PACKAGE INSERT FOR LEXAMIL 5 / 10 / 20

SCHEDULING STATUS

S5

PROPRIETARY NAME (AND DOSAGE FORM)

LEXAMIL 5 (Tablets)

LEXAMIL 10 (Tablets)

LEXAMIL 20 (Tablets)

COMPOSITION

LEXAMIL 5: Each tablet contains escitalopram oxalate equivalent to 5 mg escitalopram.

LEXAMIL 10: Each tablet contains escitalopram oxalate equivalent to 10 mg escitalopram.

LEXAMIL 20: Each tablet contains escitalopram oxalate equivalent to 20 mg escitalopram.

Inactive ingredients include croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, Opadry 04F58804 white (hydroxyl propyl methyl cellulose, titanium dioxide and macrogol) and corn starch.

Contains sugar: Mannitol:-

LEXAMIL 5: 34,36 mg/tablet

LEXAMIL 10: 68,73 mg/tablet

LEXAMIL 20: 137,45 mg/tablet

PHARMACOLOGICAL CLASSIFICATION

A 1.2 Psychoanaleptics (antidepressants).

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Escitalopram selectively inhibits the uptake of serotonin (5-HT). Escitalopram has minimal effect on the uptake of the following neurotransmitters: noradrenaline (NA), dopamine (DA) and gamma aminobutyric acid (GABA). Escitalopram also shows no or very low affinity for the following receptors: 5-HT_{1A}, 5-HT_2, DA (D_1- and D_2-receptors), α_1-, α_2,- ß-adrenoceptors, histamine H_1, muscarinic receptors, benzodiazepine, and opioid receptors.

Escitalopram has a modulating effect on the transporter of serotonin and a high affinity for the primary binding site. A more complete serotonin reuptake inhibition is a result of allosteric modulation of the serotonin transporter enhancing the binding of escitalopram to the primary binding site.

Pharmacokinetic properties

Absorption:

Absorption is not influenced by food intake (mean T_{max} is 4 hours after multiple dosing).

Distribution:

The apparent volume of distribution after oral administration ranges from approximately 12 to 26 L/kg. Escitalopram has a plasma protein binding of approximately 55 %.

Metabolism:

The liver metabolises escitalopram to the demethylated and didemethylated metabolites. Alternatively, through oxidation, the nitrogen may be converted to the N-oxide metabolite. The parent substance as well as metabolites are partly excreted as glucuronides.

In plasma escitalopram occurs predominantly as the unchanged compound. After multiple dosing the mean concentration of the demethyl metabolites ranges from 28 % to 31 %, while that of the didemethyl metabolites is less than 5 % of the escitalopram concentration. A combination of CYP2C19, CYP3A4 and CYP2D6 is responsible for the biotransformation of escitalopram to the demethylated metabolite.

Elimination:

Escitalopram has an elimination half-life after multiple dosing of approximately 30 hours. The plasma clearance after oral administration (Cl_{oral}) is approximately 0,6 L/min. It is assumed that, similar to racemic citalopram, escitalopram and its major metabolites are eliminated both by the hepatic (metabolic) and renal routes, but that renal excretion of the metabolites is the principal route of elimination.

The P450 enzyme system is mainly responsible for hepatic clearance with CYP2C19, the primary isoenzyme involved in the demethylation of escitalopram, followed by CYP3A4 and CYP2D6. Escitalopram exhibits linear pharmacokinetics. It takes approximately 1 week to reach steady state plasma levels. With a daily dose of 10 mg steady state concentrations average 50 nmol/L (range 20 to 125 nmol/L).

Elderly patients (more than 65 years of age):

The half-life of escitalopram is increased in the elderly (approximately 50 %), while decreased clearance values, due to a reduced rate of metabolism, have also been demonstrated in this patient group.

Reduced renal function:

Although escitalopram is eliminated more slowly in patients with mild to moderate impairment of renal function, mild to moderate renal impairment does not have a major impact on the serum concentration of escitalopram.

At present no information is available for the treatment of patients who suffer from severely reduced renal function (creatinine clearance less than 30 mL/min).

Reduced hepatic function:

In patients with reduced hepatic function the half-life of escitalopram is double that seen in patients with normal liver function. Steady state escitalopram concentrations at a given dose will be approximately twice as high compared to patients with normal hepatic function.

