SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lofepramine 70mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 76.1mg Lofepramine Hydrochloride (equivalent to 70mg Lofepramine base)

Excipients with known effects:

Ethanol – 395mg/5ml
Liquid maltitol (E965) – 1708mg/5ml,
Methyl hydroxybenzoate(E218) – 6mg/5ml
Propyl hydroxybenzoate (E216) – 1.5mg/5ml
Sorbitol (E420) –1364mg/5ml
Propylene glycol (E1520) – 108.4mg/5ml

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white to pale yellow/orange suspension with odour of Cherry.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of symptoms of depressive illness.

4.2 Posology and method of administration

Posology
Adults: The usual dose 70mg twice daily (140mg) or three times daily (210mg) depending upon patient response.

Elderly: Elderly patients may respond to lower doses in some cases.

Paediatric population: Not recommended

Method of administration: Oral

4.3 Contraindications

Lofepramine should not be used in patients hypersensitive to lofepramine, dibenzazepines, or any of the excipients listed in section 6.1.
Lofepramine should not be used in patients:

- with mania
- with severe liver impairment and/or severe renal impairment
- with heart block
- with cardiac arrhythmias
- during the recovery phase following a myocardial infarction
- with untreated narrow angle glaucoma
- with prostatic hypertrophy with urinary retention.
- at risk for paralytic ileus

Lofepramine should not be administered with or within 2 weeks of cessation of therapy with monoamine oxidase inhibitors (see Section 4.5).
Use of lofepramine with amiodarone should be avoided (see Section 4.5).
Use of lofepramine with terfenadine should be avoided (see Section 4.5).

Lofepramine must not be administered in patients with acute alcoholic, hypnotic, analgesic and psychotropic drug poisoning and acute deliria.

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 lofepramine are 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.

A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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.

It should be remembered that severely depressed patients are at risk of suicide. An improvement in depression may not occur immediately upon initiation of treatment, therefore the patient should be closely monitored until symptoms improve.

Lofepramine may lower the convulsion threshold, therefore it should be used with extreme caution in patients with a history of epilepsy or recent

convulsions or other predisposing factors, or during withdrawal from alcohol or other drugs with anticonvulsant properties.

Concurrent electroconvulsive therapy should only be undertaken with careful supervision.

Caution is needed in patients with hyperthyroidism, or during concomitant treatment with thyroid preparations, since aggravation of unwanted cardiac effects may occur.

Lofepramine should be used with caution in patients with cardiovascular disease, impaired liver or renal function, or porphyria.

Caution is called for where there is a history of prostatic hypertrophy, narrow angle glaucoma or increased intra-ocular pressure, because of lofepramine's anticholinergic properties.

In chronic constipation, tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients.

Care should be exercised in patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma) in whom tricyclic antidepressants may provoke hypertensive crises.

Blood pressure should be checked before initiating treatment because individuals with hypertension, or an unstable circulation, may react to lofepramine with a fall in blood pressure.

Anaesthetics may increase the risks of arrhythmias and hypotension (see Interactions), therefore before local or general anaesthesia, the anaesthetist should be informed that the patient has been taking lofepramine.

Lofepramine should be used with caution where there is a history of mania. Psychotic symptoms may be aggravated. There have also been reports of hypomanic or manic episodes during a depressive phase in patients with cyclic affective disorders receiving tricyclic antidepressants.

It is recommended that abrupt withdrawal of lofepramine be avoided unless essential, because withdrawal symptoms may occur on abrupt cessation of therapy. Withdrawal symptoms may include insomnia, irritability and excessive perspiration.

Lofepramine can prolong the QT-interval in The ECG and may lead to Torsades de Pointes. Lofepramine may only be used with particular caution when other risk factors for Torsades de Pointes are present, such as:

- congenital long QT syndrome
- other clinically significant cardiac disorders
- parallel treatment with medicinal products,

which also prolong the QT interval in the ECG or can cause hypokalaemia. If Torsades de Pointes occur the treatment with lofepramine has to be stopped.

There are isolated reports of agranulocytosis, pancytopenia and thrombocytopenia reported in association with lofepramine (see section 4.8). Monitoring of full blood count should be considered before start of treatment and periodically during treatment, particularly in patients with a history of blood dyscrasias.

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking lofepramine.

