1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

LORIEN 20 mg capsules

LORIEN TABLETS 20 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of LORIEN contains 20 mg fluoxetine as fluoxetine hydrochloride.

Contains sugar: Lactose monohydrate 130,70 mg

For full list of excipients, see section 6.1.

Each tablet of LORIEN TABLETS contains 20 mg fluoxetine as fluoxetine hydrochloride.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

LORIEN is a white powder encapsulated within a size “3” hard gelatine capsule with an opaque green body and opaque green cap.

Tablets

LORIEN TABLETS is a round, white tablet with bevelled edges, bisected 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

LORIEN is indicated for:

- Major depressive episodes, i.e. single episode and recurrent depression with associated anxiety.

- Bulimia nervosa: LORIEN has been shown to significantly decrease binge-eating and purging activity.

- Obsessive compulsive disorder: LORIEN is indicated for the treatment of obsessive-compulsive disorder. The obsession or compulsions must be experienced as intrusive, markedly distressing, time consuming or interfering significantly with the person's social or occupational functioning.

4.2. Posology and method of administration

Posology

Adults

Major depressive episodes:

A dose of 20 mg (one capsule or tablet) per day is recommended, preferably in the morning. Doses of up to 80 mg (four capsules or tablets) daily in divided doses may be employed if necessary.

Bulimia nervosa:

A dose of 60 mg (three capsules or tablets) per day is recommended.

Obsessive-compulsive disorder:

A dose of 20 mg to 60 mg (one to three capsules or tablets) per day is recommended.

Doses above 80 mg (four capsules or tablets) per day are not recommended for any indication.

Special populations

Elderly population

The effect of age upon the metabolism of LORIEN has not been fully investigated. LORIEN should be used with caution in the elderly, particularly if they have systemic illnesses or are receiving multiple medicines for concomitant diseases

Dosages over 20 mg (one capsule or tablet) per day are not recommended.

Renal impairment

Lower doses or alternate-day dosing are recommended in patients with significant renal impairment.

Hepatic impairment

Lower doses or alternate-day dosing are recommended in patients with significant hepatic impairment.

Paediatric population

The safety and efficacy of LORIEN in children have not been established (see section 4.4)

Method of administration

For oral administration.

LORIEN may be administered with or without food. The tablets may be swallowed whole or

be dispersed in approximately 100 ml of water.

Withdrawal symptoms seen on discontinuation of LORIEN: Abrupt discontinuation should be avoided. When stopping treatment with LORIEN, the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see section 4.4). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the medical practitioner may continue to decrease the dose, but at a more gradual rate.

Discontinuation of LORIEN may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, agitation, anxiety and nausea (see section 4.4).

4.3. Contraindications

LORIEN is contraindicated in:

- Patients with hypersensitivity to fluoxetine or any of the excipients in LORIEN (see section 6.1).
- Patients with severe renal failure (glomerular filtration rate < 10 ml per minute). Accumulation may occur in these patients during chronic treatment.
- Safety and efficacy in children has not been established.
- Combination with metoprolol used in cardiac failure (see section 4.5).
- Concomitant use of LORIEN with irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid) (see sections 4.4 and 4.5).

  Monoamine oxidase inhibitors:

  There have been reports of serious and sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to

delirium and coma) in patients receiving fluoxetine, as in LORIEN, in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued fluoxetine, as in LORIEN and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome (see section 4.4).

Therefore, LORIEN should not be used in combination with a MAOI, or within 14 days of discontinuing therapy with a MAOI. Since LORIEN and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping fluoxetine hydrochloride as in LORIEN before starting a MAOI.

If LORIEN has been prescribed chronically and/or at a high dose, a longer interval before starting a MAOI should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with fluoxetine, as in LORIEN and a MAOI in temporal proximity (see section 4.4).

- Thioridazine should not be administered with LORIEN or within a minimum of 5 weeks after LORIEN has been discontinued. Thioridazine administration produces a dose related prolongation of the QTc interval which is associated with serious ventricular dysrhythmias, such as Torsade's de pointes - type dysrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism.

