WARNING–SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of fluoxetine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Fluoxetine is approved for use in pediatric patients with MDD and Obsessive Compulsive Disorder (OCD).

1. NAME OF THE MEDICINAL PRODUCT

Salipax™ 20 mg, Capsules

2. QUALITATIVE AND QUANTATIVE COMPOSITION

Active substance: Fluoxetine (as fluoxetine hydrochloride).

Excipients with known effect:

Each capsule contains 146,60 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

1 capsule contains: 20 mg fluoxetine (as fluoxetine hydrochloride).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

- Major depressive episodes
- Obsessive-compulsive disorder

- Bulimia nervosa: Salipax is used alongside psychotherapy for the reduction of binge-eating and purging

Children and adolescents aged 8 years and above:

- Moderate to severe major depressive disorder, if the depression does not respond to psychological therapy after 4-6 sessions. Prozac should be offered to a child or young person with moderate to severe major depressive disorder **only** in combination with psychological therapy.

4.2 Posology and Method of Administration

Adults

Depression

The recommended daily dose is 20 mg of fluoxetine.

Although fluoxetine was administered in doses up to 80 mg/day in clinical trials, the clinical effect of 20 mg/day is comparable to that of the higher dose. The dose can be increased stepwise (20 mg) after several weeks, if required in particular cases. The maximum dose is 80 mg of fluoxetine per day.

If the daily dose exceeds 20 mg, it should be divided over the day (e.g. in the morning and in the evening).

In special cases (see below), for dose reduction the administration frequency may be reduced, e.g. 20 mg every other day.

Bulimia nervosa

The recommended dose is 60 mg per day.

Obsessive-compulsive disorder

Adults and the elderly: The recommended dose is 20mg daily. Although there may be an increased potential for undesirable effects at higher doses, in some patients, if after two weeks there is insufficient response to 20mg, the dose may be increased gradually up to a maximum of 60mg.

If no improvement is observed within 10 weeks, treatment with fluoxetine should be reconsidered. If a good therapeutic response has been obtained, treatment can be continued at a dosage adjusted on an individual basis. While there are no systematic studies to answer the question of how long to continue fluoxetine treatment, OCD 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. Some

clinicians advocate concomitant behavioural psychotherapy for patients who have done well on pharmacotherapy.

Long-term efficacy (more than 24 weeks) has not been demonstrated in OCD.

Method of administration

Fluoxetine may be taken independently of meals.

Dosage/Use

Paediatric population - Children and adolescents aged 8 years and above (Moderate to severe major depressive episode)

Treatment should be initiated and monitored under specialist supervision. The starting dose is 10mg/day given as 2.5ml of fluoxetine oral solution. Dose adjustments should be made carefully, on an individual basis, to maintain the patient at the lowest effective dose. After one to two weeks, the dose may be increased to 20mg/day. Clinical trial experience with daily doses greater than 20mg is minimal. There is only limited data on treatment beyond 9 weeks.

Lower-weight children: Due to higher plasma levels in lower-weight children, the therapeutic effect may be achieved with lower doses.

For pediatric patients who respond to treatment, the need for continued treatment after 6 months should be reviewed. If no clinical benefit is achieved within 9 weeks, treatment should be reconsidered.

In elderly patients and patients with low body weight, a daily dose of 60 mg of fluoxetine should not be exceeded; a lower dose is recommended.

Renal impairment: Repeated administration of fluoxetine leads to accumulation in renal impairment. Adjustment of the dose is generally required.

Hepatic impairment: Because its metabolism is prolonged, the planned dose of fluoxetine must be reduced. This means, e.g., 20 mg every other day.

Concomitant treatments: A lower dose or less frequent administration should be considered in patients who are on several medications.

Withdrawal symptoms on discontinuing treatment with selective serotonin re-uptake inhibitors (SSRIs): Withdrawal symptoms have been reported when SSRI treatment has been discontinued abruptly, although available findings do not indicate that this is due to dependence. Common symptoms include dizziness, sleep disturbance, paraesthesia, headache, anxiety and nausea. The majority of these reactions are mild and self-limiting.

