

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluoxetine 20mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluoxetine 20mg as Fluoxetine Hydrochloride

3 PHARMACEUTICAL FORM

Hard capsule.

Size 3. Capsule cap is light green opaque. Capsule body is standard yellow opaque. Markings are "CX59".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Depression: Fluoxetine is indicated for the treatment of the symptoms of depressive illness, with or without associated anxiety symptoms, especially where sedation is not required.

Obsessive-compulsive disorder.

Bulimia nervosa: Fluoxetine is indicated for the reduction of binge-eating and purging activity.

Pre-menstrual Dysphoric Disorder (PMDD)

Diagnosis of PMDD: The essential diagnostic features of PMDD are clear and established cyclicality (occurring during the last week of the luteal phase in most menstrual cycles) of symptoms such as depressed mood, anxiety, affective lability, accompanied by impairment in social and/or occupational function and physical symptoms (such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of bloating, weight gain) – all of which must be severe. This syndrome should be distinguished from the commoner ‘pre-menstrual tension (distinguished from PMDD by milder symptoms and less impact on normal activities)’ and from any co-existing psychiatric disorder.

4.2. Posology and method of administration

For oral administration to adults only.

Depression with or without associated anxiety symptoms - adults and the elderly:

A dose of 20 mg/day is recommended.

Obsessive-compulsive disorder:

20 mg/day to 60 mg/day, A dose of 20 mg/day is recommended as the initial dose. Although there may be an increased potential of side-effects at higher doses, a dose increase may be considered after several weeks if there is no response.

Bulimia nervosa - adults and the elderly:

A dose of 60 mg/day is recommended.

Pre-menstrual Dysphoric Disorder (PMDD):

20 mg/day is recommended. Initial treatment should be limited to 6 months after which patients should be reassessed regarding the benefit of continued therapy.

The recommended doses may be increased or decreased.

Doses greater than 80 mg/day have not been systematically evaluated

Fluoxetine may be administered with or without food.

When dosing is stopped, active drug substances will persist in the body for weeks. This should be borne in mind when starting or stopping treatment. Dosage tapering is unnecessary in most patients.

Children:

The use of Fluoxetine in children is not recommended, as safety and efficacy have not been established.

Patients with renal and/or hepatic dysfunction:

Fluoxetine should not be administered to patients with severe renal failure (GFR <10 mL/min). A lower dose, e.g. alternate day dosing, is recommended in patients with significant hepatic dysfunction or mild to moderate renal failure (GFR 10-50 mL/min).

Withdrawal symptoms seen on discontinuation of fluoxetine:

Abrupt discontinuation should be avoided. When stopping treatment with fluoxetine 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 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

4.3. Contraindications

Hypersensitivity to Fluoxetine or the ingredients of the preparation.

Monoamine oxidase inhibitors:

Cases of serious and sometimes fatal reactions have been reported in patients receiving an SSRI in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued an SSRI and have been started on a MAOI. Treatment of fluoxetine should only be started 2 weeks after discontinuation of an irreversible MAOI and the following day after discontinuation of a reversible MAOI-A.

Some cases presented with features resembling serotonin syndrome (which may resemble, and be diagnosed as, neuroleptic malignant syndrome).

Cyproheptadine or dantrolene may benefit patients experiencing such reactions. Symptoms of drug 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 a non-selective MAOI. Similarly, at least 5 weeks should elapse after discontinuing fluoxetine treatment before starting a MAOI. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered

The combination of fluoxetine with a reversible MAOI (e.g., moclobemide, linezolid, methylthioninium chloride (also called methylene blue; a reversible non-selective MAOI indicated for the treatment of medicinal or chemical product induced methaemoglobinemia)) is not recommended. Treatment with fluoxetine can be initiated the following day after discontinuation of a reversible MAOI.

In exceptional circumstances, linezolid (an antibiotic which is a reversible non-selective MAOI) can be given in combination with fluoxetine provided that there are facilities for close observation of symptoms of serotonin syndrome and monitoring of blood pressure.

Renal failure

Fluoxetine should not be administered to patients with severe renal failure (GFR <10 mL/min) because accumulation may occur in these patients during chronic treatment.

Usage in nursing mothers:

Fluoxetine should not be prescribed to nursing mothers

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 Fluoxetine 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.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Close supervision of patients and in particular those at high risk should accompany drug 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.

Akathisia/Psychomotor restlessness

The use of fluoxetine 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.

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. Fluoxetine 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 (see section 5.3).

In a 19-week clinical trial, decreased height and weight gain was observed in children and adolescents treated with fluoxetine (see section 5.1). It has not been established whether there is an effect on achieving normal adult height. The possibility of a delay in puberty cannot be ruled out (see sections 5.3 and 4.8). Growth and pubertal development (height, weight, and TANNER staging)

should therefore be monitored during and after treatment with fluoxetine. If either is slowed, referral to a paediatrician should be considered.

