PROFESSIONAL INFORMATION

SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

LILLY-FLUOXETINE 20 (20 mg, capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each LILLY-FLUOXETINE 20 capsule contains fluoxetine hydrochloride equivalent to 20 mg fluoxetine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules.

LILLY-FLUOXETINE 20 is a size 3 capsule with a transparent green cap and a transparent green body imprinted with ‘20’.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Major depressive episodes

Bulimia nervosa

Obsessive-compulsive disorder: The obsessions 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

Major depressive episode

Adults and elderly: A dose of 20 mg/day is recommended, preferably in the morning.

Bulimia nervosa

A dose of 60 mg/day is recommended.

Obsessive-compulsive disorder

A dose of 20 to 60 mg/day is recommended.

The recommended dose may be increased or decreased.

LILLY-FLUOXETINE 20 capsules cannot be used for downward dose titration.

Doses above 80 mg/day are not recommended for any indication. Upward dose titration is advised at intervals of several weeks due to the kinetic properties of LILLY-FLUOXETINE 20 (see section 5.2).

LILLY-FLUOXETINE 20 may be administered with or without food.

Usage in the elderly

LILLY-FLUOXETINE 20 should be used with caution in all elderly patients, particularly if they have systemic illness or are receiving multiple medications for concomitant diseases.

Dosages over 20 mg per day are not recommended (see section 5.2)

Hepatic impairment and/or concurrent disease

A lower or less frequent dose should be considered in patients with hepatic impairment and concurrent diseases.

Withdrawal/discontinuation

Discontinuation of LILLY-FLUOXETINE 20 may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, asthenia, agitation, anxiety and nausea (see section 4.4).

Method of administration

For oral administration to adults only.

4.3 Contraindications

- Hypersensitivity (allergy) to the active substance, fluoxetine, or to any of the excipients listed in section 6.1.
- Severe renal failure (GFR < 30 ml/min).
- Concomitant use with linezolid.
- Concomitant use with metoprolol when used in cardiac failure.
- Concomitant use with pimozide.
- Concomitant use with monoamine oxidase inhibitors (MAOI) or within 14 days of discontinuation of therapy of MAOI (see section 4.4).

Paediatric use

Safety and efficacy in children below 18 years of age have not been established.

4.4 Special warnings and precautions for use

As improvement may not occur during the first two weeks of treatment, patients should be closely monitored during this period.

Suicide/suicidal thoughts or clinical worsening

Patients 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.

Isolated cases of suicidal ideation and suicidal behaviours have been reported during LILLY-FLUOXETINE 20 therapy or early after treatment discontinuation. Although a causal role for LILLY-FLUOXETINE 20 alone in inducing such behaviours has not been established, some pooled analyses from studies of patients using antidepressants in psychiatric conditions indicate an increased risk for suicidal ideation and suicidal behaviours in paediatric and young adult (< 25 years of age) patients.

In an analysis of controlled trials in adults with major depressive disorder, the following were risk factors for suicidality:

Prior to treatment:

- greater severity of depression
- presence of thoughts of death

During treatment:

- worsening of depression
- development of insomnia

Patients being treated with LILLY-FLUOXETINE 20 should 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.

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

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric disorders (e.g. obsessive-compulsive disorders) and non-psychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and non-psychiatric disorders.

Serotonin syndrome

A serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur with the use of LILLY-FLUOXETINE 20. This syndrome is characterised by the clustering of clinical features of changes in mental state (confusion, disorientation, agitation) and neuromuscular activity (myoclonus, hyper-reflexia, tremor, rigidity, dyscoordination in combination with autonomic dysfunction (especially fever, sweating, diarrhoea). The serotonin syndrome has been seen in temporal association with the use of monoamine oxidase inhibitors and with other serotonergic medication, but may occur in the absence of any concomitant medication. LILLY-FLUOXETINE 20 should be stopped immediately as serious morbidity and death may follow the serotonin syndrome.

