Abbott Laboratories South Africa (Pty) Ltd	**Submission Date: 12 November 2021**	**Type: Post-registration variation**
FAVERIN 100	**Approval Date: 13 February 2022**	**Category: IA$_{IN}$, IB**
100 mg, film-coated tablets	**Implementation: 13 February 2022**	**Code: C.I.0.1, C.I.0.2a, C.I.0.3, C.I.13a**
Country Code: ZA	**Reg No.: 33/1.2/0354**	**Sequence No.: 0000**

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

FAVERIN 100 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains fluvoxamine maleate 100 mg.

Excipient with known effect:

Contains sugar: Each tablet contains 303 mg mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Oval, biconvex, white, film-coated, breakable tablets, inscribed with “S” on the one side and “313” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FAVERIN is indicated in adults for the treatment of major depressive episodes and for the short-term treatment of severe, disabling obsessive-compulsive disorder, where the obsessions or compulsions cause marked distress, are time-consuming or significantly interfere with social or occupational functioning.

1.3.1.1 PROFESSIONAL INFORMATION

4.2 Posology and method of administration

Posology

Major depressive episodes

The effective daily dose usually varies between 100 mg and 200 mg and should be adjusted to the individual response of the patient up to a maximum of 300 mg. The minimum recommended starting dose is 100 mg per day and can be given as a single dose, preferably in the evening. It is advisable that a total daily dose of more than 150 mg is given in 2 or 3 divided doses.

Obsessive-compulsive disorder

The effective dosage usually lies between 100 mg and 200 mg, with some patients requiring up to 300 mg per day. The recommended starting dose is 50 mg per day for 3 to 4 days. The dosage should be increased gradually until the effective dosage is achieved, with a maximum of 300 mg per day. If no improvement is observed within 10 weeks, treatment with FAVERIN should be reconsidered.

Obsessive compulsive disorder is a chronic condition and it is reasonable to consider continuation beyond 10 weeks in responding patients. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. The need for treatment should be reassessed periodically.

Upward dose titration should be done slower in the elderly and dosing should always be done with caution.

Method of administration

FAVERIN tablets should be swallowed with water and without chewing.

4.3 Contraindications

1.3.1.1 PROFESSIONAL INFORMATION

- Hypersensitivity to fluvoxamine maleate or to any of the excipients (see section 6.1).
- Pregnancy and lactation.
- Safety and efficacy have not been established in children (see section 4.4).
- Safety in patients with liver dysfunction and moderate to pronounced renal function impairment has not been established.
- Safety has not been established in epileptics.
- FAVERIN tablets are contraindicated in combination with tizanidine and monoamine oxidase inhibitors (MAOIs) (see section 4.5). Patients should not receive FAVERIN together with or within 2 weeks of terminating treatment with monoamine oxidase inhibitors. At least one week should elapse between discontinuation of FAVERIN and initiation of therapy with a monoamine oxidase inhibitor.
- FAVERIN tablets should not be used in combination with pimozide (see section 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

Other psychiatric conditions for which FAVERIN is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive disorder. The same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

1.3.1.1 PROFESSIONAL INFORMATION

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.

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.

Paediatric population

FAVERIN should not be used in the treatment of children and adolescents under the age of 18 years (see section 4.3).

Young adults (ages 18 to 24 years)

A meta-analysis of placebo controlled clinical trials of antidepressant medicines 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.

Geriatric population

Data in elderly subjects give no indication of clinically significant differences in normal daily dosages compared to younger subjects. However, upward dose titration should be done slower in the elderly, and dosing should always be done with caution.

1.3.1.1 PROFESSIONAL INFORMATION

Akathisia/psychomotor restlessness

The use of FAVERIN 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.

Renal and hepatic impairment

Patients suffering from hepatic or renal insufficiency should start on a low dose and be carefully monitored.

Treatment with FAVERIN may be associated with an increase in hepatic enzymes, generally accompanied by symptoms. In such cases treatment should be discontinued.