4.4. Special warnings and precautions for use

Monoamine oxidase inhibitors

- There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations in vital signs and mental status changes that include confusion, irritability, extreme agitation progressing to delirium and coma) in patients

receiving LORIEN in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued LORIEN and are then started on a MAOI.

Some presented with features resembling serotonin syndrome (which may be confounded with (or diagnosed as) neuroleptic malignant syndrome).

Therefore, LORIEN should not be used in combination with a MAOI, or within 14 days of discontinuing therapy with a MAOI. Since LORIEN and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping LORIEN before starting a MAOI (see section 4.3).

Suicide/suicidal thoughts or clinical worsening

- Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events).
- Patient with major depressive disorder, both adults and children, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour, whether or not they are taking antidepressant medicines. This risk may persist until significant remission occurs. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established. Patients being treated with LORIEN should, nevertheless, be observed closely for clinical worsening and suicidality, especially at the beginning of a course of therapy or at any time of dose changes, either increases or decreases. As improvement may not occur during the first two or more weeks of treatment, patients should be closely monitored during this period. Due to the risk of suicide in major depressive episodes, close supervision of high risk patients should accompany LORIEN therapy.

Medical practitioners should encourage patients to report any distressing thoughts or feelings at any time.

- Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorders should be observed when treating patients with other psychiatric and non-psychiatric disorders.
- Because of well-established co-morbidity between obsessive-compulsive disorder and depression, the same precautions observed when treating patients with depression should be observed when treating patients with obsessive-compulsive disorder.
- The following symptoms have been reported in patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric: anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness, impulsivity, akathisia, hypomania, and mania). Although a causal link between the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing LORIEN, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.
- 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 medicines such as fluoxetine, as in LORIEN, 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 medicine 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.

Serotonin syndrome

- Serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur with the use of LORIEN, particularly when given in combination with other serotonergic (among others, L-tryptophan), neuroleptic medicines and buprenorphine/opioids may result in serotonin syndrome, a potentially life threatening condition (see section 4.5).
- This syndrome is characterised by the clustering of clinical features of changes in mental state (confusion, irritability disorientation, extreme agitation, progressing to delirium and coma) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, incoordination), in combination with auto-immune dysfunction (especially fever, sweating, diarrhoea), autonomic instability with possible rapid fluctuations of vital signs and/or gastrointestinal symptoms. As this syndrome may result in potentially life-threatening conditions, treatment with LORIEN should be discontinued if such events occur and supportive symptomatic treatment should be initiated.
- Serotonin syndrome has been seen in temporal association with the use of MAOI and with other serotonergic medicines but may occur in the absence of any concomitant medicines. LORIEN should be stopped immediately as serious morbidity and death may follow the serotonin syndrome.
- If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms

Discontinuing treatment with LORIEN

- If the decision is made to discontinue treatment, LORIEN, should be tapered.
- Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 60 % of patients in both the fluoxetine, as in LORIEN and placebo groups. Of these adverse events, 17 % in the fluoxetine group as in LORIEN and 12 % in the placebo group were severe in nature. The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy with LORIEN and the rate of dose reduction.
- Discontinuation of LORIEN may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, sleep disturbances (including insomnia and intense dreams), asthenia, agitation, anxiety and nausea and/or vomiting (see section 4.2).
- Generally, these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment. 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 that LORIEN should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see section 4.2).

Rash and possibly allergic events

- Discontinue LORIEN in patients who develop a rash, anaphylactoid events and progressive systemic effects, involving the skin, lungs, kidneys or liver, have occurred in such patients.

Seizures and epilepsy

- Seizures are a potential risk with antidepressant medicines. Therefore, as with

other antidepressants, LORIEN should be introduced cautiously in patients who have a history of seizures.

- LORIEN should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency.
- LORIEN should be avoided in patients with unstable epilepsy; patients with controlled epilepsy should be carefully monitored. There have been reports of prolonged seizures in patients on LORIEN receiving ECT treatment.

Mania

- Antidepressants, such as LORIEN, should be used with caution in patients with a history of mania/hypomania. As with all antidepressants, LORIEN should be discontinued in any patient entering a manic phase.

