to inappropriate antidiuretic hormone secretion, may reported rarely with the use of SSRIs and generally resolves on discontinuation of therapy. Caution should be exercised in patients at risk, such as the elderly or patients with cirrhosis, or if used in combination with other medications which may cause hyponatraemia.

Haemorrhage may be reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. SSRIs/SNRIs may increase the risk of postpartum haemorrhage. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function and in patients with known bleeding tendencies. Patients should take special precautions if they are receiving electroconvulsive therapy. Patients should take precaution by concomitant use increases the risk of serotonin syndrome. St. John's Wort: Concomitant use of SSRIs and herbal remedies containing (Hypericum perforatum) may result in an increased incidence of adverse reactions.

Patients have coronary heart disease. Patients suffer or have suffered from heart problems or have recently had a heart attack. Patients experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up, which may indicate abnormal functioning of the heart rate

Angle-closure glaucoma: increased pressure in the eye. Sexual dysfunction: SSRIs / SNRIs may cause symptoms of sexual dysfunction. In some cases, these symptoms have continued after stopping treatment.
Pregnancy: There are no adequate and well-controlled data in pregnant women therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation: It is excreted into human milk. It should not recommend during breast-feeding.
Excipients: Escitalopram tablets contains less than 1 mmol sodium (1.7469 mg) per tablet, that is to say essentially n'sodium-free'.

5. Interaction with other medicinal products and other forms of interaction

Non-selective monoamine oxidase inhibitors: phenelzine, iproniazid, isocarboxazid, nialamide, and tranylcypromine as active ingredients. If patients taken any of these medicines need to wait 14 days before you start taking escitalopram. After stopping patients must allow 7 days before taking any of these medicines. Reversible, selective MAO-A inhibitors: moclobemide (used to treat depression). Irreversible MAO-B inhibitors: selegiline (used to treat Parkinson's disease). Buprenorphine (a type of opioid medicine). Concomitant use increases the risk of serotonin syndrome, a potentially risk condition. The antibiotic linezolid. Lithium (used in the treatment of manic-depressive disorder) and tryptophan. Imipramine and desipramine (both used to treat depression). Sumatriptan (used to treat migraine) and tramadol (used against severe pain). Cimetidine, lansoprazole and omeprazole (used to treat stomach ulcers); fluconazole (used to treat fungal infections), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). St. John's Wort (Hypericum perforatum) a herbal remedy used for depression. Acetylsalicylic acid and non-steroidal anti-inflammatory drugs. These may increase

bleeding-tendency. Warfarin, dipyridamole and phenprocoumon. Patient probably check the coagulation time of your blood when starting and stop treatment in order to verify that your dose of anticoagulant is still adequate. Mefloquin (used to treat Malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain) due to a possible risk of a lowered threshold for seizures. Neuroleptics and antidepressants (tricyclic antidepressants and SSRIs) due to a possible risk of a lowered threshold for seizures, and antidepressants. Flecainide, propafenone and metoprolol (used in cardiovascular diseases); clomipramine and nortriptyline (antidepressants) and risperidone, thioridazine and haloperidol (antipsychotics).

6. Pregnancy and Lactation

Pregnancy: There are no adequate and well-controlled data in pregnant women therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: It is excreted into human milk. It should not recommend during breast-feeding.

7. Effects on ability to Drive and use Machines

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

8. Undesirable effect

Allergy, pain in limb, fever, hot flushes, chest pain. Edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Blood and Lymphatic System Disorders: Hemolytic anemia, leukopenia, thrombocytopenia. Endocrine Disorders: Diabetes mellitus, hyperprolactinemia. Psychiatric Disorders: Acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, grand mal seizures, hypo aesthesia, myoclonus, tardive dyskinesia. Cardiac Disorders: Atrial fibrillation, cardiac failure, myocardial infarction, ventricular arrhythmia, ventricular tachycardia. Respiratory, Thoracic and Mediastinal Disorders: Pulmonary embolism, bronchitis, sinus congestion, coughing, nasal congestion, asthma, breath shortness, pneumonia, tracheitis. Gastrointestinal Disorder: GI and rectal hemorrhage, pancreatitis, abdominal cramp. Musculoskeletal and Connective Tissue Disorders: Arthralgia, myalgia, rhabdomyolysis. Hepatobiliary Disorders: Fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Renal and Urinary Disorders: Acute renal failure, uti, urinary urgency, dysuria, blood in urine. Reproductive System and Breast Disorders: Priapism, menstrual cramps, breast neoplasm.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA**

9. Overdose

The overdose is limited and many cases involve concomitant overdoses of other drugs. Doses 400-800 mg of escitalopram alone without any severe symptoms. Serious cases of alone taken escitalopram overdose have rarely,

Symptoms: most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, arrhythmia, hypokalaemia, hyponatraemia, and ECG changes. Acute renal failure very rare may be reported accompanying overdose.