Discontinuation of fluoxetine has been associated with symptoms of this nature. Therefore, when discontinuing treatment with Salipax, the dose should be tapered off gradually to reduce

the risk of withdrawal symptoms (see also “Warnings and precautions: Withdrawal reactions on discontinuing treatment with an SSRI”).

4.3 Contraindications

Hypersensitivity to fluoxetine or any of the excipients of Salipax. Treatment with fluoxetine should not be initiated during states of acute mania.

Monoamine oxidase (MAO) inhibitors (irreversible and reversible): combined use of fluoxetine and MAO inhibitors must be avoided. There have been reports of serious reactions associated with the combined use of fluoxetine and MAO inhibitors or serotonergic antidepressants (such as clomipramine, preparations containing *Hypericum perforatum*). Symptoms of an interaction with an MAO inhibitor include: hyperthermia, muscle rigidity, myoclonus, autonomic nervous system instability with the possibility of rapid fluctuations of pulse and respiration, as well as mental status changes including confusion, irritability and extreme agitation progressing to delirium and coma.

Since fluoxetine and its active metabolite have a long half-life, there should be an interval of at least 5 weeks (about 5 norfluoxetine half-lives) between discontinuation of Salipax and onset of treatment with MAO inhibitors. Administration of MAO inhibitors within 5 weeks of discontinuing Salipax can increase the risk of severe adverse events. There have been reports of death in cases where MAO inhibitors were taken shortly after fluoxetine was discontinued. If fluoxetine is prescribed for a long period and/or at a high dose, a longer interval should be considered.

Treatment with fluoxetine should not be started for at least 2 weeks after discontinuation of an irreversible MAO inhibitor or for one day after discontinuation of a reversible MAO-A inhibitor.

4.4 Special warnings and precautions for use

Paediatric population - Children and adolescents under 18 years of age:

Suicide-related behaviours (suicide attempt and suicidal thoughts) and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Salipax should only be used in children and adolescents aged 8 to 18 years for the treatment of moderate to severe major depressive episodes and it should not be used in other indications. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, only limited evidence is available concerning long-term effect on safety in children

and adolescents, including effects on growth, sexual maturation and cognitive, emotional and behavioural developments Although a causal relationship between fluoxetine and the occurrence of such events has not been demonstrated to date, pooled analyses of study data have shown that suicidal thoughts and/or behaviour in children and young adults (aged < 25 years) were increased with antidepressants compared to placebo. It is important that the prescriber discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

Suicide/suicidal thoughts or clinical worsening: In depression, there is an increased risk of suicidal thoughts, self-injury and suicide (or events related to attempted suicide). The risk persists until complete remission occurs. An increased risk of suicidal behaviour may also be associated with other psychiatric illnesses for which Salipax is used as therapy.

Patients should be monitored closely during pharmacotherapy. Regardless of the patient's age, physicians should encourage their patients to discuss the emergence of depressing thoughts or feelings with the physician at any time.

On the basis of an analysis of controlled studies in which adults with a depressive episode according to the ICD-10 classification (or Major Depressive Disorder MDD, according to the DSM-IV classification) were included, the following risk factors for suicidality with placebo and fluoxetine were established:

Before onset of therapy:

- increasing severity of depression;
- existing suicidal thoughts.

During therapy:

- worsening of depression;
- development of insomnia (sleeplessness).

Serious psychomotor activation (e.g. agitation, akathisia [see below under "Akathisia/psychomotor restlessness"], panic) during therapy with fluoxetine also represented a risk factor.

If symptoms of this kind are observed before the beginning of therapy or occur during therapy, increased clinical observation or a switch of therapy should be considered.