Monoamine oxidase inhibitors

Cases 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) have been reported in

patients receiving LILLY-FLUOXETINE 20 in combination with monoamine oxidase inhibitors (MAOI) and in patients who have recently discontinued LILLY-FLUOXETINE 20 and are then started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore LILLY-FLUOXETINE 20 is contraindicated in combination with a MAOI or within 14 days of discontinuing therapy with a MAOI. Since LILLY-FLUOXETINE 20 and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping LILLY-FLUOXETINE 20 before starting a MAOI. If LILLY-FLUOXETINE 20 has been prescribed chronically and/or at a high dose, a longer interval should be considered (see sections 4.3 and 4.5).

Cardiovascular effects

Clinical experience in acute cardiac disease is limited, therefore caution is advisable.

Cases of QT interval prolongation and ventricular dysrhythmia including torsades de pointes have been reported during the post-marketing period. LILLY-FLUOXETINE 20 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, hypomagnesaemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to LILLY-FLUOXETINE 20 (e.g., hepatic impairment), or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. 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 fluoxetine, the treatment should be withdrawn, and an ECG should be performed.

Mania

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

Rash and possibly allergic events

Rash, anaphylactoid events and progressive systemic events, sometimes serious and involving skin, kidney, liver or lung, have been reported in patients taking LILLY-FLUOXETINE 20. Upon the appearance of rash or of other possibly allergic phenomena, LILLY-FLUOXETINE 20 should be discontinued.

Seizures

LILLY-FLUOXETINE 20 should be introduced cautiously in patients who have a history of seizures. LILLY-FLUOXETINE 20 should be discontinued in any patient who develops seizures. LILLY-FLUOXETINE 20 should be avoided in patients with uncontrolled epilepsy; patients with controlled epilepsy should be carefully monitored.

Electroconvulsive therapy (ECT)

There have been reports of prolonged seizures in patients on LILLY-FLUOXETINE 20 receiving electroconvulsant treatment (see section 4.5).

Tamoxifen

LILLY-FLUOXETINE 20, a potent inhibitor of CYP2D6, may lead to reduced concentrations of endoxifen, one of the most important active metabolites of tamoxifen. Therefore, LILLY-

FLUOXETINE 20 should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Hepatic/renal function

LILLY-FLUOXETINE 20 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 30 to 80 ml/min).

Weight loss

LILLY-FLUOXETINE 20 may cause loss of mass which could be undesirable in underweight depressed patients.

Diabetes

In patients with diabetes, LILLY-FLUOXETINE 20 may alter glycaemic control. Hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when fluoxetine therapy is initiated or discontinued.

Haemorrhage

There have been reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. There have also been reports of abnormal bleeding in several patients taking fluoxetine, including cutaneous bleeding abnormalities (e.g. ecchymosis and purpura) and other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) (see section 4.5). Caution is advised in patients taking SSRI's, particularly in concomitant use with

oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other medicines which may increase risk of bleeding as well as in patients with a history of bleeding disorders (see section 4.5).

Akathisia/psychomotor restlessness

Development of severe psychomotor activation (e.g. agitation, akathisia, panic) was also a risk factor during treatment with LILLY-FLUOXETINE 20. The presence or emergence of these conditions prior to or during therapy suggests that consideration should be given to increased clinical monitoring or possible modification of therapy.

There have been reports of extrapyramidal symptoms associated with the use of LILLY-FLUOXETINE 20 and of aggravation of Parkinson's disease in patients taking LILLY-FLUOXETINE 20. LILLY-FLUOXETINE 20 should therefore be used with care in patients with extrapyramidal disorders.

Mydriasis

Mydriasis has been reported in association with LILLY-FLUOXETINE 20; therefore, caution should be used when prescribing fluoxetine in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Withdrawal symptoms on discontinuation of treatment

Discontinuation of LILLY-FLUOXETINE 20 may lead to withdrawal symptoms, including dizziness, paraesthesia, headache, insomnia, tremor, confusion, sensory disturbances, asthenia, agitation, anxiety and nausea (see section 4.2). If the decision is made to

discontinue treatment, LILLY-FLUOXETINE 20 should be tapered over a period of at least one to two weeks, according to the patient's needs (see section 4.2).

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRI), such as LILLY-FLUOXETINE 20, 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 treatment.

