Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gamanil 70mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains lofepramine hydrochloride 76.10mg equivalent to 70.0mg lofepramine.

Excipient(s) with known effect
Each tablet contains 126.05mg lactose (as lactose monohydrate) and 1.15mg Ponceau 4R Red Aluminium Lake (E124).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Round, lacquered, brown-violet tablet, with occasional white dots, with a spindle shaped score line on one side, approximately 10 mm in diameter.

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

Gamanil 70mg film-coated tablets are indicated for the treatment of symptoms of depressive illness. This includes depression/anxiety states associated with panic disorder features.

4.2 Posology and method of administration

Posology
Adults: The usual dose is 70mg twice daily (140mg) or three times daily (210mg) depending on the patient's response. The daily dose should always be given in divided doses not exceeding 70mg per dose.

In the treatment of depression/anxiety states associated with panic disorder features, the initial dosage should be 70mg daily for the first week.

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

Paediatric population: The safety and efficacy of Gamanil in children under 18 years of age have not been established. No data are available. The use of Gamanil is not recommended in children and adolescents under the age of 18.

Method of administration
Gamanil 70mg film-coated tablets are for oral use.

4.3 Contraindications

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

Gamanil must not be used in patients hypersensitive to dibenzazepines.

Gamanil 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

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

Gamanil 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 Gamanil 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.
Patients receiving anti-depressant therapy should be kept under regular surveillance with particular attention to the effects on cerebral function, haemopoietic function, cardiac conduction disorders.
Gamanil should be used with caution in patients with cardiovascular disease, because it is associated with a risk of cardiovascular adverse events in all age groups.
Moreover, caution is also required in patients with impaired liver or renal function, narrow angle glaucoma, symptoms suggestive of prostatic hypertrophy, a history of epilepsy or recent convulsions, hyperthyroidism, blood dyscrasias, porphyria or a susceptibility to paralytic ileus.
Caution is needed in patients with hyperthyroidism, or during concomitant treatment with thyroid preparations, since aggravation of unwanted cardiac effects occur.
Gamanil can prolong the QT-interval in the ECG and may lead to Torsades de Pointes. Gamanil 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 occurs the treatment with Gamanil has to be stopped.
Gamanil may lower the convulsion threshold; therefore extreme caution is necessary in patients with a history of epilepsy or recent convulsions or other predisposing

factors, or during withdrawal from alcohol or other medicinal products with anticonvulsant properties.
Concurrent electroconvulsive therapy must only be undertaken with careful supervision.
Caution is recommended if Gamanil is used in patients with impaired liver function, impaired renal function, blood dyscrasias or porphyria.
Caution is recommended in patients with a history of prostatic hypertrophy, narrow angle glaucoma or increased intra-ocular pressure, because of Gamanil's anticholinergic properties. In patients with narrow angle glaucoma. Gamanil may only be used if adequate glaucoma treatment is given.
In chronic constipation, Gamanil may cause paralytic ileus.
Caution is recommended in patients with tumours of the adrenal medulla in whom tricyclic antidepressants, such as Gamanil, may provoke hypertensive crises.
It is recommended that blood pressure be checked before initiating treatment because individuals with hypertension, or an unstable circulation, may react to Gamanil 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 must be informed that the patient has been taking Gamanil.
Caution is required in patients with 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 including Gamanil.
It is recommended that abrupt withdrawal of Gamanil be avoided unless essential, because withdrawal symptoms may occur on abrupt cessation of therapy. Withdrawal symptoms may include insomnia, irritability and excessive perspiration.
Monitoring of haemopoietic function is recommended particularly in patients with blood dyscrasias.
Gamanil contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine also contains Cochineal Red (E124), a colouring agent. This may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.
Elderly patients
The elderly are particularly liable to experience adverse reactions to tricyclic antidepressants, especially agitation, confusion and rarely, postural hypotension.
Paediatric population
Gamanil is not recommended for the treatment of children and adolescents under the age of 18 years.
Studies in depression in this age group did not show a beneficial effect for tricyclic antidepressants. Studies with other classes of antidepressants have shown a risk of suicidality, self-harm and hostility related to these compounds. This risk cannot be excluded with Gamanil.
Furthermore, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are not available.

4.5 Interaction with other medicinal products and other forms of interactions

MAO Inhibitors: Gamanil 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.

Anti-arrhythmic agents: There is an increased risk of ventricular arrhythmias, which may lead to Torsades de Pointes if Gamanil is given with anti-arrhythmic agents which prolong the QT interval e.g. disopyramide, procainamide, propafenone, quinidine, sotalol and amiodarone. Particular caution is advised if Gamanil is used in combination with such agents.