Nervous system disorders

Although in animal studies fluvoxamine has no pro-convulsive properties, caution is recommended when FAVERIN is administered to patients with a history of convulsive disorders. FAVERIN should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be carefully monitored. Treatment with FAVERIN should be discontinued if seizures occur or if seizure frequency increases.

On rare occasions development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with treatment with FAVERIN, particularly when given in combination with other serotonergic and/or neuroleptic medicines. As these syndromes may result in potentially life-threatening conditions, treatment with FAVERIN should be discontinued if such events (characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus,

1.3.1.1 PROFESSIONAL INFORMATION

autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated.

Metabolism and nutrition disorders

Hyponatraemia has been rarely reported and appears to be reversible when FAVERIN was discontinued. Some cases were possibly due to the syndrome of inappropriate anti-diuretic hormone secretion. The majority of reports were associated with older patients.

Glycaemic control may be disturbed (i.e., hyperglycaemia, hypoglycaemia, decreased glucose tolerance), especially in the early stages of treatment. When FAVERIN is given to patients with a known history of diabetes mellitus, the dosage of anti-diabetic medicines may need to be adjusted.

Nausea, sometimes accompanied by vomiting, is the most frequently observed symptom associated with FAVERIN treatment. This side effect usually diminishes within the first two weeks of treatment.

Eye disorders

Mydriasis has been reported in association with selective serotonin reuptake inhibitors (SSRIs) such as FAVERIN. Therefore caution should be used when prescribing FAVERIN in patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma.

Haematological disorders

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura as well as other haemorrhagic manifestations, such as gastrointestinal bleeding or

1.3.1.1 PROFESSIONAL INFORMATION

gynaecological/postpartum haemorrhage, with selective serotonin reuptake inhibitors, such as FAVERIN. Caution is advised in patients taking selective serotonin reuptake inhibitors, particularly in elderly patients and in patients who concomitantly use medicines known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants, aspirin, non-steroidal anti-inflammatory drugs) or medicines that increase risk of bleeding as well as in patients with a history of bleeding disorders and in those with predisposing conditions (e.g. thrombocytopenia, or coagulation disorders).

Selective serotonin reuptake inhibitors (SSRIs) may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).

Cardiac disorders

When combined with FAVERIN, plasma concentrations of terfenadine, astemizole or cisapride may be increased resulting in an increased risk for QT-prolongation/Torsade de Pointes. Therefore, FAVERIN should not be co-administered with these medicines.

Electroconvulsive therapy (ECT)

There is limited clinical experience of concomitant administration of FAVERIN and ECT, therefore caution is advisable.

Withdrawal reactions

It is possible that withdrawal reactions may occur on stopping therapy with FAVERIN although the available preclinical and clinical evidence does not suggest that this treatment causes dependence.

The most commonly reported symptoms in association with withdrawal of the product include

dizziness, sensory disturbances (including paraesthesia, visual disturbances and electric shock sensations), sleep disturbances (including insomnia and intense dreams), agitation, irritability, confusion, emotional instability, headache, nausea and/or vomiting, diarrhoea, sweating, palpitations, tremor and anxiety (see section 4.8).

Generally these events are mild to moderate and are self-limiting; however in some patients they may be severe and/or prolonged. They usually occur within the first few days of discontinuing treatment.

It is therefore advised that FAVERIN should be gradually tapered when discontinuing treatment according to the patient's needs (see section 4.2).

Mania/hypomania

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

Sexual dysfunction

Selective serotonin reuptake inhibitors (SSRIs) 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.

4.5 Interaction with other medicines and other forms of interaction

Pharmacodynamic interactions

The serotonergic effects of fluvoxamine may be enhanced when used in combination with other serotonergic medicines (including triptans, tramadol, SSRIs and St. John's Wort preparations), see section 4.4.

1.3.1.1 PROFESSIONAL INFORMATION

FAVERIN has been used in combination with lithium in the treatment of severely ill, treatment-resistant patients. However, lithium (and possibly also tryptophan) enhances the serotonergic effects of fluvoxamine. The combination should be used with caution in patients with severe, treatment-resistant depression.