In paediatric trials, mania and hypomania were commonly reported (see section 4.8). Therefore, regular monitoring for the occurrence of mania/hypomania is recommended. Fluoxetine should be discontinued in any patient entering a manic phase.

It is important that the prescriber discusses carefully the risks and benefits of treatment with the child/young person and/or their parents.

Withdrawal symptoms seen on discontinuation of SSRI treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials, adverse events seen on treatment discontinuation occurred in approximately 60% of patients in both the fluoxetine and placebo groups. Of these adverse events, 17% in the fluoxetine group and 12% in the placebo group were severe in nature.

The risk of withdrawal symptoms may be dependent on several factors, including the duration and dose of therapy 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 commonly 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 the dose of fluoxetine should be gradually tapered when discontinuing treatment over a period of at least one to two weeks according to the patient's needs (see *Withdrawal symptoms seen on discontinuation of fluoxetine* section 4.2).

Rash and allergic reactions:

Angioneurotic oedema, urticaria and other allergic reactions have been reported including progressive systemic events, sometimes serious (involving skin, kidney, liver or lung). Upon the appearance of rash or of other allergic phenomena for which an alternative aetiology cannot be identified, Fluoxetine should be discontinued.

Seizures

Seizures are a potential risk with antidepressant drugs. Fluoxetine should be discontinued in any patient who develops seizures. Fluoxetine should be avoided in patients with unstable epilepsy; patients with controlled epilepsy should be carefully monitored.

Electroconvulsive therapy (ECT)

There have been rare reports of prolonged seizures in patients on Fluoxetine receiving ECT treatment.

Mania

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

Hepatic/Renal dysfunction

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

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

Cardiovascular Effects

Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported during the post-marketing period (see sections 4.5, 4.8 and 4.9).

Fluoxetine 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 arrhythmias (e.g., hypokalemia and hypomagnesemia, bradycardia, acute myocardial infarction or uncompensated heart failure) or increased exposure to fluoxetine (e.g., hepatic impairment). If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started. If signs of cardiac arrhythmia occur during treatment with fluoxetine, the treatment should be withdrawn and an ECG should be performed.

Weight loss

Fluoxetine may cause weight loss which may be undesirable in underweight depressed patients. Weight loss is usually proportional to baseline body weight.

Diabetes

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

Haemorrhage

There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRIs. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other haemorrhagic manifestations (e.g. gynaecological haemorrhage, gastrointestinal haemorrhage and other cutaneous or mucous bleeding) have been reported

rarely. Caution is advised in patients taking SSRIs, particularly in combination with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most tricyclic antidepressants, aspirin, NSAIDs), or other drugs that may increase the risk of bleeding, as well as in patients with a history of bleeding disorders.

St John's Wort

An increase in serotonergic effects, such as serotonin syndrome may occur when SSRIs and herbal preparations containing St John's Wort (*Hypericum perforatum*) are used together.

Serotonin syndrome or neuroleptic malignant syndrome-like events

On rare occasions, development of a serotonin syndrome or neuroleptic malignant syndrome-like events have been reported in association with fluoxetine treatment, particularly when given in combination with other serotonergic or neuroleptic drugs (see section 4.5). These syndromes are characterised by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuation of vital signs and mental status changes including confusion, irritability, extreme agitation, progressing to delirium and coma. As these syndromes may result in potentially life-threatening conditions, treatment with fluoxetine should be discontinued if such events occur and supportive symptomatic treatment should be initiated.

Mydriasis:

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

4.5 Interactions with other Medicinal products and other forms of Interaction

Monoamine oxidase inhibitors (See Section 4.3).

Not recommended combinations: MAOI-A inhibitors or non-selective MAOIs (including reversible MAOIs) (see section 4.3).

Combinations requiring precautions for use: MAOI-B inhibitors (e.g. selegiline, rasagiline). Risk of serotonin syndrome. Clinical monitoring is recommended.

Serotonergic drugs

Co-administration with serotonergic drugs (e.g. tramadol, triptans) may increase the risk of serotonin syndrome. Use with triptans carries the additional risk of coronary vasoconstriction and hypertension.

Lithium

Caution is advised if the concomitant administration of Fluoxetine and lithium, is required. There have been reports of both increased and

decreased lithium levels when used concomitantly with Fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored. There have been reports of serotonin syndrome with concurrent use of SSRIs and lithium.

Tryptophan

There have been reports of increased serotonergic effects when SSRIs have been given with tryptophan and, therefore, the concomitant use of Fluoxetine with tryptophan should be undertaken with caution.

