SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lofepramine 70mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lofepramine base 70mg (as 76.1mg of lofepramine hydrochloride).

Excipients with known effect: Each tablet contains 133mg Lactose, 0.01mg Sunset yellow and 1.22mg Carmoisine.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Violet brown film coated tablet, approx 10mm diameter

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 is 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
Lofepramine tablets are for oral administration only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lofepramine must not be used in patients hypersensitive to 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.

Lofepramine must not be administered with or within 2 weeks of cessation of therapy with monoamine oxidase inhibitors.

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 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. 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, 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.

Care should be exercised in patients with tumours of the adrenal medulla (eg 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 risks 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 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
• 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 occurs 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 that inhibit the cytochrome P450-2D6 enzyme such as 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.

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.

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

Excipient warning
Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sunset yellow and Carmoisine
Lofepramine tablets contain Sunset yellow FCF (E110) and Carmoisine (E122). May cause allergic reactions.

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. Thereafter, cautious initiation of therapy is recommended using a low initial dose and the effects monitored.

SSRIs:
Co-medication of lofepramine 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 agents:
There is an increased risk of ventricular arrhythmias, which may lead to Torsade de Pointes if lofepramine is given with anti-arrhythmic agents which prolong the Q-T interval e.g. disopyramide, procainamide, propafenone, quinidine, sotalol and amiodarone. Particular caution is advised if Lofepramine is used in combination with such agents.

Sympathomimetic drugs:
Lofepramine should not be given with sympathomimetic agents e.g. adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephedrine) 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:
If surgery is necessary, the anaesthetist should be informed that the patient is being so treated because of the increased risk of arrhythmias and hypotension.

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

Neuroleptic agents:
In addition to an increased risk of arrhythmias , there may be an increased plasma levels of the tricyclic antidepressant, a lowered convulsion threshold and seizures. 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, 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, resperine, clonidine and α-methyl-dopa. Antihypertensives of a different type e.g. diuretics, vasodilators or β-blockers should therefore be given where patients require co-medication for hypertension.

Anti-coagulants:

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) 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 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

Cimetidine:
Cimetidine can increase the plasma concentration of lofepramine.

Alprazolam:
Co-medication with 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. Adverse reactions of tricyclic antidepressants may be exacerbated due to an increased plasma concentration.

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

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 cross the placenta. The administration of Lofepramine in pregnancy is therefore 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

As with other antidepressants, the 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 adverse reactions reported with Lofepramine are listed below by system organ class.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Rare: bone marrow depression including isolated reports of agranulocytosis, eosinophilia, granulocytopenia, leucopenia, pancytopenia, thrombocytopenia.

Endocrine disorders:

Rare: inappropriate secretion of antidiuretic hormone leading to hyponatraemia.

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.

Nervous system disorders:

Dizziness, headache, paraesthesia, tremor.

Rare: drowsiness, convulsions, impairment of the sense of taste.

Very rare: uncoordinated movement.

Eye disorders:

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

Ear and labyrinth disorders:

Very rare: tinnitus.

Cardiac disorders:

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

Vascular disorders:

Hypotension.

Gastrointestinal disorders:

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

Hepatobiliary disorders:

Raised liver enzyme levels, 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, and “photosensitivity reactions”.

Rare: cutaneous bleeding, sweating.

Renal and urinary disorders:

Urinary hesitancy, urinary retention.

Reproductive system and breast disorders:

Interference with sexual function, testicular disorders (e.g. testicular pain), gynaecomastia, galactorrhoea.

General disorders and administration site conditions:

Malaise, facial oedema.

Rare: inflammation of mucosal membranes.

Investigations:

Changes of blood sugar level.

Class effects

Epidemiological studies, mainly 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 website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The treatment of overdosage is symptomatic and supportive. It should include immediate gastric lavage and routine close monitoring of cardiac function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressants, Non-selective monoamine reuptake inhibitors
ATC code: N06A A07

Mechanism of action
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.

When compared with imipramine, lofepramine had significantly reduced anticholinergic side effects. Whereas imipramine increases the intensity of delta, theta and beta frequencies of the EEG, lofepramine affects only the beta band. Lofepramine produces a lesser increase in heart rate than that produced by amitriptyline when administered to normal individuals.

Pharmacodynamic effects
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 other tricyclics.

5.2 Pharmacokinetic properties

Absorption
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, 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
From the plasma it is distributed throughout the body notably to the brain, lungs, liver, and kidney.

Biotransformation
Almost all the drug is metabolised before excretion, which is mainly in the urine and in faeces. Lofepramine is metabolised by N-dealkylation, hydroxylation and glucuronidation. 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. 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.

Elimination
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. Less than 5% is excreted unchanged in the urine over 24 hours. In a study of protein binding capability it has been found that lofepramine is up to 99% protein bound.

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.

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).

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

Citric acid
Lactose
Maize starch
Povidone K25
Glycerol
Vegetable oil hydrogenated

Film Coat
Opadry Purple 03B25514
Hypromellose 6cP
Carmoisine (E122)
Indigo Carmine Aluminium Lake
Macrogol 400
Iron Oxide Red
Titanium Dioxide
Sunset Yellow FCF Aluminium Lake (E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Blister: Store below 25°C. Store in the original package.
Container: Store below 25°C. Keep the bottle tightly closed.

6.5 Nature and contents of container

White opaque PVC/PE/PVDC blister pack with aluminium foil seal and contained in cardboard cartons. Pack sizes 28, 30, 56, 60 and 100 tablets.

HDPE Duma container with white LDPE Securipac cap. Pack size 250 tablets

HDPE container with induction inner seal and polypropylene closures. Pack size 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex
HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0606

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11.11.2002

10 DATE OF REVISION OF THE TEXT

13/11/2023