SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lofepramine 70 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 76.10 mg lofepramine hydrochloride, equivalent to 70 mg lofepramine.

Excipients with known effect
Each film-coated tablet contains 126.05 mg lactose and 1.15 mg ponceau 4R (E124).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, violet-brown film-coated tablet, approximately 10 mm diameter and with a score line on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of symptoms of depressive illness.

4.2 Posology and method of administration

Posology

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

Elderly

Elderly patients may respond to lower doses in some cases.
Paediatric population

Lofepramine is not recommended in children.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to lofepramine or to any of the excipients listed in section 6.1 or dibenzazepines.

Lofepramine must not be used in patients:

- with mania
- with severe liver impairment
- with severe renal impairment
- with heart block
- with cardiac arrhythmias
- in the recovery phase following a myocardial infarction
- with untreated narrow angle glaucoma
- with prostatic hypertrophy with urinary retention
- at risk for paralytic ileus (see section 4.4)

Lofepramine must not be administered with or within 2 weeks of cessation of therapy with monoamine oxidase inhibitors (see section 4.5).

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

Use of Lofepramine with amiodarone should be avoided (see section 4.5).

Use of Lofepramine with terfenadine should be avoided (see section 4.5).

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.
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.

**Other warnings and precautions**

Lofepramine may lower the convulsion threshold, it should therefore 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, because it is associated with a risk of cardiovascular adverse reactions in all age groups.

Lofepramine should be used with caution in patients with impaired liver function, impaired renal function, blood dyscrasias 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 patients with narrow angle glaucoma, lofepramine may only be used if adequate glaucoma treatment is given.

In chronic constipation, tricyclic antidepressants may cause paralytic ileus, particularly in elderly and bedridden patients (see section 4.3).

Care should be exercised in patients with tumours of the adrenal medulla (e.g. phaeochromocytoma, neuroblastoma) in whom tricyclic antidepressants may provoke antihypertensive 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 risk of arrhythmias and hypotension (see section 4.5), 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 hypomania or manic episodes during a depressive phase in patients with cyclic affective disorders receiving 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,
- patients with a family history of QT prolongation

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.

Overall, lofepramine has a low risk to induce a QT interval prolongation at therapeutic doses. However, drugs which inhibit the cytochrome P450-2D6 enzyme like quinidine, cimetidine, phenothiazine (e.g. chlorpromazine, levomepromazine), selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline, paroxetine) may increase the plasma concentrations of lofepramine. Therefore, concomitant use of these drugs might have an impact on the QT interval.

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.

The film-coated tablets contain ponceau 4R (E124), which may cause allergic reactions.

These tablets also contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
**MAO Inhibitors:** Lofepramine must not be administered with or within 2 weeks of cessation of therapy with monoamine oxidase inhibitors (see section 4.3). Thereafter, cautious initiation of therapy is recommended using a low initial dose and the effects monitored.

**Terfenadine:** Concomitant use with lofepramine should be avoided (see section 4.3).

**Antiarrhythmic drugs:** There is an increased risk of ventricular arrhythmias, which may lead to Torsades de Pointes if lofepramine is given with drugs which prolong the QT interval e.g. disopyramide, procainamide, propafenone, quinidine, sotalol and amiodarone. Particular caution is advised if lofepramine is used in combination with such agents. Concomitant use with amiodarone should be avoided (see section 4.3).

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

**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.

**Sympathomimetic Drugs:** Lofepramine should not be given with sympathomimetic agents (e.g. adrenalin, 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. If surgery is necessary, the anaesthetist should be informed that a patient is being treated because of the increased risk of arrhythmias and hypotension.

**Neuroleptics:** In addition to increased risk of arrhythmias, there may be an increased plasma level of the tricyclic antidepressant, a lowered convulsion threshold and seizures.

**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, 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.

**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.

**Anticoagulants:** Lofepramine may inhibit hepatic metabolism leading to an enhancement of anticoagulant effect. 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, biperiden) on the central nervous system, eye, bowel and bladder.

**Analgesics:** There is an increased risk of ventricular arrhythmias.

**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 may increase the plasma concentration of lofepramine.

**Diuretics:** There is an increased risk of postural hypotension.

**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.

**Cimetidine:** Can increase the plasma concentration of lofepramine.

**Clonidine:** The effect of antihypertensive agents of the clonidine type can be weakened.

**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 led to dryness of the mouth.

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

### 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 cross the placenta. The administration of lofepramine in pregnancy 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 has been shown to be excreted in breast milk. The administration of lofepramine in breast-feeding is not advised unless there are compelling medical reasons.