In patients on oral anticoagulants and FAVERIN, the risk for haemorrhage may increase and these patients should therefore be closely monitored.

As with other psychotropic medicines patients should be advised to avoid alcohol use while taking FAVERIN.

Monoamine oxidase inhibitors

FAVERIN should not be used in combination with MAOIs, including linezolid, due to risk of serotonin syndrome (see section 4.3).

Effect of fluvoxamine on the oxidative metabolism of other medicines

FAVERIN can inhibit the metabolism of medicines metabolised by certain cytochrome P450 isoenzymes (CYPs). A strong inhibition of CYP1A2 and CYP2C19 is demonstrated in *in vitro* and *in vivo* studies. CYP2C9, CYP2D6 and CYP3A4 are inhibited to a lesser extent. Medicines which are largely metabolised via these isoenzymes may have higher /lower (e.g. in case of prodrugs like clopidogrel) plasma concentrations of the active substance/metabolite when co-administered with FAVERIN. Concomitant therapy of FAVERIN and these medicines should be initiated at or adjusted to the low vs high end of their dose range. Plasma concentrations, effects or adverse effects of co-administered medicines should be monitored and their dosage should be reduced/increased if necessary. This is particularly relevant for medicines with a narrow

1.3.1.1 PROFESSIONAL INFORMATION

therapeutic index.

Medicines with narrow therapeutic index

Co-administration of FAVERIN and medicines with a narrow therapeutic index (such as tacrine, theophylline, methadone, mexiletine, phenytoin, carbamazepine and ciclosporin) should be carefully monitored when these medicines are metabolised exclusively or by a combination of CYPs inhibited by fluvoxamine.

If necessary, dose adjustment of these medicines is recommended.

Due to the narrow therapeutic index of pimozide and its known ability to prolong QT interval, concomitant us of pimozide and FAVERIN is contraindicated, see section 4.3.

Tricyclic antidepressants and neuroleptics

An increase in previously stable plasma levels of those tricyclic antidepressants (e.g., clomipramine, imipramine, amitriptyline) and neuroleptics (e.g., chlorpromazine, clozapine, olanzapine, quetiapine) which are largely metabolised through cytochrome P450 1A2 when given together with FAVERIN, has been reported. A decrease in the dose of these medicines should be considered if treatment with FAVERIN is initiated.

Benzodiazepines

The plasma levels of oxidatively metabolised benzodiazepines (e.g. triazolam, midazolam, alprazolam, and diazepam) are likely to be increased when co-administered with FAVERIN. The dosage of these benzodiazepines should be reduced during co-administration with FAVERIN.

Cases of increased plasma concentration

As plasma concentrations of ropinirole may be increased in combination with FAVERIN thus

increasing the risk of overdose, surveillance and reduction in the posology of ropinirole during FAVERIN treatment and after its withdrawal may be required.

As plasma concentrations of propranolol are increased in combination with FAVERIN, the propranolol dose may need to be lowered.

When given with FAVERIN, warfarin plasma concentrations were significantly increased and prothrombin times prolonged.

Cases of increased side effects

Isolated cases of cardiac toxicity have been reported when FAVERIN was combined with thioridazine.

Caffeine plasma levels are likely to be increased during co-administration with FAVERIN. Thus, patients who consume high quantities of caffeine-containing beverages should lower their intake when FAVERIN is administered and adverse caffeine effects (like tremor, palpitations, nausea, restlessness, insomnia) are observed.

Terfenadine, astemizole, cisapride, sildenafil: see section 4.4.

Glucuronidation

FAVERIN does not influence plasma concentrations of digoxin.

Renal excretion

FAVERIN does not influence plasma concentrations of atenolol.

4.6 Fertility, pregnancy and lactation

Pregnancy

FAVERIN is contraindicated in pregnancy (see section 4.3).

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Isolated cases of withdrawal symptoms in the newborn child have been described after the use of FAVERIN at the end of pregnancy.