General

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 such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing LILLY-FLUOXETINE 20 in patients for whom such symptoms are severe, abrupt in onset or were not part of the patient's presenting symptoms.

4.5 Interaction with other medicines and other forms of interaction

The long elimination half-lives of fluoxetine and its active metabolite should be borne in mind (see section 5.2) when considering pharmacodynamic or pharmacokinetic medicine interactions, or the potential consequence when medicines are prescribed that might interact with either substance following the discontinuation of LILLY-FLUOXETINE 20.

Medicines metabolised by cytochrome CYP2D6 isoenzyme

LILLY-FLUOXETINE 20 has the potential to inhibit the cytochrome CYP2D6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively 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 the low end of the dose range if a patient is receiving LILLY-FLUOXETINE 20 concurrently or has taken it in the previous 5 weeks. If LILLY-FLUOXETINE 20 is added to the treatment regimen of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

Metoprolol

Metoprolol used in cardiac failure: risk of metoprolol adverse events, including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine (see section 4.3).

Monoamine oxidase inhibitors

LILLY-FLUOXETINE 20 should not be used concomitantly with monoamine oxidase inhibitors (see sections 4.3 and 4.4).

CNS active medicines

Caution is advised if the concomitant administration of LILLY-FLUOXETINE 20 and CNS active medicines, including lithium, is required. There have been reports of both increased and decreased lithium levels when used concomitantly with fluoxetine. Lithium levels should be monitored.

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.

Concomitant use of other medicines with serotonergic activity (e.g. Serotonin and Norepinephrine Reuptake Inhibitors, Selective Serotonin Reuptake Inhibitors, such as triptans, tramadol, tryptophane, selegiline, or St. John's Wort) may result in serotonin syndrome. Therefore, the concomitant use of LILLY-FLUOXETINE 20 with these medicines should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).

There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when LILLY-FLUOXETINE 20 has been administered in combination with these medicines.

Patients receiving LILLY-FLUOXETINE 20 in combination with tryptophan have been reported to experience adverse reactions, including agitation, restlessness and gastrointestinal distress.

The half-life of concurrently administered diazepam may be prolonged.

Medicines affecting haemostasis

LILLY-FLUOXETINE 20 use may increase the risk of bleeding abnormalities. Concomitant use of aspirin, NSAIDS, other antiplatelet aggregation inhibitors, warfarin and other anticoagulants may add to this risk. Additional clinical evaluation and more frequent INR

monitoring if receiving warfarin, should be implemented. Dose adjustments may be necessary during the initiation, ongoing treatment and/or discontinuation of LILLY-FLUOXETINE 20.

Tamoxifen

Pharmacokinetic interaction between CYP2D6 inhibitors 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 inhibitors, such as LILLY-FLUOXETINE 20, should whenever possible be avoided (see section 4.4).

Alcohol

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

QT interval prolongation

Pharmacokinetic and pharmacodynamic studies between fluoxetine and other medicinal products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicinal products cannot be excluded. Therefore, co-administration of fluoxetine, as in LILLY-FLUOXETINE 20, with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, 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).

Cyproheptadine

There are individual case reports of reduced antidepressant activity of fluoxetine, as in LILLY-FLUOXETINE 20, when used in combination with cyproheptadine.

Medicines inducing hyponatremia

Hyponatremia is an undesirable effect of fluoxetine, as in LILLY-FLUOXETINE 20. 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 fluoxetine, as in LILLY-FLUOXETINE 20. 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.

Plasma protein binding

Fluoxetine is bound to plasma protein and concurrent administration may alter plasma concentrations of other plasma protein bound medicines, e.g. warfarin, digitoxin, or conversely, fluoxetine binding may be changed by other medicines.

Electroconvulsive therapy (ECT)

There have been reports of prolonged seizures in patients on LILLY-FLUOXETINE 20 receiving ECT treatment (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been demonstrated.

LILLY-FLUOXETINE 20 use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential risk of cardiovascular defects in infants of women exposed to LILLY-FLUOXETINE 20 during the first trimester of pregnancy compared to infants of women who were not exposed to LILLY-FLUOXETINE 20.