Hepatic and renal impairment

- Fluoxetine, as in LORIEN is extensively metabolised by the liver and excreted by the kidneys. A lower dose e.g. alternate day dosing is recommended in patients with significant hepatic dysfunction or mild to moderate renal failure (GFR 10 to 50 ml/min).
- When given fluoxetine, as in LORIEN 20 mg daily for 2 months, patients with severe renal failure (GFR <10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Tamoxifen

- LORIEN, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, LORIEN should, whenever possible, be avoided during tamoxifen treatment (see section 4.5).

Cardiac disease

- Clinical experience in acute cardiac disease is limited, therefore caution is advisable.
- Cases of QT interval prolongation and ventricular dysrhythmia including torsade de pointes have been reported with the use of LORIEN (see sections 4.5, 4.8 and 4.9).
- LORIEN should be used with caution in patients with conditions such as congenital long QT syndrome, a family history of QT prolongation or other clinical conditions that predispose to dysrhythmias (e.g., hypokalaemia, hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to LORIEN (e.g., hepatic impairment) or concomitant use with medicines known to induce QT prolongation and/or torsade de points (see section 4.5).
- 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 LORIEN, the treatment should be withdrawn, and an ECG should be performed.

Loss of weight

- LORIEN may cause loss of weight usually proportional to baseline body weight, which could be undesirable in underweight depressed patients.

Diabetes

- In patients with diabetes, LORIEN may alter glycaemic control. Hypoglycaemia has occurred during therapy with LORIEN and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Akathisia/psychomotor restlessness

- The use of fluoxetine, as in LORIEN 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 within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Haemorrhage

- SSRIs/SNRIs such as LORIEN may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8).
- There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura with SSRIs including LORIEN. Ecchymosis has been reported as an infrequent event during treatment with LORIEN. Other haemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported.
- There have been reports of altered platelet function and/or abnormal results from laboratory studies in patients taking LORIEN. While there have been reports of abnormal bleeding in several patients taking LORIEN, it is unclear whether LORIEN had a causative role.
- Caution is advised in patients taking SSRIs such as LORIEN, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g., atypical antipsychotics, such as clozapine, phenothiazines, most TCAs, aspirin, NSAIDs), or other medicines that may increase risk of bleeding, as well as in patients with a history of bleeding disorders (see section 4.5).

Mydriasis

- Mydriasis has been reported in association with the use of LORIEN, therefore, caution should be used when prescribing LORIEN in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Electroconvulsive therapy (ECT)

- There have been rare reports of prolonged seizures in patients on LORIEN receiving ECT treatment; therefore, caution is advisable.

Sexual dysfunction

- SSRIs/SNRIs such as LORIEN may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of the SSRIs/SNRI.

Paediatric population

Suicide-related behaviours (suicidal attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo.

In addition, only limited evidence is available concerning long-term effect on safety in children and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments.

In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine, as in LORIEN. It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see section 4.8).

Growth and pubertal development (height, weight, and TANNER staging) should therefore be monitored during and after treatment with LORIEN. If either is slowed, referral to a paediatrician should be considered.

In paediatric trials, mania and hypomania were reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. LORIEN should be discontinued in any patient entering a manic phase. It is important that the doctor or healthcare practitioner prescribing LORIEN carefully discusses the risks and benefits of treatment with the child/young person and/or their parents.

Excipients

LORIEN capsules contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take LORIEN capsules.

4.5. Interaction with other medicines and other forms of interaction

INTERACTIONS

The long elimination half-lives of both fluoxetine and norfluoxetine as in LORIEN should be borne in mind (see section 5.2) when considering pharmacodynamic or pharmacokinetic medicine interactions (e.g., when switching from fluoxetine to other antidepressants).

Monoamine oxidase inhibitors

- LORIEN should not be used concomitantly with monoamine oxidase inhibitors (see section 4.3 and 4.4).).
- Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI such as LORIEN in combination with an irreversible, non-selective monoamine oxidase inhibitor (MAOI). These cases presented with features resembling serotonin syndrome (which may be confounded with or diagnosed as neuroleptic malignant syndrome). Cyproheptadine or dantrolene may benefit patients experiencing such reactions.
- Symptoms of a medicine interaction with a MAOI include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes that include confusion, irritability and extreme agitation progressing to delirium and coma (see section 4.3 and 4.4).
- Because of the two weeks-lasting effect of treatment with an irreversible, non-

selective MAOI, LORIEN should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing LORIEN treatment before starting an irreversible, non-selective MAOI.