Serotonin syndrome
Concomitant administration of lofepramine and buprenorphine, buprenorphine/naloxone may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5). If concomitant treatment with buprenorphine-containing drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Excipient Warnings
This product contains:

- 10%v/v ethanol. This medicine contains 395mg of alcohol (ethanol) in each 5 ml dose which is equivalent to 10ml of beer or 4ml of wine per dose. A dose of 15ml of this medicine administered to an adult weighing 70 kg would result in exposure to 17mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 3mg/100ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects.
- Liquid maltitol (E965). Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Sorbitol (E420). This medicine contains 1364mg sorbitol in each 5ml dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicine.
- Methyl (E218) and propyl hydroxybenzoates (E216). May cause allergic reactions (possibly delayed)
- Propylene glycol (E1520). This medicine contains 108.4mg propylene glycol per 5ml dose.
- Sodium. This medicine contains less than 1mmol sodium (23mg) per 5ml dose, that is to say essentially ‘sodium-free’.

Paediatric population
Lofepramine is not recommended for the treatment of children and adolescents under the age of 18 years.

4.5 Interaction with other medicinal products and other forms of interaction

MAO Inhibitors: Lofepramine should not be administered concurrently with or within 2 weeks of cessation of therapy of monoamine oxidase inhibitors. It should then be introduced cautiously using a low initial dosage.

SSRI Inhibitors: co-medication may lead to additive effects on the serotonergic system. Fluvoxamine and fluoxetine may also increase plasma concentrations of lofepramine resulting in a lowered convulsion threshold and seizures.

Anti-arrhythmic drugs: There is an increased risk of ventricular arrhythmias if lofepramine is given with drugs which prolong the Q-T interval e.g. disopyramide, procainamide, propafenone, quinidine and amiodarone. Concomitant use with amiodarone should be avoided (See Section 4.3)

Sympathomimetic drugs: Lofepramine should not be given with sympathomimetic agents (e.g. adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephedrine, phenylpropanolamine) since their cardiovascular effects may be potentiated.

CNS depressants: Lofepramine's effects may be potentiated when administered with CNS depressant substances e.g. barbiturates, general anaesthetics and alcohol.

Anaesthetics: Anaesthetics given during tricyclic antidepressant therapy may increase the risk of arrhythmias and hypotension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated (see Section 4.4).

Anxiolytics and Hypnotics: An enhanced sedative effect has been reported when taken with lofepramine.

Antipsychotics: There is an increased risk of ventricular arrhythmias with antipsychotics and lofepramine. Plasma levels of tricyclic antidepressant may increase and a lowered convulsion threshold and seizures may occur. It is advised to avoid concomitant use with pimozide and sertindole. There have been incidences of increased plasma concentrations of tricyclic antidepressants and increased antimuscarinic side effects with phenothiazines and possibly clozapine.

Non-antiarrhythmic agents which may prolong the QT interval: There is an increased risk of ventricular arrhythmias which may lead to Torsades de Pointes if Lofepramine is given with non- anti-arrhythmic agents which prolong the QT interval e.g. certain antibiotics (e.g. macrolides), malaria agents (e.g. halofantrine), antihistamines, neuroleptic agents. Particular caution is advised if Lofepramine is used in combination with such agents.

Medicinal products that may cause hypokalaemia: Combination with medicinal products that may cause hypokalaemia may increase the risk for ventricular arrhythmias including Torsades de Pointes. Particular caution is advised if Lofepramine is used in combination with such agents.

Adrenergic neurone blockers: Lofepramine may decrease or abolish the antihypertensive effects of some adrenergic neurone blocking drugs e.g. guanethidine, betanidine, resperine, clonidine and α-methyl-dopa. Antihypertensives of a different type e.g. diuretics, vasodilators or β-blockers should be given therefore where patients require co-medication for hypertension.

Anticoagulants: Lofepramine may change the anticoagulant effect by inhibiting hepatic metabolism. Possible interactions between lofepramine and warfarin, leading to an enhancement of anticoagulant effect, have been reported rarely. Careful monitoring of plasma prothrombin is advised.

Anti-cholinergic agents: Lofepramine may potentiate the effects of these drugs (e.g. phenothiazine, antiparkinson agents, antihistamines, atropine, beperiden) on the central nervous system, eye, bowel and bladder.

Analgesics: There is an increased risk of ventricular arrhythmias with lofepramine and analgesics. Increased side effects may result with nefopam. There is a possible risk of convulsions with tramadol and a possibility of increased sedation with opioid analgesics.