Polymorphism:

Based on the results of *in vitro* trials with escitalopram and *in vivo* trials with racemic citalopram, genetic polymorphism with respect to CYP2D6 is not known, while it may be of clinical relevance with respect to CYP2C19.

INDICATIONS

LEXAMIL is indicated for the:

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.

CONTRAINDICATIONS

The use of LEXAMIL is contraindicated in the following circumstances:

- Hypersensitivity to escitalopram or to any of the excipients of LEXAMIL.
- Children younger than 18 years of age (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- ***Monoamine oxidase inhibitor usage*** – Serious reactions have been reported in some patients who received an SSRI, such as LEXAMIL, in combination with a monoamine oxidase inhibitor (MAOI) as well as in patients who had recently discontinued an SSRI and had been started on a MAOI (see **"INTERACTIONS"**).

  In some instances patients presented with features resembling serotonin syndrome (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE-EFFECTS"**).

  LEXAMIL should not be prescribed in combination with a MAOI.

  Treatment with LEXAMIL may be initiated 14 days after treatment with a MAOI has been discontinued.

  A minimum of 7 days should elapse after LEXAMIL has been discontinued before starting treatment with a MAOI.
- Co-administration with linezolid (see **"INTERACTIONS"**).

- LEXAMIL is contraindicated in patients with known QT interval prolongation or congenital long QT syndrome (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- The concomitant use of LEXAMIL with medicinal products that are known to prolong the QT interval, such as pimozide, is contraindicated (see **"INTERACTIONS"**).

WARNINGS AND SPECIAL PRECAUTIONS

Safety and efficacy in children younger than 18 years have not been established (see **"CONTRAINDICATIONS"**). In clinical trials in major depressive disorder, there were increased reports of hostility and suicide-related adverse events such as suicidal ideation and self-harm.

Suicide or clinical worsening

Patients should be closely monitored during the first few weeks or more of therapy as improvement may not occur during this period. The possibility of a suicide attempt which is inherent in depression, may persist until significant therapeutic effect has been established.

Both adults and children diagnosed with major depressive disorder may experience worsening of their depression and/or emergence of suicidal ideation and behaviour, whether or not they are receiving treatment with antidepressant medicine. Suicide risk may persist until significant remission occurs. However, it has not been established that antidepressant medicine plays a causal role in inducing such behaviour. Patients who are receiving treatment with LEXAMIL should be closely

monitored for clinical worsening of their symptoms and suicidality, especially at the start of a course of therapy or at any time dosages are altered (including both increases and decreases).

Due to the possibility of co-morbid psychiatric and non-psychiatric disorders occurring in conjunction with major depressive disorder, the same precautions taken when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Patients who have received treatments with antidepressants for major depressive disorder as well as for other indications (both psychiatric and non-psychiatric), reported the following symptoms: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania and mania. Although a causal link between the use of antidepressants and the emergence of suicidal impulses has not been demonstrated, consideration should be given to changing the therapeutic regimen, including possibly discontinuing LEXAMIL, in patients for whom such symptoms are severe, abrupt in onset, or in whom such symptoms did not form part of the patient's presenting complaints.

If the decision is made to discontinue treatment, administration of LEXAMIL should be tapered (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Mania

Usage of LEXAMIL should be discontinued in any patient entering a manic phase. In patients with a history of mania/hypomania, LEXAMIL should be used with caution.

Paradoxical anxiety

Some patients who suffer from panic disorder may experience increased anxiety symptoms after initiation of treatment with antidepressants, including LEXAMIL. With continued treatment this paradoxical reaction usually subsides within 2 weeks. The likelihood of a paradoxical anxiogenic effect may be reduced with the use of low starting doses.

Seizures

LEXAMIL administration should be discontinued in any patient who develops seizures for the first time. Patients with controlled epilepsy should be carefully monitored, but use of LEXAMIL should be avoided in patients with unstable epilepsy. Should a patient develop an increase in seizure frequency, the administration of LEXAMIL should be discontinued.

Diabetes mellitus

Treatment with LEXAMIL may alter glycaemic control in diabetics. This may possibly be due to an improvement of depressive symptoms. It may be necessary to adjust insulin and/or oral hypoglycaemic medicine dosages.

Haemorrhage

Cutaneous bleeding abnormalities, including ecchymoses and purpura, have been reported with the use of LEXAMIL. Caution is advised in patients who are receiving treatment with LEXAMIL, especially in instances where there is concomitant administration of medicines known to affect platelet function [such as atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin and non-

steroidal anti-inflammatory drugs (NSAIDS)], as well as in patients with a history of bleeding disorders (see **"INTERACTIONS"**).