Some newborns experience feeding and/or respiratory difficulties, seizures, temperature instability, hypoglycaemia, tremor, abnormal muscle tone, jitteriness, cyanosis, irritability, lethargy, somnolence, vomiting, difficulty in sleeping and constant crying after third trimester exposure to SSRIs and may require prolonged hospitalisation.

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

Breastfeeding

FAVERIN is excreted in human milk in small quantities. Therefore, FAVERIN should not be used in women who are breastfeeding (see section 4.3).

1.3.1.1 PROFESSIONAL INFORMATION

Fertility

Reproductive toxicity studies in animals have shown that fluvoxamine impairs male and female fertility. The relevance of these findings to humans is unknown.

FAVERIN should not be used in patients attempting to conceive unless the clinical condition of the patient requires treatment with FAVERIN.

4.7 Effects on ability to drive and use machines

FAVERIN up to 150 mg has no or negligible influence on the ability to drive and use machines. It showed no effect on psychomotor skills associated with driving and operating machinery in healthy volunteers. However, somnolence has been reported during treatment with FAVERIN. Therefore, caution is recommended until the individual response to the medicine has been determined.

4.8 Undesirable effects

Nausea with or without vomiting is the most frequently seen symptom associated with FAVERIN treatment. This may diminish within the first two weeks of treatment. In children reports of hostility, suicidal ideations and self-harm may occur. The most common side effects seen during clinical studies with FAVERIN, more than an isolated case is listed below, by system organ class and by frequency.

Frequencies are defined as: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1 000, < 1/100), rare (< 1/1 000).

Metabolism and nutrition disorders:

Common: anorexia

1.3.1.1 PROFESSIONAL INFORMATION

Psychiatric disorders:

Rare: mania

Nervous system disorders:

Common: agitation, anxiety, dizziness, headache, insomnia, nervousness, somnolence, tremor

Uncommon: ataxia, confusion, extrapyramidal symptoms, hallucinations

Rare: convulsions

Cardiac disorders:

Common: palpitations/tachycardia

Vascular disorders:

Uncommon: (Orthostatic) hypotension

Gastrointestinal disorders:

Common: abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, nausea, vomiting

Hepatobiliary disorders:

Rare: abnormal hepatic function

Skin and subcutaneous tissue disorders:

Common: sweating

Uncommon: cutaneous hypersensitivity reactions (including rash, pruritus, angioedema)

Rare: photosensitivity

1.3.1.1 PROFESSIONAL INFORMATION

Musculoskeletal and connective tissue disorders:

Uncommon: arthralgia, myalgia

Reproductive system and breast disorders:

Uncommon: abnormal (delayed) ejaculation

Rare: galactorrhoea

General disorders and administration site conditions:

Common: asthenia, malaise

Post-marketing experience

Endocrine disorders: hyperprolactinemia, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders: hyponatraemia, increased weight, decreased weight.

Psychiatric disorders: suicidal ideation (see section 4.4).

Nervous system disorders: serotonin syndrome, neuroleptic malignant syndrome-like events, paraesthesia, dysgeusia, and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported (see also section 4.4). Psychomotor restlessness/akathisia (see section 4.4).

Eye disorders: Glaucoma, mydriasis.

Renal and urinary disorders: micturition disorder (including urinary retention, urinary incontinence, pollakiuria, nocturia and enuresis).

1.3.1.1 PROFESSIONAL INFORMATION

Vascular disorders: Haemorrhage (e.g. gastrointestinal haemorrhage, gynaecological, haemorrhage, ecchymosis, purpura).

Musculoskeletal, connective tissue and bone disorders: **Bone fractures.

**Class effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.

Reproductive system and breast disorders: Anorgasmia, menstrual disorders such as amenorrhea, hypomenorrhea, metrorrhagia, menorrhagia), ***postpartum haemorrhage.

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

General disorders and administration site reactions: medicine withdrawal syndrome including neonatal medicine withdrawal syndrome (see section 4.6).