Anti-epileptics: Antagonism can lead to a lowering of the convulsive threshold. Plasma levels of some tricyclic antidepressants, and therefore the therapeutic effect, may be reduced.

Calcium channel blockers: diltiazem and verapamil increase the plasma concentration of lofepramine.

Diuretics: There is an increased risk of postural hypotension.

Antihistamines: Avoid concomitant use with terfenadine due to increased risk of ventricular arrhythmias (see Section 4.3). When taken with lofepramine an increased antimuscarinic and sedative effect is observed.

Rifampicin: The metabolism of lofepramine is accelerated by rifampicin leading to a reduced plasma concentration

Digitalis glycosides: With digitalis glycosides there is a higher risk of arrhythmias.

Sotalol: The risk of ventricular arrhythmias associated with sotalol is increased.

Cisapride: The risk of ventricular arrhythmias associated with cisapride is increased.

Cimetidine: Cimetidine can increase the plasma concentration of lofepramine.

Altretamine: There is a risk of severe postural hypotension when co-administered with tricyclic antidepressants

Disulfiram and alprazolam: Co-medication with either disulfiram or alprazolam may require a reduction in the dose of lofepramine.

Nitrates: The effectiveness of sublingual nitrates may be reduced where the tricyclic antidepressant's anticholinergic effect has lead to dryness of the mouth.

Ritonavir: There may be an increased plasma concentration of lofepramine.

Thyroid hormone therapy: During concomitant treatment, there may be aggravation of unwanted cardiac effects.

Oral contraceptives: Oestrogens and progestogens may antagonise the therapeutic effect of tricyclic antidepressants whilst the latter's side effects may be exacerbated due to an increased plasma concentration.

Dopaminergics: CNS toxicity has been reported with selegiline. Avoid concomitant use of lofepramine with entacapone.

Muscle relaxants: An enhanced muscle relaxant effect occurs with baclofen when administered with lofepramine.

Lofepramine should be used cautiously when co-administered with: drugs containing buprenorphine (buprenorphine, buprenorphine / naloxone) as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

4.6 Fertility, Pregnancy and lactation

Pregnancy

The safety of Lofepramine for use during pregnancy has not been established and there is evidence of harmful effects in pregnancy in animals when high doses are given. Lofepramine has been shown to be excreted in breast milk. The administration of Lofepramine in pregnancy and during breast feeding therefore, is not advised unless there are compelling medical reasons.

Adverse effects such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers have taken tricyclic antidepressants during the last trimester of pregnancy.

Breast-feeding
Lofepramine is excreted in breast milk. The administration of lofepramine during breast-feeding is not advised unless there are compelling medical reasons.

4.7 Effects on ability to drive and use machines

Ability to drive a car and operate machinery may be affected. Therefore caution should be exercised initially until the individual reaction to treatment is known.

4.8 Undesirable effects

The following side effects have been reported with Lofepramine:

Investigations:
Changes of blood sugar level

Cardiac disorders:
Tachycardia, cardiac conduction disorders, increase in cardiac insufficiency, QT-prolongation, arrhythmias (including ventricular arrhythmias or Torsades de Pointes.)

Nervous system disorders:
Dizziness, headache, paraesthesia, tremor; rarely, drowsiness, convulsions, impairment of the sense of taste; very rarely, uncoordinated movement.

Reproductive system and breast disorders:
Interference with sexual function, testicular disorders (e.g. testicular pain), gynaecomastia, galactorrhoea.

Skin and subcutaneous tissue disorders:

Skin rash, allergic skin reactions, “photosensitivity reactions”; rarely, cutaneous bleeding, sweating.

Gastrointestinal disorders:
Gastrointestinal disturbances including nausea, vomiting, diarrhoea; constipation and dryness of mouth.

Endocrine disorders:
Rarely, inappropriate secretion of antidiuretic hormone leading to hyponatraemia.

Blood and lymphatic system disorders:
Rarely, bone marrow depression including isolated reports of: agranulocytosis, eosinophilia, granulocytopenia, leucopenia, pancytopenia, thrombocytopenia.

Eye disorders:
Visual disturbances including blurred vision, mydriasis, disturbances of accommodation; induction of glaucoma.