A change in therapeutic regime including a possible withdrawal of medication should be considered in patients whose condition continues to deteriorate or whose emerging symptoms of suicide risk are pronounced, are of sudden onset or were not present among the patient's initial symptoms. Patients and their caregivers must be made aware of the potential risk for

suicide within the context of antidepressant therapy and of the urgent necessity to consult the treating physician in such cases.
Even after discontinuing treatment, patients must be closely monitored as such symptoms may indicate signs of withdrawal or the start of a relapse.
Psychiatric diagnoses other than depression may also be associated with an increased risk of suicidal behaviour.
Psychiatric diagnoses like these may also occur in the context of depression. Therefore, the same precautions with regard to suicide risk must be considered with these conditions as with depression.
To reduce the risk of overdose, the quantity of capsules prescribed should be as small as possible, depending on the individual patient.
Mania/hypomania: Patients should be adequately monitored for the occurrence of manic and hypomanic symptoms until the antidepressant effect sets in (1-3 weeks). Like all antidepressants, fluoxetine must be stopped if a patient enters a manic phase.
In studies with fluoxetine in the USA, hypomanic or manic states occurred in 0.1% of patients with depression and in 0.7% of all patients.
Haemorrhages: The risk of haemorrhaging, including gynaecological haemorrhages and gastrointestinal haemorrhages may be raised in patients taking SSRIs and SNRIs, including fluoxetine (see "Undesirable effects"). Caution is therefore advised with the concomitant use of anticoagulants, medicines known to affect platelet function (e.g. NSAIDs, acetylsalicylic acid, atypical neuroleptics such as clozapine, phenothiazines, most tricyclic antidepressants) with fluoxetine and in patients with a history of bleeding.
There are reports of cutaneous haemorrhages such as ecchymosis and purpura associated with SSRIs. During treatment with fluoxetine there have been uncommon reports of ecchymosis.
Cardiovascular problems: The usual precautions should be taken in patients who have problems with their heart or their blood pressure (see "Undesirable effects").
QT interval prolongation may occur during fluoxetine treatment. Post-marketing cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported. Caution must be exercised when administering fluoxetine to patients with diseases such as long QT syndrome, acquired long QT syndrome, (e.g. in cases of concomitant use of a drug that prolongs the QT interval), and positive familial anamnesis for QT interval prolongation, or in other clinical situations that predispose to arrhythmias (e.g. hypokalaemia or hypomagnesaemia) or in cases of raised levels of fluoxetine exposure (e.g. due to hepatic impairments).

Interactions/serotonin syndrome: For MAO inhibitors see "Contraindications". In rare cases, serotonin syndrome may occur in combination with other serotonergic substances such as triptans, lithium, L-tryptophan and/or neuroleptic medicines. The clinical picture manifests as typical symptoms such as hyperreflexia, tremor, myoclonus, muscle rigidity, mental changes such as restlessness, anxiety, confusion, hallucinations and irritability progressing to delirium and coma, as well as tachycardia, blood pressure fluctuations, hyperthermia, nausea, vomiting and diarrhoea.

Akathisia/psychomotor restlessness: The use of fluoxetine has been associated with the development of akathisia, characterized by a subjectively unpleasant and distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This usually occurs during the first weeks of treatment. In patients who develop such symptoms increasing the dose may be detrimental.

Withdrawal reactions on discontinuing treatment with a serotonin re-uptake inhibitor: Withdrawal reactions occur commonly on discontinuation of treatment, particularly if the treatment is withdrawn abruptly (see "Undesirable effects"). In clinical trials adverse events occurred in 60% of patients after discontinuation of treatment in both the fluoxetine and the placebo group. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were serious. The risk of withdrawal reactions can depend on several factors, including treatment duration, dose and dose reduction rate.

Dizziness, sensory disturbances (including paraesthesias), sleep disorders (including insomnia and vivid dreaming), weakness, agitation or anxiety, nausea and/or vomiting, tremor and headache are the most commonly reported reactions. In general, these symptoms are mild to moderate, but in some patients they may be serious. They usually occur within the first few days of discontinuing treatment. Generally these symptoms regress spontaneously and resolve within 2 weeks. In some people they may persist for longer periods (2-3 months or more). It is therefore recommended that the dose be gradually tapered off over a period of several weeks or months according to the patient's needs when discontinuing treatment with Salipax (see "Posology/Administration: Withdrawal symptoms on discontinuing treatment with an SSRI").