Metoprolol

- Metoprolol, used in cardiac failure can cause adverse events including excessive bradycardia, may be increased because of an inhibition of its metabolism by LORIEN (see section 4.3).

Alcohol

- In formal testing, fluoxetine as in LORIEN did not raise blood alcohol levels or enhance the effects of alcohol. However, the combination of SSRI treatment such as LORIEN and alcohol is not advisable.

Tamoxifen

- Pharmacokinetic interaction between CYP2D6 inhibitors such as LORIEN and tamoxifen, showing a 65 to 75 % reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 19 inhibitors (including LORIEN) should whenever possible be avoided (see section 4.4).

MAOI-A including linezolid and methylthioninium chloride (methylene blue)

- Risk of serotonin syndrome including diarrhoea, tachycardia, sweating, tremor, confusion or coma. If concomitant use of these medicines with LORIEN cannot be avoided, close clinical monitoring should be undertaken, and the concomitant medicines should be initiated at the lower recommended doses (see section 4.4).

Mequitazine

- Risk of mequitazine adverse events (such as QT prolongation) may be increased

because of an inhibition of its metabolism by LORIEN.

Buprenorphine/opioids

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

Serotonergic medicines

- Concomitant use of other medicines with serotonergic activity (e.g., lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St. John's 1 Wort *(Hypericum perforatum)* may result in mild serotonin syndrome.

  Therefore, the concomitant use of LORIEN with these medicines should be undertaken with caution and closer, more frequent clinical monitoring (see section 4.4).

QT interval prolongation:

- Pharmacokinetic and pharmacodynamic studies between LORIEN and other medicines that prolong the QT interval have not been performed. An additive effect of LORIEN and these medicines cannot be excluded.
- Therefore, co-administration of LORIEN with medicines that prolong the QT interval, such as Class IA and III antidysrhythmic, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial medicines (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine), anti-malaria treatment particularly halofantrine, certain antihistamines (astemizole, mizolastine), should be used with caution (see sections 4.4, 4.8 and 4.9)

CNS active medicines

- Caution is advised if the concomitant administration of LORIEN and CNS active medicines, including lithium, is required. There have been reports of both increased

and decreased lithium levels when used concomitantly with LORIEN. Lithium levels should be monitored.

- There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when LORIEN has been administered in combination with these medicines.
- Patients receiving LORIEN in combination with tryptophan have been reported to experience adverse reactions, including agitation, restlessness and gastrointestinal distress.
- Changes in blood levels of phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, imipramine and desipramine, and in some cases clinical manifestations of toxicity, have been observed. Consideration should be given to using conservative titration schedules of the concomitant medicine and monitoring of clinical status.
- The half-life of concurrently administered diazepam may be prolonged.

Warfarin and digoxin

- Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported when fluoxetine, as in LORIEN is co-administered with warfarin. As is prudent in concomitant use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful coagulation monitoring when LORIEN is initiated or stopped *(see below on medicines affecting haemostasis)*
- LORIEN is bound to plasma protein and concurrent administration may alter plasma concentrations of other plasma protein bound medicines, e.g. warfarin, digoxin, or conversely, LORIEN binding may be changed by these medicines.

Cyproheptadine

- There are individual case reports of reduced antidepressant activity of LORIEN

when used in combination with cyproheptadine.

Electroconvulsive therapy (ECT)

- There have been reports of prolonged seizures in patients on fluoxetine, as in LORIEN receiving ECT treatment (see section 4.4).

Medicines inducing hyponatremia

- Hyponatremia is an undesirable effect of LORIEN. Use in combination with other medicines associated with hyponatremia (e.g. diuretics, desmopressin, carbamazepine and oxcarbazepine) may lead to an increased risk. (see section 4.8).

Medicines lowering the epileptogenic threshold

- Seizures are an undesirable effect of LORIEN. Use in combination with other medicines which may lower the seizure threshold (for example, TCAs, other SSRIs, phenothiazines, butyrophenones, mefloquine, chloroquine, bupropion, tramadol) may lead to an increased risk (see section 4.8).