Ear and labyrinth disorders:
Very rarely, tinnitus

Renal and urinary disorders:
Urinary hesitancy, urinary retention

Vascular disorders:
Hypotension

General disorders and administration site conditions:
Malaise, facial oedema; rarely, inflammation of mucosal membranes.

Hepatobiliary disorders:
Increases in liver enzymes, sometimes progressing to clinical hepatitis and jaundice, have been reported in some patients, usually occurring within the first 3 months of starting therapy.

Psychiatric disorders:
Sleep disturbances, agitation, confusion, nightmares, hallucinations, hypomania, mania, psychoses, delirium.
Cases of suicidal ideation and suicidal behaviours have been reported during lofepramine therapy or early after discontinuation (see section 4.4)
It should be remembered that severely depressed patients are at risk of suicide until there is a complete remission of symptomatology.
Epidemiological studies, mainly in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRls and TCAs. The mechanism leading to this risk is unknown.

Reporting of suspected adverse reactions:

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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Treatment of overdosage is symptomatic and supportive. It should include immediate gastric lavage and routine close monitoring of cardiac function. Reports of overdosage with Lofepramine, with quantities ranging from 0.7g up to 6.72g, have shown no serious sequelae directly attributable to the drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors
ATC code: N06AA07

Lofepramine inhibits the re-uptake of monoamines in peripheral adrenergic nerves. Lofepramine produces a lesser increase in heart rate than that produced by Amitriptyline when administered to normal individuals.

5.2 Pharmacokinetic properties

Absorption
Lofepramine is rapidly absorbed with peak plasma concentration being reached within 1 hour and having a plasma half-life of 5 hours. In common with Imipramine, Lofepramine appears to undergo significant presystemic metabolism.

Distribution
Plasma protein binding is approximately 99%. After oral administration higher concentrations of Lofepramine and its metabolites can be found in blood, lungs, liver, kidney and brain.

Biotransformation and Elimination

Almost all the drug is metabolized before excretion, which is mainly in the urine and in faeces. Lofepramine is metabolized by N-dealkylation, hydroxylation and glucuronidation. It is extensively metabolized to its principal metabolite, desmethylimipramine, on first pass through the liver. During chronic administration, the plasma level of desmethylimipramine is typically three times greater than that of lofepramine, except in the first few hours following administration of each dose, during which time the plasma level of the parent drug can exceed that of its metabolite. Desipramine, which is also an antidepressant is converted to 2-hydroxydesipramine in the liver. Both compounds are excreted mainly in the urine as glucuronides, but also by biliary excretion in the faeces. Less than 5% is excreted unchanged in the urine over 24 hours.

Neither renal disease nor old age has any appreciable effect on the kinetics of desipramine. Elimination may be reduced and bioavailability increased in hepatic disease.

5.3 Preclinical safety data

Lofepramine Hydrochloride is a well established active substance.

Lofepramine, like other tricyclic antidepressants, has been shown to inhibit the neuronal uptake of noradrenaline and to potentiate serotonergic transmission.

The safety of Lofepramine for use during pregnancy has not been established and there is evidence of harmful effects in pregnancy in animals when high doses are given. Lofepramine has been shown to be excreted in breast milk. The administration of Lofepramine in pregnancy and breast feeding therefore, is not advised unless there are compelling medical reasons.

Adverse effects such as withdrawal symptoms, respiratory depression and agitation have been reported in neonates whose mothers have taken tricyclic antidepressants during the last trimester of pregnancy.

The toxicological data available in the published literature on lofepramine have not revealed any hazards, which are likely to occur at the usual oral therapeutic dosage. The excipients in the formulation would not be anticipated to influence the pharmacology or toxicology of the drug.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water, sodium ascorbate, sorbitol solution 70% (non-crystallising)(E420), liquid maltitol (E965), methyl hydroxybenzoate (E218), propyl hydroxybenzoate (E216), propylene glycol (E1520), ethanol (absolute), colloidal silicon dioxide (aerosil) and cherry flavour (contains propylene glycol) 28T7704.

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store between 4°C and 25°C. Protect from light.

6.5 Nature and contents of container

Bottle: Amber (type III) glass bottle
Capacity: 150ml
Closure: HDPE, EPE wadded, tamper evident, child resistant

6.6 Special precautions for disposal

Keep out of the sight and reach of children. Shake before use.

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

7 MARKETING AUTHORISATION HOLDER

Essential Pharma Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 41871/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

19/09/2024