Skin rash: Since the introduction of fluoxetine hydrochloride, systemic complaints occurring in patients with rashes, possibly related to vasculitis, have been observed. Although these complaints are rare, they may be serious because of their effect on the lung, kidney, or liver. Death has been reported to occur in association with these systemic complaints. Anaphylactic events, e.g. with bronchospasm, angioneurotic oedema and urticaria, have been reported.

Upon the appearance of a rash or any other possible allergic reaction for which an alternative aetiology cannot be identified, fluoxetine should be discontinued.

Seizures: Seizures are a possible risk with antidepressants. Therefore, as with other antidepressants, treatment with fluoxetine should be instituted with caution in patients with a history of seizures. If seizures occur in a patient for the first time or if the incidence of seizures increases, treatment must be discontinued. Treatment with fluoxetine should be avoided in patients with unstable seizure disorder/epilepsy. Patients with well-stabilized epilepsy must be monitored carefully.

Hyponatraemia: Cases of hyponatraemia (some with plasma sodium concentrations lower than 110 mmol/l) have been reported. Most of them occurred in elderly patients and patients taking diuretics or otherwise volume-depleted patients (see "Undesirable effects").

Glycaemic control: In patients with diabetes mellitus, hypoglycaemia occurred during the treatment with fluoxetine, and hyperglycaemia developed after discontinuation of the drug. Insulin and oral antidiabetic dosage may require adjustment when treatment with fluoxetine is started or discontinued.

Physical and psychological dependence: As with other CNS-active agents, physicians should carefully evaluate patients for a history of drug dependence and monitor such patients closely, looking for signs of Salipax abuse (e.g. development of tolerance, dose increase, drug-seeking behaviour).

Electroconvulsive therapy: See "Interactions".

St John's wort (Hypericum perforatum): Undesirable effects may occur with the simultaneous administration of serotonin re-uptake inhibitors and plant-based preparations containing *St John's wort*. An increase in serotonergic effects such as serotonin syndrome may occur in particular.

Mydriasis: There have been reports of mydriasis associated with fluoxetine therapy. Therefore caution is advised when prescribing fluoxetine in patients with increased intraocular pressure or patients at risk for acute closed-angle glaucoma.

Because of the long elimination half-lives of the parent drug and its metabolites, changes in dose will not be fully reflected in the plasma within the first weeks, affecting both strategies for titration to final dose and withdrawal from treatment, where applicable (see "Pharmacokinetics"). The same considerations apply to the possible occurrence of interactions.

Caution with respect to the dose is advised in the case of concomitant therapy of fluoxetine with CNS-active agents since they may reciprocally intensify their effects (see "Interactions").

Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug highly bound to plasma protein (e.g. oral anticoagulants, digitoxin) may cause a shift in plasma concentrations, in turn potentially resulting in adverse reactions (see "Interactions").

4.5 Interactions with other medicinal products and other forms of interaction

Co-administration of fluoxetine with other serotonergic active substances (MAO inhibitors, triptans, L-tryptophan, lithium, tricyclic antidepressants, preparations containing St John's wort, etc.) may result in serotonin syndrome (see "Contraindications" and "Warnings and precautions").

Drugs that are metabolized by the cytochrome P450 2D6 isoenzyme: As fluoxetine has the potential to inhibit the cytochrome P450 2D6 isoenzyme, a medication taken concomitantly with or within 5 weeks after fluoxetine therapy, and which is metabolized predominantly by the P450 2D6 enzyme (e.g. imipramine, desipramine, risperidone, venlafaxine, haloperidol, clozapine, flecainide, propafenone), in particular any with a narrow therapeutic index, should be introduced gradually, or, alternatively, a lower dose should be selected.

Drugs that are metabolized by CYP3A4 or CYP2C: Changes in the blood concentrations of alprazolam, carbamazepine, diazepam or phenytoin, and in some cases symptoms of toxicity, have been observed. A more careful titration of the co-prescribed product and monitoring of clinical status should be considered.