Medicines metabolised by cytochrome P450IID6 isoenzyme

- LORIEN has the potential to inhibit the cytochrome P450IID6 isoenzyme. Therapy with medicines that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index should be initiated at the low end of the dose range if a patient is receiving LORIEN concurrently or has taken it in the previous 5 weeks. If LORIEN is added to the treatment regimen of a patient already receiving such a medicine, the need for decreased dose of the original medicines should be considered.

Medicines metabolised by CYP2D6

- LORIEN is a strong inhibitor of CYP2D6 enzyme, therefore concomitant therapy with medicines also metabolised by this enzyme system may lead to medicine interactions, notably those having a narrow therapeutic index (such as flecainide, propafenone and nebivolol) and those that are titrated, but also with atomoxetine,

carbamazepine, tricyclic antidepressants and risperidone. They should be initiated at or adjusted to the low end of their dose range. This may also apply if LORIEN has been taken in the previous 5 weeks.

Medicines affecting haemostasis

- Medicines affecting haemostasis (oral anticoagulants, whatever their mechanism, platelets antiaggregants including aspirin and NSAIDs): risk of increased bleeding. Clinical monitoring, and more frequent monitoring of INR with oral anticoagulants, should be made dose adjustment during the fluoxetine treatment, such as LORIEN, and after its discontinuation may be suitable (see sections 4.4 and 4.8).

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

Some epidemiological studies suggest an increased risk of cardiovascular defects associated with the use of fluoxetine as in LORIEN during the first trimester. The mechanism is unknown. Overall the data suggest that the risk of having an infant with a cardiovascular defect following maternal fluoxetine exposure is in the region of 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population.

Epidemiological data have suggested that the use of SSRIs such as LORIEN in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the new-born (PPHN). The observed risk was approximately 5 cases per 1 000 pregnancies. In the general population 1 to 2 cases of PPHN per 1 000 pregnancies occur.

If LORIEN is used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour, since some other effects have been reported

in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of LORIEN (4 to 6 days) and its active metabolite, norfluoxetine (4 to 16 days).

There is data of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between fluoxetine, as in LORIEN, treatment and postpartum haemorrhage, there is a potential risk, considering the related mechanism of action (see section 4.4).

Lactation

The safety of LORIEN has not been established in breastfeeding women. LORIEN is excreted in human milk. Adverse events have been reported in breastfeeding infants.

If treatment with LORIEN is considered necessary, discontinuation of breastfeeding should be considered. However, if breastfeeding is continued, the lowest effective dose of LORIEN should be prescribed.

Fertility

Human case reports with some SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7. Effects on ability to drive and use machines

LORIEN has a moderate influence on the ability to drive and use machinery.

Since adverse reactions such as convulsions, headaches and visual disturbances have been reported in patients receiving LORIEN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LORIEN does not adversely affect their ability to do so safely (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions in patients treated with LORIEN were headache, nausea, insomnia, fatigue and diarrhoea. Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

b) Tabulated list of adverse reactions

The adverse reactions observed with fluoxetine treatment, as in LORIEN, in adult and paediatric populations are listed in the table below. Some of these adverse reactions are common with other SSRIs.

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Blood and the lymphatic system disorders		Anaemia, blood dyscrasias, hypochromic anaemia, leucopenia, lymphoedema, lymphocytosis, petechia, purpura, thrombocythaemia, thrombocytopenia, l neutropenia	Aplastic anaemia, eosinophilic pneumonia, pancytopenia, immune related haemolytic anaemia, thrombocytopenic purpura
Immune system disorders		Anaphylactic reaction, serum sickness	
Endocrine disorders		Hypothyroidism, diabetic acidosis, diabetes mellitus, inappropriate antidiuretic hormone secretion	

