This submission: Compliant response to recommendation received via DVP on 8 August 2021
Date of implementation: 8 August 2021

Approved Professional Information for FLUOXETINE BIOTECH 20

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

FLUOXETINE BIOTECH 20 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg fluoxetine (as fluoxetine hydrochloride).

Excipient with known effect:

Contains sugar (140 mg lactose monohydrate per capsule).

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Capsules, hard.

Ivory opaque body, green opaque cap, hard gelatine capsules. White powder fill.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1. MAJOR DEPRESSIVE EPISODES

This includes a single episode or recurrent depression with associated anxiety.

2. BULIMIA NERVOSA

FLUOXETINE BIOTECH has been shown to significantly decrease binge-eating and purging activity.

3. OBSESSIVE COMPULSIVE DISORDER

FLUOXETINE BIOTECH is indicated for the treatment of 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 function.

4.2 Posology and method of administration

Posology:

For administration to adults only.

1. MAJOR DEPRESSIVE EPISODES

For the treatment of a major depressive episode: The usual initial dosage is 20 mg administered once daily in the morning. The daily dose should not exceed a maximum of 80 mg per day.

2. BULIMIA NERVOSA

The recommended dosage is 60 mg per day.

3. OBSESSIVE COMPULSIVE DISORDER

A dose range of 20 mg/day to 60 mg/day is recommended for the treatment of obsessive-compulsive disorder.

The recommended dose may be increased or decreased. 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 fluoxetine (see section 5.2).

Special populations:

Use in the elderly: The effect of age on the metabolism of fluoxetine has not yet been fully

established. Thus, FLUOXETINE BIOTECH should be used cautiously in the elderly patients especially if they have a systemic illness or are taking multiple medications for concomitant diseases. Dosages over 20 mg per day are not recommended.

Use in patients with renal impairment: Dosage reduction, for example, alternate day dosing, may be required in patients with mild to moderate renal failure (GFR 10 – 15 mL/min), as fluoxetine is metabolised by the liver and excreted in the urine.
FLUOXETINE BIOTECH is contraindicated in patients with severe renal failure (GFR < 10 mL/min) (see section 4.3).

Use in patients with hepatic or concurrent disease: A lower or less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic and concurrent disease, or in patients where concomitant medication has the potential for interaction with FLUOXETINE BIOTECH.

Discontinuation of FLUOXETINE BIOTECH:

Abrupt discontinuation of FLUOXETINE BIOTECH should be avoided. When stopping treatment with FLUOXETINE BIOTECH, 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).

Method of administration:

For oral use only.

4.3 Contraindications

- FLUOXETINE BIOTECH is contraindicated in patients with known hypersensitivity to fluoxetine hydrochloride or to any of the excipients listed in section 6.1.

- *Monoamine oxidase inhibitors:*

  There have been reports of serious, 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 in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

  Therefore, FLUOXETINE BIOTECH should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with the MAOI (see section 4.5).

  Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping FLUOXETINE BIOTECH before starting an MAOI.

  If FLUOXETINE BIOTECH has been prescribed chronically and/or at a high dose, a longer interval 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 BIOTECH and an MAOI in temporal proximity (see section 4.4).
- FLUOXETINE BIOTECH is contraindicated in combination with metoprolol, used in cardiac failure (see section 4.5).
- Thioridazine should not be administered with FLUOXETINE BIOTECH or within a minimum of 5 weeks after FLUOXETINE BIOTECH has been discontinued. Thioridazine administration produces a dose related prolongation of the QTc interval which is associated with serious ventricular dysrhythmias, such as torsades de pointes-type dysrhythmias and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism.
- Patients with severe renal failure (GFR < 10 mL/min) should not be prescribed FLUOXETINE BIOTECH as during chronic treatment accumulation of fluoxetine may occur.
- Children under the age of 18 years (see section 4.4).

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4.4 Special warnings and precautions for use

Rash and possible allergic events:

Upon the appearance of rash or other possible allergic phenomena for which an alternative etiology cannot be identified FLUOXETINE BIOTECH (fluoxetine hydrochloride) should be discontinued.

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. A causal role, however, for antidepressant medicine in inducing such behaviour has not been established.

Patients being treated with FLUOXETINE BIOTECH 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.

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.

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 with the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing FLUOXETINE BIOTECH, in patients for whom such symptoms are

severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision is made to discontinue treatment, FLUOXETINE BIOTECH should be tapered (see section 4.2) because of the risk that FLUOXETINE BIOTECH can lead to discontinuation effects (see section 4.8).

Children under 18 years of age:

Safety and efficacy in children under 18 years of age have not been established. 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 (see section 4.3).