Protein binding: Since fluoxetine is highly bound to plasma protein, the concomitant use of fluoxetine with another drug that is highly bound to proteins may change the plasma concentration of both of these drugs.

There have been some reports of interactions with digoxin. Therefore, if fluoxetine is administered concomitantly with digoxin, it is recommended that the digoxin levels be monitored.

Warfarin and other oral anticoagulants: Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms) without a clear clinical picture but with increased bleeding have been reported rarely when fluoxetine is co-administered with warfarin. Patients receiving a concomitant coumarin preparation should receive careful coagulation monitoring when treatment with fluoxetine is initiated or stopped.

Electroconvulsive therapy (ECT): There have been reports of prolonged epileptic seizures in patients on fluoxetine undergoing ECT treatment. Caution should therefore be exercised.
Elimination half-life: The long elimination half-lives of fluoxetine and its main metabolite, norfluoxetine, may have potential effects after fluoxetine is discontinued if medications are prescribed that interact with one of the substances.
Tryptophan
Fluoxetine should not be administered concomitantly with L-tryptophan. See "Warnings and precautions" regarding the risk of serotonin syndrome. Therefore, simultaneous administration is not recommended.
Centrally depressant pharmaceutics
The effect of centrally depressant medicines may be enhanced by Salipax. Furthermore, combination with Salipax may result in increased plasma levels of other antidepressants.
Lithium
Fluoxetine may increase the lithium levels, which should therefore be monitored frequently when these two agents are administered together. See "Warnings and precautions**"** regarding the risk of serotonin syndrome.
Alcohol
Although specific studies have not shown any increase in the effect of alcohol due to fluoxetine, alcohol should be avoided during the treatment.
Other substances frequently taken concomitantly
Interactions have not been observed so far with simultaneous administration of alcohol, barbiturates, other tranquillizers and hypnotics and thiazide diuretics, blood pressure and pain drugs, thyroid hormones, antihistamines, antibiotics, cimetidine and other antacids.
St John's wort (Hypericum perforatum)
Undesirable effects may occur with the simultaneous administration of serotonin re-uptake inhibitors and plant-based preparations containing St John's wort.

4.6 Fertility, Pregnancy and lactation

Pregnancy
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. 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.

Fluoxetine should not be used during pregnancy unless the clinical condition of the woman requires treatment with fluoxetine and justifies the potential risk to the foetus. Abrupt discontinuation of therapy should be avoided during pregnancy. If fluoxetine is used during pregnancy, caution should be exercised, especially during late pregnancy or just prior to the onset of labour since some other effects have been reported in neonates: irritability, tremor, hypotonia, persistent crying, difficulty in sucking or in sleeping. These symptoms may indicate either serotonergic effects or a withdrawal syndrome. The time to occur and the duration of these symptoms may be related to the long half-life of fluoxetine (4-6 days) and its active metabolite, norfluoxetine (4-16 days).

Breast-feeding

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 fluoxetine is considered necessary, discontinuation of breastfeeding should be considered; however, if breastfeeding is continued, the lowest effective dose of fluoxetine 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

As drowsiness and dizziness have been reported with fluoxetine, caution should be exercised when driving and using machines until the individual response to the product is apparent. Concomitant intake of alcohol and other medicines (see “Interactions”) causes additional impairment of responsiveness and psychomotor activity. Patients should be made aware of this risk accordingly.

4.8 Undesirable effects

The most commonly reported adverse reactions in patients treated with fluoxetine were headache, nausea, insomnia, fatigue and diarrhoea.

The list below includes the adverse reactions observed in clinical trials (n = 9297) and from spontaneous reporting. Some of these adverse reactions are consistent with those of other SSRIs.

Frequency estimate:

Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, pancytopenia.

Immune system disorders

Rare: anaphylactic reactions, serum sickness.

Metabolism and nutrition disorders

Common: decreased appetite (including anorexia), weight loss.