Metabolism and nutrition disorders	Weight gain, increased appetite, decreased appetite[1]	Alcohol intolerance, anorexia, dehydration, gout, hyperkalaemia, hyperuricaemia, hypokalaemia, iron deficiency anaemia, weight loss, hypocalcaemia	Hyponatraemia
Psychiatric disorders	Amnesia, emotional lability, insomnia[2], anxiety, decreased libido[3], sleep disorder, abnormal dreams[4],restlessness, tension,	Antisocial reaction, delusions, apathy, hostility, hypomania, increased libido, mania, paranoid reaction, personality disorder, psychosis, stupor, depersonalisation, elevated mood, euphoric mood, abnormal thinking, abnormal orgasm[5], bruxism, hallucinations, agitation, panic attacks, confusion, dysphemia, aggression, suicidal thoughts and behaviour[6]	Violent Behaviour,
Nervous system disorders	Headache, nervousness, drowsiness, tremor, disturbance in attention, dizziness, dysgeusia, lethargy, somnolence[7]	Abnormal electroencephalogram, abnormal gait, acute brain syndrome, akathisia, ataxia, bucco glossal syndrome, circumoral paraesthesia, CNS depression, coma, dizziness, dysarthria, dystonia, extrapyramidal syndrome, fatigue, foot drop, hyperaesthesia, hyperkinesia, hypertonia, hypoaesthesia, incoordination, mania, myoclonus, neuralgia, neuritis, neuropathy, neurosis, paralysis, decreased reflexes, increased reflexes, vertigo, memory impairment, balance disorder, convulsion, serotonin syndrome, migraine, taste loss / ageusia, parosmia, psychomotor hyperactivity	Dyskinesia, seizures, movement disorders, cerebral embolism
Eye disorders	Vision blurred	Blepharitis, conjunctivitis, diplopia, dry eyes, exopthalmos, eye haemorrhage, iritis, mydriasis, photophobias, scleritis, strabismus, visual disturbances, visual field defect, glaucoma,	

Ear and labyrinth disorders	Ear pain, tinnitus	Deafness, hyperacusis	
Cardiac disorders	Hypertension, palpitations, electrocardio-gram QT prolonged QTcF ≥450 msec)[8]	Angina pectoris, dysrhythmia, atrial fibrillation, bradycardia, cerebral ischaemia, cerebrovascular accident, congestive heart failure, extrasystoles, heart arrest, heart block, myocardial infarct, postural syncope, tachycardia, ventricular dysrhythmia including torsade de pointes, ventricular extrasystoles, ventricular fibrillation,	
Vascular disorders	Haemorrhage, flushing[9]	Pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, hypotension, vasculitis, vasodilation	
Respiratory, thoracic and mediastinal disorders	Yawning	Apnoea, dyspnoea, asthma, atelectasis, decreased cough, emphysema, epistaxis, haemoptysis, hiccup, hyperventilation, hypoventilation, hypoxia, larynx oedema, lung oedema, pneumothorax, stridor, pharyngitis, pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)[10]	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, dyspepsia, dry mouth	Aphthous stomatitis, biliary pain, bloody diarrhoea, cholecystitis, cholelithiasis, colitis, , duodenal ulcer, dysphagia, enteritis, eructation, oesophageal ulcer, oesophagitis, faecal incontinence, gastritis, gastroenteritis, gastrointestinal haemorrhage[11], glossitis, gum haemorrhage, haematemesis, haemorrhage of colon, hepatitis, hyperchlorhydria, increased salivation, intestinal obstruction, melaena, mouth ulceration, pancreatitis, peptic ulcer, rectal haemorrhage, salivary gland enlargement, stomach ulcer haemorrhage, thirst, tongue oedema, melena.	

Hepatobiliary disorders		Liver function tests abnormal (increased alkaline phosphatase, increased ALT), liver fatty deposit, idiosyncratic hepatitis	
Skin and subcutaneous tissue disorders	Excessive sweating, rash[12], urticaria, pruritus, hyperhidrosis	Acne, alopecia, contact dermatitis, eczema, furunculosis, herpes zoster, hirsutism, maculopapular rash, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhoea, skin discolouration, skin ulcer, vesiculobullous rash, increased tendency to bruise, cold sweat, ecchymosis, photosensitivity reaction, purpura, erythema multiforme, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (Lyell Syndrome), angioedema	
Musculoskeletal and connective tissue disorders	Arthritis, arthrosis, bone pain, bursitis, chondrodystrophy, leg cramps, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, tenosynovitis, arthralgia	Muscle twitching, myalgia	
Renal and urinary disorders	Frequent urination[13]	Albuminuria, increased blood urea nitrogen, cystitis, dysuria, haematuria, nocturia, polyuria, urinary incontinence, urinary urgency, glycosuria, kidney pain, oliguria, uterine haemorrhage, enlarged uterine fibroids, micturition disorder, urinary incontinence, urinary retention, urinary urgency,	
Reproductive system and breast disorders	Sexual dysfunction (delayed or inhibited orgasm), gynaecological bleeding[14], erectile dysfunction, ejaculation disorder[15]	Abortion, amenorrhoea, breast enlargement, breast engorgement, breast pain, female lactation, fibrocystic breast, hypomenorrhoea, leucorrhoea, menorrhagia, metrorrhagia, priapism, vaginal haemorrhage, galactorrhoea, hyperprolactinaemia	postpartum haemorrhage*