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 Gamanil is given with non- anti-arrhythmic agents which prolong the QT interval e.g. certain antibiotics (e.g. macrolides), cisapride, malaria agents, antihistamines (e.g. terfenadine), neuroleptic agents. Particular caution is advised if Gamanil 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 Gamanil is used in combination with such agents.

Sympathomimetic agents: Concomitant use of Gamanil with sympathomimetic agents is not recommended since their cardiovascular effects may be potentiated.

Adrenergic neurone blockers: Gamanil may decrease or abolish the antihypertensive effects of some adrenergic neurone blocking drugs. Antihypertensive agents of a different type are therefore recommended where patients require co-medication for hypertension.

CNS depressants: Gamanil'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 so treated because of the increased risk of arrhythmias and hypotension.

Anti-cholinergic agents: Gamanil may potentiate the effects of these drugs on the central nervous system, eye, bowel and bladder.

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

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

Anticoagulants: Gamanil may inhibit hepatic metabolism leading to an enhancement of anticoagulant effect. Careful monitoring of plasma prothrombin is advised.

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 Gamanil.

Diuretics: There is an increased risk of postural hypotension.

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

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

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 Gamanil.

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.

Oral contraceptives: Oestrogens and progestogens may antagonize the therapeutic effect of tricyclic antidepressants. Adverse reactions of tricyclic antidepressants may be exacerbated due to an increased plasma concentration.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Gamanil 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 Gamanil 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 Gamanil 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 is recommended initially until the individual reaction to treatment is known.

4.8 Undesirable effects

The adverse reactions reported with Gamanil 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:
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, hypomania, mania, psychoses, delirium.
Cases of suicidal ideation and suicidal behaviours have been reported during Gamanil 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.
Rarely: Drowsiness, convulsions, impairment of the 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 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"
Rarely: 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.
Rarely: Inflammation of mucosal membranes.

Investigations:
Changes of blood sugar level
Anticholinergic:
Some of the above mentioned adverse reactions may be due to the anticholinergic activity of Gamanil, these include:

- dryness of mouth, constipation, visual disturbances including e.g. blurred vision,
- mydriasis, disturbances of accommodation
- induction of glaucoma,
- urinary hesitancy, urinary retention,
- sweating, tachycardia, impairment of the sense of taste
- tremor, confusion, delirium,
- nightmares, hallucinations, psychoses,
- mania and hypomania

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.
The following adverse effects have been encountered in patients under treatment with tricyclic antidepressants and should therefore be considered as theoretical hazards of Gamanil even in the absence of substantiation: psychotic manifestations, including mania and paranoid delusions may be exacerbated during treatment with tricyclic antidepressants; withdrawal symptoms may occur on abrupt cessation of therapy and include insomnia, irritability and excessive perspiration; 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.
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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
Overdose may be characterised by central nervous system depression or excitation, severe anticholinergic effects or cardiotoxicity.

In particular, depending on the amount taken, overdose with Gamanil may lead to epileptiform seizures or cardiac events, such as conduction disorders, QT- prolongation, arrhythmias including Torsades de Pointes.

Management
The treatment of overdose is directed to symptoms.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant, non-selective monoamine reuptake inhibitor.
ATC Code: N06AA07

Mechanism of action
Gamanil 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.

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.

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

Biotransformation
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.

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. In a study of protein binding capability it has been found that lofepramine is up to 99% protein bound.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Maize starch
Ascorbic acid
Talc
Glycerol 85%
Glycerol monostearate 40-55
Disodium edetate (Titriplex III)
Dimeticone 1000
Silica, colloidal anhydrous (E551)
Hypromellose (HPMC 15)

Coating:
Macrogol 400
Hypromellose (HPMC 15)
Hypromellose (HPMC 5)
Cochineal Red (E124)
Talc
Titanium dioxide (E171)
Indigotine Lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package/container in order to protect from light and moisture.

6.5 Nature and contents of container

Gamanil comes in 3 different types of containers:

1. PVDC/AL foil blister packs containing 56 tablets
2. Polypropylene containers of 250 tablets
3. Amber glass bottles containing 56 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Zentiva k.s.
U kabelovny 130
102 37 Prague 10
Czech Republic

8 MARKETING AUTHORISATION NUMBER

PA1701/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14 May 1984

Date of last renewal: 14 May 2009

10 DATE OF REVISION OF THE TEXT

October 2021