Rare: hyponatraemia.

Reversible inadequate ADH secretion with hyponatraemia and cerebral oedema have been reported (mostly in elderly patients and with diuretic treatment).

Hypoglycaemia has been reported (see "Warnings and precautions")

Hypokalaemia has been reported.

Psychiatric disorders

Very common: insomnia (15.0%).

Common: anxiety, nervousness, restlessness, tension, decreased libido (including loss of libido), sleep disturbances, abnormal dreams (including nightmares).

Uncommon: depersonalization, elevated mood, euphoric mood, abnormal thinking, abnormal orgasm (including anorgasmia), teeth grinding.

Rare: manic/hypomanic reaction, hallucinations, agitation.

Confusion has been reported.

Nervous system disorders

Very common: headache (19.9%).

Common: attention deficit disorder, dizziness, dysgeusia, lethargy, somnolence (including hypersomnia and sedation), tremor.

Uncommon: psychomotor hyperactivity, dyskinesia, ataxia, balance disorders, myoclonus, syncopes.

Rare: seizures, akathisia, buccoglossal syndrome, coma.

Very rare: memory impairment.

Serotonin syndrome has been reported.

Eye disorders

Common: impaired vision.

Uncommon: mydriasis.

Cardiac disorders

Common: palpitations. QT interval prolongation in the ECG (QTcF ≥450 msec based on ECG measurements from clinical studies)

Uncommon: angina pectoris, myocardial infarct, tachycardia (see "Overdose").

Rare: cardiac conduction or impulse generation disorders.

In clinical studies, there have been rare reported cases of ventricular arrhythmia, including torsade de pointes.

Vascular disorders

Common: flushing.

Uncommon: hypotension.

Rare: vasculitis, vasodilatation, thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Common: yawning.

Uncommon: dyspnoea.

Rare: pharyngitis.

Nose bleed has been reported.

Gastrointestinal disorders

Very common: diarrhoea (11.0%), nausea (18.5%).

Common: vomiting, dyspepsia, dry mouth.

Uncommon: dysphagia.

Rare: oesophageal pain.

Very rare: pancreatitis.

Gastrointestinal bleeding, including bleeding of oesophageal varices, bleeding of gums and mouth, bloody vomit, blood in stools, haematomas (intra-abdominal, peritoneal), bleeding (anal, oesophageal, gastric, gastrointestinal (upper and lower gastrointestinal tract), haemorrhoidal, peritoneal, rectal), haemorrhagic diarrhoea and enterocolitis, haemorrhagic diverticulitis, haemorrhagic gastritis, tarry stools and haemorrhagic ulcers (oesophageal, gastric, duodenal) has been reported.

Hepatobiliary disorders

Common: abnormal hepatic function tests.

Very rare: hepatitis.

Skin and subcutaneous tissue disorders

Common: rash, urticaria, pruritus, hyperhidrosis.

Uncommon: alopecia, increased bruising tendency, cold sweats. Exanthema – in very rare cases possibly accompanied by systemic symptoms such as joint pain, adenopathy and fever.

Rare: angioedema, ecchymosis, photosensitivity reactions.

Erythema multiforme has been reported, which can lead to Stevens-Johnson syndrome or toxic epidermal necrolysis (Lyell's syndrome).

Musculoskeletal and connective tissue disorders

Uncommon: Muscle twitching.

Renal and urinary disorders

Common: frequent urination (including pollakiuria).

Uncommon: dysuria.

Rare: urinary retention.

Disorders affecting emptying of the urinary bladder have been reported.

Reproductive system and breast disorders

Common: gynaecological bleeding, erectile dysfunction, ejaculation disorders.

Uncommon: sexual dysfunctions (sometimes persisting after discontinuation of therapy).

Rare: hyperprolactinaemia (amenorrhoea, breast enlargement, etc.), galactorrhoea

Priapism has been reported.

General disorders and administration site conditions

Very common: fatigue (12.8%) (including asthenia).

Common: nervousness, chills.