General disorders and administrative site conditions	Chest pain, chills, fatigue[16], feeling jittery	Asthenia, fever, generalised oedema, facial oedema, malaise, pelvic pain, peripheral oedema, acute abdominal syndrome, hypothermia, intentional injury, neuroleptic malignant syndrome, photosensitivity reaction, feeling abnormal, feeling hot, mucosal haemorrhage, intentional overdose	
Investigations		Increased creatine phosphokinase, hypercholesterolaemia, hyperlipidaemia, transaminases increased, gamma-glutamyl transferase increased	

[1] Includes anorexia

[2] Includes early morning awakening, initial insomnia, middle insomnia

[3] Includes loss of libido

[4] Includes nightmares

[5] Includes anorgasmia

[6] Includes completed suicide, depression suicidal, intentional self-injury, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt, morbid thoughts, self-injurious

behaviour. These symptoms may be due to underlying disease.

[7] Includes hypersomnia, sedation

[8] Based on ECG measurements from clinical trials

[9] Includes hot flush

[10] Includes atelectasis, interstitial lung disease, pneumonitis

[11] Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea haemorrhagic, melaena, and gastric ulcer haemorrhage

[12] Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash

[13] Includes pollakiuria

[14] Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorhagia, menorrhagia, metrorrhagia, polymenorrhea, postmenopausal

haemorrhage, uterine haemorrhage, vaginal haemorrhage

[15] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation

[16] Includes asthenia

* This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4 and 4.6).

c) *Description of selected adverse reactions*

Metabolism and nutrition disorders

Hyponatraemia (including serum sodium lower than 110 mmol/l) has been reported. The hyponatraemia may be reversible when LORIEN is discontinued. Although these cases were complex with varying possible aetiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). More often these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted.

Nervous system disorders

Dyskinesia (including, for example a case of buccallingual-masticatory syndrome, which resolved following medicine discontinuation), seizures (see section 4.4). Movement disorders developing in patients with risk factors (including medicines associated with such events) and worsening of pre-existing movement disorders.

There have been reports of extrapyramidal symptoms associated with the use of LORIEN and of aggravation of Parkinson's disease in patients taking LORIEN. Therefore, LORIEN should be used with care in patients with extrapyramidal disorders.

Eye disorders

Glaucoma has been reported with the use of LORIEN, the symptoms usually subsided within 2 days of medicine withdrawal. Intra-ocular pressure following LORIEN administration was recorded in some patients.

Respiratory, thoracic and mediastinal disorders

Dyspnoea. Pulmonary events (including inflammatory processes of varying histopathology and/or fibrosis) have been reported. Dyspnoea may be the only preceding symptom.

Skin and subcutaneous tissue disorders

Serious systemic events, possibly related to vasculitis, have developed in patients with rash and death has been reported.

Bone fractures

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs, such as LORIEN and TCAs. The mechanism leading to the risk is unknown.

Withdrawal symptoms seen on discontinuation of LORIEN treatments:

Discontinuation of LORIEN commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), confusion asthenia, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. Generally, these events are mild to moderate and are self-limiting, however, in some patients they may be severe and/or prolonged (see section 4.4). It is therefore advised that when LORIEN is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

d) Paediatric population

In paediatric clinical trials, suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (the events reported were: anger, irritability, aggression, agitation, activation syndrome), manic reactions, including mania and hypomania (no prior episodes reported in these patients) and epistaxis, were commonly reported and were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo.