ECT (electroconvulsive therapy)

Caution is advised inpatients who require concomitant ECT while taking LEXAMIL because of limited published clinical experience.

Risk of serotonin syndrome

Co-administration of LEXAMIL with MAO inhibitors can lead to serotonin syndrome. Co-administration with other antidepressants with serotonergic properties, as well as other serotonergic medicines (e.g. tramadol, sumatriptan) may result in an enhancement of serotonin associated effects, e.g. the serotonin syndrome (see **"INTERACTIONS"**). A combination of symptoms (agitation, tremor, myoclonus and hyperthermia) may indicate the development of serotonin syndrome. LEXAMIL and the serotonergic medicine should be discontinued immediately if these symptoms occur and symptomatic treatment initiated.

QT interval prolongation

Escitalopram, as found in LEXAMIL, has been found to cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular dysrhythmia, including torsade de pointes, have been reported during the post-marketing period, predominantly in patients of female gender, with hypokalaemia, or with pre-existing QT interval prolongation or other cardiac diseases (see **"CONTRAINDICATIONS"**, **"INTERACTIONS"** and **"SIDE-EFFECTS"**).

Caution is advised in patients with significant bradycardia; or in patients with recent acute myocardial infarction or uncompensated heart failure.

Electrolyte disturbances, such as hypokalaemia and hypomagnesaemia, increase the risk for life-threatening dysrhythmias and should be corrected before treatment with LEXAMIL is started.

If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If signs of cardiac dysrhythmia occur during treatment with LEXAMIL, the treatment should be withdrawn and an ECG should be performed.

Akathisia / psychomotor restlessness

The use of SSRIs, such as LEXAMIL, has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur during the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental (see **"SIDE-EFFECTS"**) and it may be necessary to review the use of LEXAMIL.

Hyponatraemia

Hyponatraemia, probably due to inappropriate antidiuretic hormone secretion (SIADH), has been reported 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 LEXAMIL is used in combination with other medications which may cause hyponatraemia.

St. John's Wort

Concomitant use of LEXAMIL and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions (see **"INTERACTIONS"**).

Coronary heart disease

Due to limited clinical experience, caution is advised in patients with coronary heart disease.

Risk of bone fractures

Epidemiology studies conducted mainly in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs, including LEXAMIL, and TCAs (tricyclic antidepressants). The mechanism leading to this risk is unknown.

Angle-Closure Glaucoma

SSRIs including escitalopram, as in LEXAMIL, may have an effect on pupil size resulting in mydriasis. This mydriatic effect has the potential to narrow the eye angle resulting in increased intraocular pressure and angle-closure glaucoma, especially in patients pre-disposed. LEXAMIL should therefore be used with caution in patients with angle-closure glaucoma or history of glaucoma.

Discontinuation symptoms seen when stopping treatment

Discontinuation symptoms when stopping treatment are common, particularly if discontinuation is abrupt (see **"SIDE-EFFECTS"**). The risk of discontinuation symptoms may be dependent on several factors, including the duration and dose of

therapy and the rate of dose reduction. They usually occur within the first few days of discontinuing treatment, but there have been reports of such symptoms in patients who have inadvertently missed a dose. Generally, these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2 to 3 months or more). It is therefore advised, when discontinuing treatment, that LEXAMIL should be gradually tapered over a period of several weeks or months, according to the patient's needs (see **"DOSAGE AND DIRECTIONS FOR USE"**).

Effects on ability to drive and use machines

Use of LEXAMIL is not associated with impairment of intellectual function or psychomotor performance. However, patients who suffer from depression and who require treatment may have an impaired ability to drive or operate machinery and should therefore be warned of the potential risk. Patients should be advised to avoid such tasks if so affected.

INTERACTIONS

LEXAMIL has a low potential for causing clinically significant medicine interactions. The biotransformation of escitalopram to its demethylated metabolites depends on three parallel pathways, namely cytochrome P450 (CYP) 2C19, 3A4 and 2D6). Escitalopram, as in LEXAMIL, inhibits iso-enzymes CYP1A2, 2C9, 2C19, 2E1 and 3A very weakly, while it inhibits 2D6 weakly.

Effects of other medicines on escitalopram *in vivo*

Ritonavir:

Co-administration of a single dose of ritonavir (CYP3A4 inhibitor) does not change the pharmacokinetics of single doses of LEXAMIL.