Uncommon: malaise, feeling abnormal, feeling hot, feeling cold.

<u>Paediatric population</u>

Adverse reactions that have been observed specifically or with a different frequency in this population are described below. Frequencies for these events are based on paediatric clinical trial exposures (n = 610).

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

Isolated cases of growth retardation have been reported from clinical use (See also section 5.1).

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

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

Systemic symptoms probably caused by vasculitis have been observed very rarely in patients with skin rashes; deaths have been reported in association with these events.
It is not known whether these systemic adverse events and the skin rashes have a common cause or are of different pathogeneses. Immunological connections have not been established to date.

To report any side effects:

- ***Saudi Arabia:***

The National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340.
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

- ***Other GCC States:***

-Please contact the relevant competent authority.

4.9 Overdose

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose: nausea; vomiting; epileptic seizures; cardiac dysfunctions, which can range from asymptomatic arrhythmia (including AV junctional rhythm and ventricular arrhythmias) or ECG changes suggesting a QTc interval prolongation to cardiac arrest (including very rare cases of torsades de pointes), pulmonary function disorders, and signs of central nervous system changes, which can range from excitation to coma. Fatal outcomes associated with fluoxetine overdose alone have been extremely rare.

Treatment

Monitoring of cardiac findings and vital parameters is recommended, together with general symptomatic and supportive measures. No specific antidote is known. Forced diuresis,

dialysis, haemoperfusion and exchange transfusion will be of little use owing to the large distribution volume of fluoxetine. When treating an overdose, the possibility that several drugs have been taken should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N06AB03

Fluoxetine is an antidepressant for oral use which is not chemically related to tri- or tetracyclic or other antidepressants. Based on animal studies it is presumed that fluoxetine, unlike tricyclic antidepressants, has no direct effect on noradrenergic or on dopaminergic neurons.

The clinical effect is probably based on the inhibition of serotonin re-uptake into the presynaptic neurons. In subjects who received 30 mg of fluoxetine per day for a week, serotonin uptake into platelets decreased by more than 60%.

5.2 Pharmacokinetic properties

Absorption

Fluoxetine is readily absorbed (at least 85%) after oral administration.

Peak plasma levels occur 6 hours after oral administration. After a single oral dose of 40 mg, peak plasma levels in the range of 15 to 55 ng/ml have been reported after 6-8 hours. After 30 days of administration of 40 mg/day of fluoxetine, plasma concentrations of fluoxetine in a range from 91-302 ng/ml and of norfluoxetine in a range from 72-258 ng/ml have been reported. Simultaneous administration with food slightly delays absorption but does not change total absorption.

Metabolism

About 3 to 10% of the healthy population has reduced activity of the cytochrome-450 isoenzyme P450 2D6 due to a genetic defect. Such individuals are referred to as “poor metabolizers” of substances such as debrisoquin, dextromethorphan, and tricyclic antidepressants. Many substances, including most of the antidepressants such as fluoxetine and other SSRIs, are metabolized by this isoenzyme; therefore, the pharmacological properties and the relative proportions of the metabolites are changed in “poor metabolizers”. However, in the case of fluoxetine and its metabolites, the total plasma concentration of the 4 active enantiomers in “poor metabolizers” is comparable to that in “fast metabolizers”.

Distribution

The volume of distribution of fluoxetine and the desmethyl metabolite of fluoxetine (norfluoxetine) is 20 to 45 l/kg of body weight. The plasma protein binding level is about 94.5%.

Elimination

Fluoxetine is metabolized extensively, so that only small amounts of the unchanged original active substance are excreted into the urine. In investigations with radiolabelled substance, 60% of the radioactivity was recovered in the urine and 16% in the faeces after 5 weeks. A known metabolite is desmethyl-fluoxetine (norfluoxetine), which likewise inhibits serotonin uptake selectively.

In healthy subjects, the half-life of fluoxetine is 4-6 days, and the half-life of its desmethyl metabolite (norfluoxetine) is 4-16 days.