Use in the third trimester

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (e.g. transient jitteriness, difficulty feeding, tachypnoea and irritability) have been reported rarely in the neonate after maternal use near term.

Some neonates exposed to LILLY-FLUOXETINE 20 late in the third trimester developed complications resulting in prolonged hospitalisation, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness,

irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs, or possibly, withdrawal syndrome. In some cases, the clinical picture is consistent with serotonin syndrome (see section 4.4).
LILLY-FLUOXETINE 20 use late in the third trimester of pregnancy may increase the risk of persistent pulmonary hypertension in the newborn.

Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).

Breastfeeding

Fluoxetine and its metabolite norfluoxetine, are known to be excreted in human breast milk. Adverse events have been reported in breastfeeding infants. If treatment with LILLY-FLUOXETINE 20 is considered necessary, discontinuation of breastfeeding should be considered; however if breastfeeding is continued, the lowest effective dose of LILLY-FLUOXETINE 20 should be prescribed.

Fertility

Animal data have shown that fluoxetine may affect sperm quality (see section 5.3).
Human case reports with some SSRI's 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

Although LILLY-FLUOXETINE 20 has been shown not to affect psychomotor performance in healthy volunteers, LILLY-FLUOXETINE 20 may impair judgement, thinking or motor skills.

Patients should be cautioned that their ability to perform potentially hazardous tasks (e.g. driving a motor vehicle or operating machinery) may be impaired. They should refrain from doing so until certain how they are affected by LILLY-FLUOXETINE 20.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse reactions in patients treated with fluoxetine 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

Clinical Trial Data: Events are classified within body system categories using the following frequencies: very common adverse events (≥ 1/10), common adverse events (≥ 1/100, < 1/10), uncommon adverse events (≥ 1/1 000, < 1/100), rare events (≥ 1/10 000, < 1/1 000), not known (cannot estimate from the available data).

Very Common	Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders				
			Thrombocytopenia Neutropenia Leucopenia	
Immune system disorders				
			Anaphylactic reaction	

			Serum sickness	
Endocrine disorders				
			Inappropriate antidiuretic hormone secretion	
Metabolism and nutrition disorders				
	Decreased appetite[1]		Hyponatraemia	
Psychiatric disorders				
Insomnia[2]	Anxiety Nervousness Restlessness Tension Libido decreased[3] Sleep disorder Abnormal dreams[4]	Depersonalisation Elevated mood Euphoric mood Thinking abnormal Orgasm abnormal[5] Bruxism Suicidal thoughts and behaviour [6]	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia Aggression	
Nervous system disorders				

Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence[7] Tremor	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder Myoclonus Memory impairment	Convulsion Akathisia Buccoglossal syndrome Serotonin syndrome	
Eye disorders				
	Vision blurred	Mydriasis		
Ear and labyrinth disorders				
		Tinnitus		
Cardiac disorders				
	Palpitations Electrocardiogram QT prolonged (QTcF ≥ 450 msec)[8]		Ventricular arrhythmia including torsades de pointes	
Vascular disorders				
	Flushing[9]	Hypotension	Vasculitis Vasodilatation	
Respiratory, thoracic and mediastinal disorders				
	Yawning	Dyspnoea Epistaxis	Pharyngitis	

			Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis) [10]	
Gastrointestinal disorders				
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia Gastrointestinal haemorrhage[11]	Oesophageal pain	
Hepato-biliary disorders				
			Idiosyncratic hepatitis	
Skin and subcutaneous tissue disorders				
	Rash[12] Urticaria Pruritus Hyperhidrosis	Alopecia Increased tendency to bruise Cold sweat	Angioedema Ecchymosis Photosensitivity reaction Purpura Erythema multiforme Stevens-Johnson syndrome	

			Toxic Epidermal Necrolysis (Lyell Syndrome)	
Musculoskeletal and connective tissue disorders				
	Arthralgia	Muscle twitching	Myalgia	
Renal and urinary disorders				
	Frequent urination[13]	Dysuria	Urinary retention Micturition disorder	
Reproductive system and breast disorders				
	Gynaecological bleeding[14] Erectile dysfunction Ejaculation disorder[15]	Sexual dysfunction[16]	Galactorrhoea Hyperprolactinaemia Priapism	Postpartum haemorrhage[17]
General disorders and administration site conditions				
Fatigue[18]	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot	Mucosal haemorrhage	

Investigations				
	Weight decreased	Transaminases increased Gamma-glutamyltransferase 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] Occasionally persisting after treatment discontinuation

[17] This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).