Treatment: There are no specific antidotes. Establish and maintain an airway, ensure adequate oxygenation and respiratory function. Gastric lavage and the use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic Group: Antidepressants, selective serotonin reuptake inhibitors
ATC Code: N 06 AB 10
It is a selective inhibitor of serotonin (5-HT) re-uptake with high affinity for the primary binding site. It also binds to an allosteric site on the serotonin transporter, with a 1000fold lower affinity. It has no or low affinity for serotonergic or other receptors including alpha and beta-adrenergic (α1, α2, β), dopamine (DA D1 and D2), histamine (H1, 5-HT1A, 5-HT2), muscarinic, and benzodiazepine and opioid receptors. The inhibition of 5-HT re-uptake is the only likely mechanism of action explaining the pharmacological and clinical effects of escitalopram.

5.2 Pharmacokinetic Properties

Absorption: 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 is expected to be about 80%. **Distribution:** The volume of distribution is about 12 to 26 L/kg. The plasma protein binding is below 80% for escitalopram and its main metabolites. **Metabolism:** It is metabolised in the liver to the demethylated citalopram and didemethylated citalopram metabolites. Alternatively, the nitrogen may be oxidised to form the N-oxide metabolite. Both parent substance and metabolites are partly excreted as glucuronides. Unchanged escitalopram is the predominant compound in plasma. After multiple dosing the mean concentrations of the dimethyl and didemethyl metabolites are usually 28 - 31% and <5% of the escitalopram concentration, respectively. Biotransformation of escitalopram to the demethylated metabolite is mediated by a combination of CYP2C19, CYP3A4 and CYP2D6. **Elimination:** The elimination half-life (t½β) after multiple dosing is about 30 hours and the oral plasma clearance is about 0.6 L/min. The major metabolites have a significantly longer half-life. Major metabolites 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.

Special population:

Linearity: Average steady-state concentrations of 50 nmol/L (range 20-125 nmol/L) achieved at a (daily dose of 10 mg) in about 1 week.

Elderly patients (>65 years): It appears to be eliminated more slowly (systemic exposure (AUC 50 %) higher in elderly patients compared to younger patients.

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 (CLcr 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.

5.3 Preclinical Safety Data

No complete conventional battery of preclinical studies was performed with escitalopram since the bridging toxicokinetic and toxicological studies conducted in rats with escitalopram and citalopram showed a similar profile. Therefore, all the citalopram information can be extrapolated to escitalopram.

In comparative toxicological studies in rats, escitalopram and citalopram caused cardiac toxicity, including congestive heart failure, after treatment for some weeks, when using dosages that caused general toxicity. The cardiotoxicity seemed to correlate with peak plasma concentrations rather than to systemic exposures (AUC). Peak plasma concentrations at no-effect-level were in excess (8-fold) of those achieved in clinical use, while AUC for escitalopram was only 3 - to 4 -fold higher than the exposure achieved in clinical use. For citalopram AUC values for the S-enantiomer were 6- to 7-fold higher than exposure achieved in clinical use. The findings are probably related to an exaggerated influence on biogenic amines i.e. secondary to the primary pharmacological effects, resulting in hemodynamic effects (reduction in coronary flow) and ischaemia. However, the exact mechanism of cardiotoxicity in rats is not clear. Clinical experience with citalopram, and the clinical trial experience with escitalopram, does not indicate that these findings have a clinical correlate.

Increased content of phospholipids has been observed in some tissues e.g. lung, epididymides and liver after treatment for longer periods with escitalopram and citalopram in rats. Findings in the epididymides and liver were seen at exposures similar to that in man. The effect is reversible after treatment cessation. Accumulation of phospholipids(phospholipidosis) in animals has been observed in connection with many cationic amphiphilic medicines. It is not known if this phenomenon has any significant relevance for man.

In the developmental toxicity study in the rat, embryotoxic effects (reduced foetal weight and reversible delay of ossification) were observed at exposures in terms of AUC in excess of the exposure achieved during clinical use. No increased frequency of malformations was noted. A pre- and postnatal study showed reduced survival during thelactation period at exposures in terms of AUC in excess of the exposure achieved during clinical use.

Animal data have shown that citalopram induces a reduction of fertility index and pregnancy index, reduction in number in implantation and abnormal sperm at exposure well in excess of human exposure. No animal data related to this aspect are available for Escitalopram.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose (PH 102)
Croscarmellose Sodium
Colloidal Anhydrous Silica (Aerosil)
Povidone (PVPK-30)
Magnesium Stearate
Isopropyl Alcohol (IPA)
Purified water

Insta coat Universal :
Hydroxy Propyl Methyl Cellulose
Polyethylene Glycol
Titanium dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

3 x 10 Tablets Alu-PVDC blister pack.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.MARKETING AUTHORIZATION HOLDER

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
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Website: www.lincolnpharma.com

7.2 Name and Address of Manufacturing Site(s)

Lincoln Pharmaceuticals Limited
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Website: www.lincolnpharma.com

8 MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0496

9 DATE OF FIRST <REGISTRATION> / RENEWAL OF THE REGISTRATION

05th December, 2022

10 DATE OF REVISION OF THE TEXT