Cardiovascular effects:

Cases of QT interval prolongation and ventricular dysrhythmia including torsades de pointes have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9). FLUOXETINE BIOTECH 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 fluoxetine (e.g. hepatic impairment), or concomitant use with medicines known to induce QT prolongation and/or torsade de pointes (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 FLUOXETINE BIOTECH, the treatment should be withdrawn, and an ECG should be performed.

Serotonin syndrome:

A serotonin syndrome, which may be confused with neuroleptic malignant syndrome, may occur

with the use of FLUOXETINE BIOTECH. 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, incoordination), in combination with auto-immune 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 medicines but may occur in the absence of any concomitant medication. FLUOXETINE BIOTECH should be stopped immediately as serious morbidity and death may follow the serotonin syndrome.

Withdrawal symptoms seen on discontinuation of FLUOXETINE BIOTECH:

Withdrawal symptoms when treatment is discontinued occur frequently, particularly if discontinuation is abrupt (see section 4.8).

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy and the rate of dose reduction. 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 reported reactions. 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 – 3 months or more). It is therefore advised that FLUOXETINE BIOTECH should be gradually tapered when discontinuing treatment over a period of at least one to two weeks, according to the patient's needs (see “Discontinuation of FLUOXETINE BIOTECH”, section 4.2).

Other precautions:

Bipolar illness: Fluoxetine is not usually considered a suitable therapy for the depressive component of bipolar illness.

Mania: Antidepressants such as FLUOXETINE BIOTECH should be used in caution with patients with a history of mania/hypomania. FLUOXETINE BIOTECH should be discontinued in any patient entering a manic phase.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRIs as in FLUOXETINE BIOTECH. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported. SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6 and 4.8). Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, medicines known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants [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).

Seizures: Seizures are a potential risk with antidepressant medicines as in FLUOXETINE BIOTECH, and therefore it should be introduced cautiously in patients who have a history of seizures. If a patient develops seizures, fluoxetine should be discontinued. Fluoxetine should not be administered to patients with unstable epilepsy and when administered to patients with controlled epilepsy, the patient should be carefully monitored.

Electroconvulsive therapy (ECT): There have been reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, therefore caution is advisable.

Tamoxifen: Fluoxetine, a potent inhibitor of CYP2D6, may lead to reduced concentrations of

endoxifen, one of the most important active metabolites of tamoxifen. Therefore, FLUOXETINE BIOTECH should whenever possible be avoided during tamoxifen treatment (see section 4.5).

Akathisia/psychomotor restlessness: The use of FLUOXETINE BIOTECH 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.

Weight loss: Caution must be observed when administering fluoxetine to underweight, depressed patients as fluoxetine may cause weight loss.

Diabetes: Diabetic patients receiving FLUOXETINE BIOTECH must be closely observed as fluoxetine may alter glycaemic control leading to hypoglycaemia. Dosage adjustments of oral hypoglycaemic medicines and insulin may be necessary. These must be readjusted when fluoxetine therapy is discontinued.

Sexual dysfunction: Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) 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 SSRIs/SNRI.

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

FLUOXETINE BIOTECH contains lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take FLUOXETINE BIOTECH.

Laboratory tests: Altered platelet function and/or abnormal laboratory results for patients receiving fluoxetine have been reported. There have also been reports of abnormal bleeding in patients receiving fluoxetine, but it is not clear whether fluoxetine is the causative agent.

Due to the fact that improvement of the condition may not begin for the first couple of weeks, patients should be observed during this early phase of treatment. Patients suffering from major depressive episodes are at a high risk for suicide and should be closely supervised.

4.5 Interaction with other medicines and other forms of interaction

When considering medicine interactions, the long half-lives of fluoxetine and norfluoxetine should be taken into consideration.

Fluoxetine concurrently administered with medicines that are also plasma protein bound may lead to an alteration in the plasma concentrations of these medicines, e.g. warfarin and digoxin or an alteration of the fluoxetine plasma concentration.

Concurrent administration of fluoxetine and diazepam may lead to an increase in the half-life of the diazepam.

Stable plasma levels of other antidepressants have been reported to increase by more than two times when administered in combination with fluoxetine.

Contraindicated combinations:

Irreversible, non-selective monoamine oxidase inhibitors (e.g. iproniazid): Some cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI 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.

Therefore, fluoxetine is contraindicated in combination with an irreversible, non-selective MAOI (see section 4.3). Because of the two weeks-lasting effect of the latter, treatment with fluoxetine should only be started 2 weeks after discontinuation of an irreversible, non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting an irreversible, non-selective MAOI.