Ketoconazole:

The pharmacokinetics of racemic citalopram is not affected by the co-administration of ketoconazole (a potent CYP3A4 inhibitor).

Cimetidine:

When cimetidine (potent CYP2D6, 3A4 and 1A2 inhibitor) is administered in conjunction with citalopram, the plasma concentrations of the racemate is increased (AUC by 43 % and C_{max} by 39 %). Caution is therefore advised at the upper end of the dose range of LEXAMIL when used concomitantly with high doses of cimetidine.

Omeprazole:

Co-administration of escitalopram, as in LEXAMIL, with omeprazole 30 mg once daily (a CYP2C19 inhibitor) resulted in moderate (approximately 50 %) increases in the plasma concentrations of escitalopram.

Thus, caution should be exercised when LEXAMIL is used concomitantly with CYP2C19 inhibitors (e.g. omeprazole, esomeprazole, fluvoxamine, lansoprazole, ticlopidine). A reduction in the dose of LEXAMIL may be necessary based on monitoring of side-effects during concomitant treatment.

Monoamine oxidase inhibitors (MAOIs), sumatriptan and tramadol:

Co-administration of LEXAMIL with MAO inhibitors may give rise to the development of serotonin syndrome. When LEXAMIL is co-administered with other serotonergic medicines (such as tramadol and sumatriptan), including antidepressants with serotonergic properties, it may cause an enhancement of serotonin associated effects, e.g. the serotonin syndrome (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Linezolid (reversible non-selective MAO inhibitor):

The antibiotic linezolid is a reversible non-selective MAO inhibitor and should not be given to patients treated with LEXAMIL (see **"CONTRAINDICATIONS"**).

Lithium and tryptophan:

Reports have indicated that concomitant use of LEXAMIL and lithium or tryptophan may lead to enhanced effects. Co-administration of LEXAMIL with these medicines should therefore be undertaken with caution.

St. John's Wort:

Concomitant use of LEXAMIL and herbal remedies containing St. John's Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Medicines which lower the seizure threshold:

SSRIs, including LEXAMIL, can lower the seizure threshold. Caution is advised when concomitantly using other medicines capable of lowering the seizure threshold

[e.g. antidepressants (tricyclics, SSRIs), neuroleptics (phenothiazines, thioxanthenes and butyrophenones), mefloquine, bupropion and tramadol].

Effects of escitalopram on other medicines *in vivo*

Desipramine:

When LEXAMIL is co-administered with a single dose of desipramine (a CYP2D6 substrate) it leads to a twofold increase in plasma levels of desipramine. Co-administration of LEXAMIL and desipramine should therefore be undertaken with caution. A similar increase in plasma levels of desipramine, following administration of imipramine, is seen when administered concomitantly with racemic citalopram.

Metoprolol:

When LEXAMIL is co-administered with a single dose of metoprolol 100 mg (a CYP2D6 substrate) it results in a twofold increase in the C_{max} and a 52 % increase in the AUC of metoprolol. Despite this, the combination did not produce clinically significant effects on blood pressure and heart rate.

Selegiline:

The AUC of selegiline is increased by 29 % following co-administration with racemic citalopram. The combination with selegiline (irreversible MAO B inhibitor) is contraindicated due to the risk of developing serotonin syndrome (see "**CONTRAINDICATIONS**").

Medicines which prolong the QT interval:

Pharmacokinetic and pharmacodynamic studies of escitalopram, as contained in LEXAMIL, combined with other medicines that prolong the QT interval have not been performed. An additive effect of LEXAMIL and these medicines cannot be excluded.

Co-administration of a single dose of pimozide 2 mg to patients treated with racemic citalopram 40 mg per day for 11 days caused an increase in AUC and C_{max} of pimozide. The co-administration of pimozide and citalopram resulted in a mean increase in the QTc interval of approximately 10 msec.

Therefore, co-administration of LEXAMIL with medicines that prolong the QT interval, such as Class IA and III antidysrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin, pentamidine, antimalarial treatment particularly halofantrine), certain antihistamines (e.g. mizolastine), is contraindicated (see **"CONTRAINDICATIONS"** and **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Other

Results from pharmacokinetic interaction studies with racemic citalopram did not show any clinically significant interactions with carbamazepine (CYP3A4 substrate), triazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate) (single dose), warfarin (CYP3A4 and CYP2C9 substrate), levomepromazine (CYP2D6 inhibitor), and digoxin. There was a slight increase in prothrombin time following administration of a single dose of 25 mg warfarin. The International Normalised Ratio (INR) needs

to be carefully monitored in patients who require treatment with a combination of LEXAMIL and warfarin.