[18] Includes asthenia

The following have been reported in association with LILLY-FLUOXETINE 20, but no causal relationship has been established: Aplastic anaemia, cerebral vascular accident, confusion, seizures, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome, which resolved following drug discontinuation), eosinophilic pneumonia, gastrointestinal haemorrhage, hyperprolactinaemia, erythema multiforme, angioedema, movement disorders developing in patients with risk factors (including medicines associated with such events) and worsening of pre-existing movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, suicidal ideation, pancytopenia, immune related haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after withdrawal of the medication and violent behaviour.

See section 4.6 for information on side effects of persistent pulmonary hypertension in the newborn.

c. Description of selected adverse reactions

Suicide/suicidal thoughts or clinical worsening

Cases of suicidal ideation and suicidal behaviour have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4).

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 and TCAs. The mechanism leading to the risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine treatments

Discontinuation of fluoxetine commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), 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 LILLY-FLUOXETINE 20 treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

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 via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:

https://www.sahpra.org.za/Publications/Index/8. Alternately, report suspected adverse reactions to the company at ade_za@lilly.com.

4.9 Overdose

Symptoms

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

Management

Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for LILLY-FLUOXETINE 20. Due to the large volume of distribution of LILLY-FLUOXETINE 20, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. In managing overdosage, the possibility of multiple medicine involvement should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors, ATC code: N06A B03.

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.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is well absorbed after oral administration. The bioavailability is not affected by food intake.

Distribution

Fluoxetine is extensively bound to plasma proteins (about 95 %) and is widely distributed (volume of distribution 2 to 40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Biotransformation

Fluoxetine has a non-linear pharmacokinetic profile with first pass liver effect. Peak plasma concentration is reached in 6 to 8 hours after a single dose of 40 mg.
Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by desmethylation.

Elimination

Because of the long elimination half-lives of the parent drug (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). This is to be taken into consideration during dose titration or cessation of treatment. Excretion is mainly (about 60 %) via the kidney. Fluoxetine is secreted into breast milk.

Special populations

Elderly

The disposition of single doses of fluoxetine in healthy elderly subjects (> 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.

Hepatic insufficiency

In case of hepatic insufficiency (alcoholic cirrhosis), fluoxetine and norfluoxetine half-lives are increased to 7 and 12 days, respectively. A lower or less frequent dose should be considered.

Renal insufficiency

After single-dose administration of fluoxetine in patients with mild, moderate or complete (anuria) renal insufficiency, kinetic parameters have not been altered when compared to healthy volunteers. However, after repeated administration, an increase in steady-state plateau of plasma concentrations may be observed.

5.3 Preclinical safety data

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch flowable powder

Dimeticone

Capsule components:

Black iron oxide

Indigo Carmine

Quinoline yellow

Gelatin

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Store at or below 30 °C in blister packs. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

LILLY-FLUOXETINE 20 capsules are supplied in blister packs of 28.

6.6 Special precautions for disposal and other handling

Not applicable

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Eli Lilly (S.A.) (Pty) Limited

Golden Oak House, Ballyoaks Office Park,

35 Ballyclare Drive

Bryanston, 2191

8. REGISTRATION NUMBER(S)

29/1.2/0491

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

25 October 1995

10. DATE OF REVISION OF THE TEXT

04 April 2024

Registration Details for Botswana		
Lilly Fluoxetine 20 mg Capsules	Reg. No.: BOT9700100	Schedule 2
Please report any suspected ADRs to BoMRA through e-reporting https://primaryreporting.who-umc.org/BW and e-mail reportadr@bomra.co.bw.		

Registration Details for Namibia		
Lilly Fluoxetine 20	Reg. No.: 04/1.2/0657	Schedule NS3