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).

Not recommended combinations:

Tamoxifen: Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen, showing a 65 – 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 (including FLUOXETINE BIOTECH) 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.

MAOI-A including linezolid and methylthioninium chloride (methylene blue): Risk of serotonin syndrome including diarrhoea, tachycardia, sweating, tremor, confusion or coma. If the concomitant use of these medicines with FLUOXETINE BIOTECH cannot be avoided, a 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 FLUOXETINE BIOTECH.

Combinations requiring caution:
FLUOXETINE BIOTECH should be used cautiously when co-administered with:

Phenytoin: Changes in blood levels have been observed when combined with fluoxetine. In some cases, manifestations of toxicity have occurred. Consideration should be given to using conservative titration schedules of the concomitant medicine and to monitoring clinical status.

Serotonergic medicines (lithium, tramadol, triptans, tryptophan, selegiline (MAOI-B), St John's wort (Hypericum perforatum)*:* There have been reports of mild serotonin syndrome when SSRIs were given with medicines also having a serotoninergic effect. Therefore, the concomitant use of FLUOXETINE BIOTECH with these medicines should be undertaken with caution, with closer and more frequent clinical monitoring (see section 4.4).

Buprenorphine/opioids: As the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

QT interval prolongation: Pharmacokinetic and pharmacodynamic studies between fluoxetine and other products that prolong the QT interval have not been performed. An additive effect of fluoxetine and these medicines cannot be excluded. Therefore, co-administration of FLUOXETINE BIOTECH with medicines that prolong the QT interval, such as class IA and III antidysrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants (TCA), 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).

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. A dose adjustment during FLUOXETINE BIOTECH treatment and after its discontinuation may be suitable (see sections 4.4 and 4.8).

Cyproheptadine: There are individual case reports of reduced antidepressant activity of FLUOXETINE BIOTECH when used in
combination with cyproheptadine.

Medicines inducing hyponatremia: Hyponatraemia is an undesirable effect of FLUOXETINE BIOTECH. Use in combination with other medicines associated with hyponatraemia (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 BIOTECH. 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.

Other medicines metabolised by CYP2D6: Fluoxetine 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 FLUOXETINE BIOTECH has been taken in the previous 5 weeks.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been demonstrated.

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

Epidemiological data have suggested that the use of SSRIs (as in FLUOXETINE BIOTECH) during pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The risk was approximately 5 cases per 1 000 pregnancies. In the general population 1 to 2 cases of PPHN per 1 000 pregnancies occur.

Some epidemiological studies suggest an increased risk of cardiovascular defects associated with

the use of fluoxetine 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.

Lactation:

Safety of FLUOXETINE BIOTECH has not been established in breastfeeding women. Fluoxetine is secreted in human milk.

Fertility:

Animal data have shown that fluoxetine may affect sperm quality. 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

As fluoxetine is a psychoactive medicine it may impair judgement or skills, although these were not affected in healthy volunteers. Patients should be warned that their ability to drive or perform hazardous tasks may be impaired.

4.8 Undesirable effects

Tabulated list of adverse reactions:

Blood and lymphatic system disorders:	
Less frequent	Thrombocytopenia, neutropenia, leucopenia.
Immune system disorders:	
Less frequent	Anaphylactic reaction, serum sickness.

Endocrine disorders:	
Less frequent	Inappropriate antidiuretic hormone secretion.
Metabolism and nutrition disorders:	
Frequent	Decreased appetite[1].
Less frequent	Hyponatraemia.
Psychiatric disorders:	
Frequent	Insomnia[2], anxiety, nervousness restlessness, tension, libido decreased[3], sleep disorder, abnormal dreams[4].
Less frequent	Depersonalisation, elevated mood, euphoric mood, abnormal thinking, abnormal orgasm[5], bruxism, suicidal thoughts and behaviour[6], hypomania, mania, hallucinations, agitation, panic attacks, confusion, dysphemia, aggression.
Nervous system disorders:	
Frequent	Headache, disturbance in attention, dizziness, dysgeusia, lethargy, somnolence[7], tremor.
Less frequent	Psychomotor hyperactivity, dyskinesia, ataxia, balance disorder, myoclonus, memory impairment, convulsion, akathisia, buccoglossal syndrome, serotonin syndrome.
Eye disorders:	
Frequent	Vision blurred.
Less frequent	Mydriasis.
Ear and labyrinth disorders:	
Less frequent	Tinnitus.
Cardiac disorders:	
Frequent	Palpitations, electrocardiogram QT prolonged[8].