Haemorrhage:

Altered anticoagulant effects may occur when LEXAMIL is combined with oral anticoagulants. Patients receiving oral anticoagulant therapy should receive careful coagulation monitoring when LEXAMIL is started or stopped. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase bleeding-tendency (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Alcohol

No pharmacodynamic or pharmacokinetic interactions are expected between escitalopram, as in LEXAMIL, and alcohol. However, as with other psychotropic medicines, the combination with alcohol is not advisable.

PREGNANCY AND LACTATION

The use of LEXAMIL during pregnancy and lactation is not recommended as safety and efficacy have not been established.

Neonates should be observed if maternal use of LEXAMIL continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

The following symptoms may occur in the neonate after maternal SSRI / SNRI, including LEXAMIL, use in later stages of pregnancy: respiratory distress, cyanosis,

apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypertonia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, lethargy, constant crying, somnolence and difficulty sleeping. These symptoms could be due to either serotonergic effects or discontinuation symptoms. In a majority of instances the complications begin immediately or soon (< 24 hours) after delivery.

Epidemiological data have suggested that the use of SSRIs, such as LEXAMIL, in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).

DOSAGE AND DIRECTIONS FOR USE

Adults

Major depressive episodes

In otherwise healthy adult patients LEXAMIL should be administered as a single oral dose of 10 mg daily. This dose may be increased to a maximum of 20 mg daily depending on individual patient response.

It usually takes 2 to 4 weeks for an antidepressant response to become evident.

Panic disorder with or without agoraphobia

A single oral dose of 5 mg is recommended 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 obtained after about 3 months and the treatment lasts several months.

Social anxiety disorder

Usual dose is 10 mg once daily. This dose may be increased to a maximum of 20 mg daily depending on individual patient response. Usually, 2 to4 weeks of treatment are necessary to obtain symptom relief. Treatment for three months is recommended to consolidate response. Long-term treatment of responders for 6 months has been shown to prevent relapse and can be considered on an individual basis. Treatment benefits should be re-evaluated at regular intervals.

Generalised anxiety disorder

The recommended dosage is 10 mg once daily. The dose may be increased to a maximum of 20 mg daily depending on individual patient response. Long-term treatment of responders has been studied for at least 6 months and can be considered on an individual basis to prevent relapse.

Obsessive-compulsive disorder

Usual dose is 10 mg once daily. The dose may be increased to a maximum of 20 mg daily depending on individual patient response. Long-term treatment of patients responding to a 16-week open treatment phase has been studied for at least 24 weeks in patients receiving 10 mg or 20 mg a day. Because OCD is a chronic disease, patients should be treated for a sufficient period to ensure that they are symptom free, which may be several months or even longer.

Elderly patients (> 65 years of age)

Lower initial and maximum dosages should be considered in elderly patients due to a longer half-life and a decreased clearance.

Children and adolescents (<18 years of age)

Safety and efficacy have not been investigated in this population (see "**CONTRAINDICATIONS**").

Reduced renal function

It is not necessary to adjust the dosage in patients who suffer from mild or moderate renal impairment. No information is available on the treatment of patients who have severe renal impairment (creatinine clearance < 30 mL/min).

Reduced hepatic function

In patients who have hepatic impairment, dosages should be halved to the lower end of the dose range.

LEXAMIL is given as a single daily dose.

LEXAMIL may be taken with or without food.

Discontinuation of treatment

When LEXAMIL is to be discontinued, gradual dose reduction should be considered. Abrupt discontinuation of LEXAMIL should be avoided. When discontinuing LEXAMIL the dose should be gradually reduced over a period of at least one to two weeks, thereby reducing the risk of discontinuation symptoms (see **"WARNINGS AND SPECIAL PRECAUTIONS"** and **"SIDE-EFFECTS"**). Should unpleasant symptoms occur following treatment discontinuation or when the dose is decreased,

then the doctor may consider resuming the previously prescribed dose. Thereafter, the doctor may continue decreasing the dose, but more gradually.

SIDE-EFFECTS

Adverse reactions following administration of LEXAMIL are most frequently observed during the first one or two weeks of treatment. Adverse events may decrease in intensity and frequency with continued treatment.