Plasma clearance of fluoxetine and desmethyl-fluoxetine is about 20 l/h and 9 l/h, respectively.

Optimal plasma concentration range

Steady-state plasma concentrations are reached after 2-3 weeks. Effective or detectable plasma levels are maintained for 5 half-lives after the discontinuation of the medicinal product.

The achieved steady-state concentrations are proportional to the dose but vary considerably from patient to patient.

Kinetics in special patient groups

For a single dose, the pharmacokinetic profiles of *elderly* subjects did not differ significantly from those of young subjects.

Repeated administration of fluoxetine in patients with *renal impairment* leads to an accumulation and generally necessitates a dose adjustment.

The elimination of fluoxetine is reduced considerably in patients with advanced *liver cirrhosis*. The half-life of fluoxetine is prolonged on average to 7.6 days (usually 4-6 days) and that of norfluoxetine to 12 days (usually 4-16 days). In all three of these situations, it is recommended that the dose be adjusted (see “Posology/Administration”).

So far there are no data available on humans on the distribution of fluoxetine in the cerebrospinal fluid (CSF) or on fluoxetine crossing the placenta.

5.3 Preclinical safety data

In vitro and animal studies reveal no evidence of carcinogenicity or mutagenicity.

Fertility

No impairment of fertility has been observed in adult animals at doses of up to 12.5 mg/kg/day (about 1.5 times the maximum recommended dose in mg/m^2 in humans). In a juvenile toxicology study in CD rats, administration of 30 mg/kg/day of fluoxetine hydrochloride on postnatal days 21 to 90 resulted in irreversible testicular degeneration and necrosis, epididymal epithelial vacuolation, immaturity and inactivity of the female reproductive tract and decreased fertility. Delays in sexual maturation occurred in males (10 and 30 mg/kg/day) and females (30 mg/kg/day). The significance of these findings in humans is unknown. Rats administered 30 mg/kg also had decreased femur lengths compared with controls and skeletal muscle degeneration, necrosis and regeneration. At 10 mg/kg/day, plasma levels achieved in animals were approximately 0.8 to 8.8 fold (fluoxetine) and 3.6 to 23.2 fold (norfluoxetine) those usually observed in paediatric patients. At 3 mg/kg/day, plasma levels achieved in animals were approximately 0.04 to 0.5 fold (fluoxetine) and 0.3 to 2.1 fold (norfluoxetine) those usually achieved in paediatric patients.

Reprotoxicology

Embryofoetal development studies in rats and rabbits after administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times the maximum recommended human dose [MRHD] of 80 mg on an mg/m^2 basis) throughout organogenesis revealed no evidence of teratogenicity. In reproduction studies in rats, however, there was an increase in the number of stillborn offspring, a decrease in pup weight and an increase in pup mortality during the first 7 days postpartum when the dams received 12 mg/kg/day (1.5 times the MRHD on an mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on an mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offsprings of rats treated with 12 mg/kg/day during gestation. The no-effect dose for postpartum rat mortality was 5 mg/kg/day (0.6 times the MRHD on an mg/m^2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Silica colloidal anhydrous.

Capsule: Gelatin, Titanium dioxide (E 171, CI 77891), Iron oxide yellow (E 172, CI 77492), Indigo carmine (E 132, CI 73015), Quinoline yellow (E 104, CI 47005)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

The medicinal product may only be used up to the date marked with “EXP” on the package.

6.4 Special precautions for storage

Keep this medicine out of the sight & reach of children.
Do not store above 30°C.

6.5 Nature and contents of container

The capsules are sealed into PVC/PE/PVDC-Aluminium blisters (foils) and the blister strips are embossed with the batch number and packed together with the package leaflet into coded cardboard boxes.

Capsules with 20 mg: 14, 30 and 100 (B).

Not all presentations may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORISATION HOLDER

Acino Pharma AG, Liesberg, Switzerland

8. MARKETING AUTHORISATION NUMBER

11-222-01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorization in Saudi Arabia

2001

10. DATE OF REVISION OF THE TEXT

June 2018.