Isolated cases of growth retardation have also been reported from clinical use.

In paediatric clinical trials, fluoxetine treatment as in LORIEN was also associated with a decrease in alkaline phosphatase levels.

Isolated cases of adverse events potentially indicating delayed sexual maturation or sexual dysfunction have been reported from paediatric clinical use (see section 5.3).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

Cases of overdose of LORIEN alone usually have a mild course.

Symptoms of overdose included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic dysrhythmias to cardiac arrest (including nodal rhythm and ventricular dysrhythmias) or ECG changes indicative of QTc prolongation to cardiac arrest (including very rare cases of Torsade de Pointes), pulmonary dysfunction and signs of altered CNS status ranging from excitation to coma.

Fatality attributed to overdose of LORIEN alone has been extremely rare.

Treatment

Treatment of overdosage is symptomatic and supportive.

Cardiac and vital signs monitoring is recommended

There are no specific antidotes for LORIEN.

Due to the large volume of distribution of LORIEN, forced diuresis, dialysis, haemoperfusion and exchange transfusions are unlikely to be of benefit.

Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis. In managing overdosage, consider the possibility of multiple medicines involvement. An extended time for close medical observation may be needed in patients who have taken excessive quantities of a tricyclic antidepressant if they are also taking or have recently taken LORIEN.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 1.2 Psychoanaleptics (antidepressants)

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors

ATC code: N06AB03

Mechanism of action

The antidepressant and anti-obsessive-compulsive action of fluoxetine is presumed to be linked to its inhibition of central nervous system (CNS) neuronal uptake of serotonin.

Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets and

inhibits the neuronal uptake of serotonin into the central nervous system.

5.2. Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed after oral administration.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95 %) and is widely distributed (volume of distribution: 2 to40 l/kg). Steady-state plasma concentrations are achieved after dosing for several weeks.

Peak plasma concentration is reached in 6 to 8 hours after a single dose of 40 mg.

Biotransformation

Because of the long elimination half-lives of fluoxetine (4 to 6 days) and its major active metabolite, norfluoxetine (4 to 16 days), changes in dose will not be fully reflected in plasma for several weeks (approximately 4 half-lives).

Elimination

Fluoxetine has a long elimination half-life

These long half-lives must be taken into account when doses are titrated or when treatment is stopped.

The elderly

The disposition of single doses of fluoxetine in healthy elderly patients (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and non-linear disposition of the medicine, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple medicines for concomitant diseases.

The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209,3 ± 85,7 ng/ml at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

LORIEN

Colloidal anhydrous silica, gelatine, lactose monohydrate, magnesium stearate, maize starch, patent blue, povidone, titanium, dioxide yellow iron oxide

LORIEN TABLETS

Colloidal silicon dioxide, magnesium stearate, maize starch, microcrystalline cellulose.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

LORIEN

49 months Securitainer

24 months blister

15 months metalised patient ready packs

LORIEN TABLETS

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep the plastic container tightly closed.

Keep in original packaging until required for use.

6.5. Nature and contents of container

LORIEN: 28 and 112 capsules are packed in a clear, polyvinylchloride/polyethylene/Aclar

blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

The capsules are packed in a white polypropylene container with a white, round, flat-topped linear low density polyethylene cap, with ridges on the side and a tamper evident seal, together with a silica gel sachet and a leaflet.

The capsules are packed in a metallised polyester/laminant/ opaque white linear low density polyethylene lay flat bag with a low density polyethylene zip.

LORIEN TABLETS: 28 or 30 tablets are packed in a clear polyvinylchloride/polyethylene/Aclar blister strip sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

28 or 30 tablets are packed in a white polypropylene container with a linear low density polyethylene tamper proof snap cap together with a white foam insert or silica gel sachet and a leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

LORIEN: 30/1.2/0024

LORIEN TABLETS: 34/1.2/0381

DATE OF FIRST AUTHORISATION

LORIEN:	27 March 1996
LORIEN TABLETS:	05 August 2002

9. DATE OF REVISION OF TEXT

27 June 2021

Namibia: LORIEN: NS3 04/1.2/0180

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