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. Health care 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.

4.9 Overdose

Symptoms

1.3.1.1 PROFESSIONAL INFORMATION

Symptoms include gastro-intestinal complaints (nausea, vomiting and diarrhoea), somnolence and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions and coma have also been reported.

Treatment

There is no specific antidote to FAVERIN.

In cases of overdosage the stomach should be emptied as soon as possible after tablet ingestion and symptomatic and supportive treatment should be given. The repeated use of medical charcoal, if necessary accompanied by an osmotic laxative is also recommended. Forced diuresis or dialysis are unlikely to be of benefit.

The highest documented dose of FAVERIN ingested by a patient is 12 g. This patient recovered completely.

Deaths have been reported where FAVERIN had apparently been taken alone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.1.2 Psychoanaleptics (antidepressants).

Pharmacotherapeutic group: Antidepressants, Selective serotonin reuptake inhibitors.

ATC code: N06AB08

Mechanism of action

Fluvoxamine is a psychotropic substance. Its mechanism of action is thought to be related to its specific serotonin reuptake inhibition in brain neurones, whilst there is minimum interference with noradrenergic processes.

1.3.1.1 PROFESSIONAL INFORMATION

5.2 Pharmacokinetic properties

Absorption

Fluvoxamine is completely absorbed following oral administration. Maximum plasma concentrations occur within 3 – 8 hours of dosing. The mean absolute bioavailability is 53 % due to first-pass metabolism.

The pharmacokinetics of fluvoxamine is not influenced by concomitant food intake.

Distribution

In vitro plasma protein binding of fluvoxamine is 80 %. Volume of distribution in humans is 25 L/kg.

Biotransformation

Fluvoxamine undergoes extensive metabolism in the liver. Although CYP2D6 is *in vitro* the main isoenzyme involved in fluvoxamine's metabolism, plasma concentrations in poor metabolisers for CYP2D6 are not much higher than those in extensive metabolisers.

The mean plasma half-life is approximately 13 – 15 hours after a single dose and slightly longer (17 – 22 hours) during repeated dosing, when steady-state plasma levels are usually achieved within 10 – 14 days.

Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, into at least nine metabolites, which are excreted by the kidneys. The two major metabolites showed negligible pharmacological activity. The other metabolites are not expected to be pharmacologically active. Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19. A moderate inhibition was found for CYP2C9, CYP2D6 and CYP3A4.

1.3.1.1 PROFESSIONAL INFORMATION

Fluvoxamine displays linear single-dose pharmacokinetics. Steady-state concentrations are higher than calculated from single-dose data, and this disproportional increase is more pronounced with higher daily doses.

Special patient groups

The pharmacokinetics of fluvoxamine is similar in healthy adults, elderly patients, and patients with renal insufficiency. The metabolism of fluvoxamine is impaired in patients with liver disease.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Colloidal anhydrous silica

Maize starch

Mannitol

Pregelatinised starch

Sodium stearyl fumarate

Film-coating (Opadry White):

Hypromellose

Macrogol 6000

Talc

Titanium dioxide E171

6.2 Incompatibilities

Not applicable.

1.3.1.1 PROFESSIONAL INFORMATION

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 °C in original packs, protect from direct sunlight.

6.5 Nature and contents of container

Clear PVC/PVdC/aluminium blisters strips in an outer carton.

Available in packs of 30 tablets.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Abbott Laboratories S.A. (Pty) Ltd

Abbott Place, 219 Golf Club Terrace

Constantia Kloof 1709

South Africa

8. REGISTRATION NUMBER

33/1.2/0354

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 January 2001

1.3.1.1 PROFESSIONAL INFORMATION

10. DATE OF REVISION OF THE TEXT

13 February 2022

NAME AND ADDRESS OF MANUFACTURER

Mylan Laboratories S.A.S.

Route de Belleville

Lieu dit Maillard

01400 Châtillon sur Chalaronne

France

NAMIBIA:

NS3 FAVERIN

Reg. No.: 04/1.2/1111