Less frequent	Ventricular dysrhythmia including torsades se pointes.
Vascular disorders:	
Frequent	Flushing[9].
Less frequent	Hypotension, vasculitis, vasodilatation.
Respiratory, thoracic and mediastinal disorders:	
Frequent	Yawning.
Less frequent	Dyspnoea, epistaxis, pharyngitis, pulmonary events (inflammatory processes of varying histopathology and/or fibrosis)[10].
Gastrointestinal disorders:	
Frequent	Diarrhoea, nausea, vomiting, dyspepsia, dry mouth.
Less frequent	Dysphagia, gastrointestinal haemorrhage[11], oesophageal pain.
Hepatobiliary disorders:	
Less frequent	Idiosyncratic hepatitis.
Skin and subcutaneous tissue disorders:	
Frequent	Rash[12], urticaria, pruritus, hyperhidrosis.
Less frequent	Alopecia, increased tendency to bruise, cold sweat, angioedema, ecchymosis, photosensitivity reaction, purpura, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell syndrome).
Musculoskeletal, connective tissue disorders:	
Frequent	Arthralgia.
Less frequent	Muscle twitching, myalgia.
Renal and urinary disorders:	
Frequent	Frequent urination[13].
Less frequent	Dysuria, urinary retention, micturition disorder.

Reproductive system and breast disorders:	
Frequent	Gynaecological bleeding[14], erectile dysfunction, ejaculation disorder[15].
Less frequent	Sexual disfunction[16], galactorrhoea, hyperprolactinaemia, priapism.
Frequency unknown:	Postpartum haemorrhage[17].
General disorders and administration site conditions:	
Frequent	Fatigue[18], feeling jittery, chills.
Less frequent	Malaise, feeling abnormal, feeling cold, feeling hot, mucosal haemorrhage.
Investigations:	
Frequent	Weight decreased.
Less frequent	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, suicidal depression, 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, haemorrhagic diarrhoea, melaena, and gastric ulcer haemorrhage

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

[13] Includes pollakiuria

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

[15] Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, delayed ejaculation, 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 and 4.6)

[18] Includes asthenia.

The following side effects have been reported with fluoxetine but a causal relationship is yet to be established: aplastic anaemia, cerebral vascular accident, confusion, dyskinesia, ecchymoses, eosinophilic pneumonia, gastro-intestinal haemorrhage, hyperprolactinaemia, movement disorders, neuroleptic malignant syndrome-like events, pancreatitis, suicidal ideation, pancytopenia, immune related haemolytic anaemia, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after withdrawal of medication and violent behaviour.

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 this risk is unknown.

Withdrawal symptoms seen on discontinuation of fluoxetine: 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 frequently 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 treatment with FLUOXETINE BIOTECH 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 FLUOXETINE BIOTECH is important. It allows continued monitoring of the benefit/risk balance of FLUOXETINE BIOTECH. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms:

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have 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. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Management:

Cardiac and vital signs monitoring are recommended, along with general symptomatic and supportive measures. No specific antidote is known.

Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. In managing overdosage, consider the possibility of multiple medicine 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, FLUOXETINE BIOTECH.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Selective serotonin reuptake inhibitors.

ATC code: N06A B03.

The antidepressant, anti-obsessional compulsive actions of fluoxetine are presumed to be linked to its ability to inhibit the CNS neuronal uptake of serotonin. At clinically relevant doses, fluoxetine blocks the uptake of serotonin into human platelets.

5.2 Pharmacokinetic properties

Absorption:

Fluoxetine is well absorbed after oral administration. Peak plasma concentration is reached in 6 to 8 hours after a single dose of 40 mg.

Distribution:

Fluoxetine is extensively bound to plasma proteins (about 95 %) and is well distributed (volume of distribution: 2 – 40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks.

Elimination:

The parent drug has an elimination half-life of two to three days and the major active metabolite norfluoxetine has an elimination half-life of 7 to 9 days. As a result of these long half-lives, changes in dosage regimen will not be reflected in the plasma for approximately four half-lives. This must be taken into consideration during dosage titration or cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Corn starch

Talc

Stearic acid.

The capsule shell contains:

Gelatine

Patent blue (E131)

Iron oxide yellow (E172)

Quinoline yellow (E104)

Erythrosine (E127)

Titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

FLUOXETINE BIOTECH 20 is packed in:

White high-density polyethylene bottles containing 28, 30, 100 or 500 capsules.

Or

Alu paper backed foil & clear PVC blisters, packed in outer carton boxes containing 28, 30, 100 or 500 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

400 16th Road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBER

30/1.2/0356

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 April 1997

10. DATE OF REVISION OF THE TEXT

8 August 2021