After prolonged administration, abrupt discontinuation of LEXAMIL may cause withdrawal symptoms in some patients.

Blood and lymphatic system disorders

Frequency unknown: Thrombocytopenia.

Immune system disorders

Less frequent: Anaphylactic reactions.

Endocrine disorders:

Frequency unknown: Inappropriate ADH secretion.

Metabolism and nutrition disorders

Frequent: Decreased appetite, increased appetite, weight increased.

Less frequent: Weight decreased.

Frequency unknown: Hyponatraemia, anorexia.

Psychiatric disorders

Frequent:	Anxiety, restlessness, abnormal dreams, decreased libido (males and females), anorgasmia (females).
Less frequent:	Bruxism, agitation, nervousness, panic attack, confusional state, aggression, depersonalisation, hallucinations.
Frequency unknown:	Mania, suicidal ideation, suicidal behaviour.

Nervous system disorders

Frequent:	Headache, insomnia, somnolence, dizziness, paraesthesia, tremor.
Less frequent:	Serotonin syndrome (typically characterised by a rapid onset of changes in mental state, with confusion, mania, agitation, hyperactivity, shivering, fever, tremor, ocular movements, myoclonus, hyperreflexia, and incoordination), sleep disorder, taste disturbances, syncope.
Frequency unknown:	Dyskinesia, movement disorder, convulsion, psychomotor restlessness / akathisia (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

Eye disorders

Less frequent:	Mydriasis, visual disturbances.

Ear and labyrinth disorders

Less frequent:	Tinnitus.

Cardiac disorders

Less frequent:	Tachycardia, bradycardia.
Frequency unknown:	Electrocardiogram QT prolonged, ventricular dysrhythmia including torsade de pointes.

Vascular disorders

Frequency unknown:	Orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders

Frequent:	Sinusitis, yawning.
Less frequent:	Epistaxis.

Gastrointestinal disorders

Frequent:	Nausea, diarrhoea, constipation, vomiting, dry mouth.
Less frequent:	Gastrointestinal haemorrhages (including rectal haemorrhage).

Hepatobiliary disorders

Frequency unknown:	Hepatitis, abnormal liver function tests.

Skin and subcutaneous tissue disorders

Frequent:	Increased sweating.

Less frequent: Urticaria, alopecia, rash, pruritus.

Frequency unknown: Ecchymosis, angioedema.

Musculoskeletal, connective tissue and bone disorders

Frequent: Arthralgia, myalgia.

Renal and urinary disorders

Frequency unknown: Urinary retention.

Reproductive system and breast disorders

Frequent: Ejaculation disorder, impotence (males).

Less frequent: Metrorrhagia, menorrhagia.

Frequency unknown: Galactorrhoea, priapism.

General disorders

Frequent: Fatigue, pyrexia.

Less frequent: Oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Doses of 190 mg have been ingested without any reports of adverse reactions.

Treatment

LEXAMIL does not have a specific antidote. Treatment of an overdose is supportive and symptomatic.

Management should include monitoring of cardiac and vital signs along with general symptomatic supportive measures.

IDENTIFICATION

LEXAMIL 5: White, round, biconvex, film-coated tablets plain on both sides.

LEXAMIL 10: White, round, biconvex, film-coated tablets plain on both sides.

LEXAMIL 20: White, round, biconvex, film-coated tablets plain on both sides.

PRESENTATION

LEXAMIL 5: Outer carton containing Aluminium foil/PVC/PVDC blister strips of 10 tablets packed in 30's.

LEXAMIL 10: Outer carton containing Aluminium foil/PVC/PVDC blister strips of 10 tablets packed in 30's.

LEXAMIL 20: Outer carton containing Aluminium foil/PVC/PVDC blister strips of 10 tablets packed in 30's.

STORAGE INSTRUCTIONS

Store at or below 30 ºC.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

LEXAMIL 5: 41/1.2/0394

LEXAMIL 10: 41/1.2/0395

LEXAMIL 20: 41/1.2/0396

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

DATE OF PUBLICATION OF THIS PACKAGE INSERT

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NAMIBIA AND BOTSWANA REGISTRATION NUMBER OTHER MARKETS

Namibia: NS3
LEXAMIL 5: 09/1.2/0023
LEXAMIL 10: 09/1.2/0022
LEXAMIL 20: 09/1.2/0021