4.7 Effects on ability to drive and use machines

As with other antidepressants, ability to drive a car and operate machinery may be affected, especially in conjunction with alcohol. 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:

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

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

Psychiatric disorders:
Sleep disturbances, agitation, confusion, nightmares, hallucinations, mania, psychoses, delirium; rarely, hypomania.

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

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

Ear and labyrinth disorders:
Very rarely, tinnitus.

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

Vascular:
Hypotension.

**Gastrointestinal disorders:**
Gastrointestinal disturbance including nausea, vomiting, diarrhoea, constipation, dryness of mouth.

**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.

**Skin and subcutaneous tissue disorders:**
Skin rash, allergic skin reactions, photosensitivity reactions; rarely, cutaneous bleeding, sweating.

**Renal and urinary disorders:**
Urinary hesitancy, urinary retention.

**Reproductive system and breast disorders:**
Testicular disorders (e.g. testicular pain); rarely, interference with sexual function, gynaecomastia, galactorrhoea.

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

**Investigations:**
Rarely, changes of blood sugar level.

The following adverse effects have been encountered in patients under treatment with tricyclic antidepressants and should therefore be considered as theoretical hazards of lofepramine even in the absence of substantiation: psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants.

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.

**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.

**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](http://www.mhra.gov.uk/yellowcard)
4.9 Overdose

The treatment of overdosage is symptomatic and supportive. It should include immediate gastric lavage and routine close monitoring of cardiac function. Reports of overdosage with 0.7 to 6.72 g have shown no serious sequelae directly attributable to lofepramine.

5  PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Lofepramine is a tricyclic antidepressant. It exerts its therapeutic effect by blocking the uptake of noradrenaline by the nerve cell thus increasing the amine in the synaptic cleft and hence the effect on the receptors. There is evidence to suggest that serotonin may also be involved. Other pharmacological effects are due to anti-cholinergic activity, but less sedation is observed than with many other tricyclics.

5.2 Pharmacokinetic properties

Lofepramine is a tertiary amine, similar in structure to imipramine but with improved lipophilicity and lower base strength. It is readily absorbed when given orally. From the plasma it is distributed throughout the body notably to the brain, lungs, liver and kidney. It is metabolised in the liver by cleavage of the p-chlorophenacyl group from the lofepramine molecule, leaving desmethylimipramine (DMI).

The latter is pharmacologically active. The p-chlorobenzoyl portion is mainly metabolised to p-chlorobenzoic acid which is then conjugated with glycine. The conjugate is excreted mostly in the urine. DMI has been found excreted in the faeces. In a study of protein binding capability it has been found that lofepramine is up to 99% protein bound.

5.3 Preclinical safety data

Acute and chronic animal toxicity studies, a mutagenicity test, carcinogenicity test and studies to investigate reproduction toxicity, have shown no further hazards which are not already described under section 4.4.

Preclinical studies investigating effects of lofepramine and desipramine, its major active metabolite, on cardiac repolarisation are limited. Both compounds are able to block various ion channels participating in cardiac depolarisation and repolarisation with effects only at concentrations above the free plasma level at the recommended human dose. Decrease in heart rate and QTc-prolongation were seen in dogs at dose
levels of 25 mg/kg and higher, approximately 6 times above the therapeutic dosage of 140 mg lofepramine per day calculated on a mg/m² basis (60 kg patient).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:
Lactose
Maize starch
Ascorbic acid
Talc
Glycerol
Glycerol monostearate 40-55
Disodium edetate
Dimeticone
Hypermellose
Silica, colloidal anhydrous

The film-coating contains:
Propylene glycol
Hypermellose
Ponceau 4R (E124)
Talc
Titanium dioxide (E171)
Indigotine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC-Alu blister pack in packs of 28, 56, 1008 and 2016 film-coated tablets.

Polypropylene pot with polyethylene cap and optional use of polyethylene ullage filler in packs of 56, 250, 500 and 1000 film-coated tablets.

Amber glass bottle in packs of 56 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0307

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

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10 DATE OF REVISION OF THE TEXT

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