CYP2D6 and CYP3A isoenzymes

Because Fluoxetine's metabolism (like tricyclic anti-depressants and other selective serotonin antidepressants) involves the hepatic cytochrome CYP2D6 isoenzyme systems, concomitant therapy with drugs also metabolised by these enzyme systems may lead to drug interactions.

Concomitant therapy with drugs predominantly metabolised by this isoenzymes, and which have a narrow therapeutic index (such as flecainide, encainide, vinblastine, carbamazepine and tricyclic antidepressants), should be initiated at or adjusted to the low end of their dose range- This will also apply if Fluoxetine has been taken in the previous 5 weeks.

Pharmacokinetic interactions 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 endotoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI anti-depressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should wherever possible be avoided (see section 4.4)

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 drug and to monitoring clinical status.

Fluoxetine may reduce the convulsive threshold and antagonise the anticonvulsant effects of antiepileptic medications (see section 4.4).

Carbamazepine – see above.

Oral anticoagulants

Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with oral anticoagulants. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped (see section 4.4 Haemorrhage).

Alcohol

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

St John's Wort

Dynamic interactions between Fluoxetine and the herbal remedy, St. John's wort (*Hypericum perforatum*) can occur, resulting in an increase in undesirable effects.

Half-lives

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

Electroconvulsive therapy

There have been rare reports of prolonged seizures in patients on fluoxetine receiving electroconvulsive therapy, and therefore caution is advisable.

QT interval prolongation

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

4.6. Fertility, pregnancy and lactation

Pregnancy:

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

Epidemiological data have suggested that the use to SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in 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.

Furthermore, although fluoxetine can be 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).

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.

Breast-feeding

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

4.7. Effects on ability to drive and use machines

Fluoxetine has no or negligible influence on the ability to drive and use machines. Although Fluoxetine has been shown not to affect psychomotor performance in healthy volunteers, any psychoactive drug may impair judgement or skills. Patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

4.8 Undesirable Effects

a. Summary of the safety profile

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

Undesirable effects may decrease in intensity and frequency with continued treatment and do not generally lead to cessation of therapy.

b. Tabulated list of adverse reactions

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

The following frequencies have been calculated from clinical trials in adults (n = 9297) and from spontaneous reporting.

Frequency estimate: Very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$)

Very Common	Common	Uncommon	Rare
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<i>Blood and lymphatic system disorders</i>			
			Thrombocytopenia
<i>Immune system disorders</i>			
			Anaphylactic Reaction Serum sickness
<i>Endocrine disorders</i>			
			Inappropriate antidiuretic hormone secretion,
<i>Metabolism and nutrition disorders</i>			
	Decreased appetite ¹		Hyponatraemia
<i>Psychiatric disorders</i>			
Insomnia ²	Anxiety Nervousness Restlessness Tension Libido decreased ³ Sleep disorder Abnormal dreams ⁴	Depersonalisation Elevated mood Euphoric mood Thinking abnormal Orgasm abnormal ⁵ Bruxism Suicidal thoughts and behavior ⁶	Hypomania Mania Hallucinations Agitation Panic attacks Confusion Dysphemia
<i>Nervous system disorders</i>			
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence ⁷ Tremor	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder Memory impairment Myoclonus	Convulsion Akathisia Buccoglossal syndrome Serotonin syndrome
<i>Eye disorders</i>			
	Vision blurred	Mydriasis	
<i>Ear and labyrinth disorders</i>			
		Tinnitus	

<i>Cardiac disorders</i>			
	Palpitations		Ventricular arrhythmia including torsade de pointes Electrocardiogram QT prolonged
<i>Vascular disorders</i>			
	Flushing ⁸	Hypotension	Vasculitis Vasodilatation

<i>Respiratory, thoracic and mediastinal disorders</i>			
	Yawning	Dyspnoea Epistaxis	Pharyngitis Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis) ⁹
<i>Gastrointestinal disorders</i>			
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia Gastrointestinal haemorrhage ¹⁰	Oesophageal pain
<i>Hepato-biliary disorders</i>			
			idiosyncratic hepatitis
<i>Skin and subcutaneous tissue disorders</i>			
	Rash ¹¹ Urticaria Pruritus Hyperhidrosis	Alopecia Increased tendency to bruise Cold sweat	Angioedema Ecchymosis Photosensitivity reaction Purpura Erythema multiforme ¹²
<i>Musculoskeletal, connective tissue and bone disorders</i>			
	Arthralgia	Muscle twitching	Myalgia
<i>Renal and urinary disorders</i>			
	Frequent Urination ¹³	Dysuria	Urinary retention Micturition disorder

<i>Reproductive system and breast disorders</i>			
	Gynaecological bleeding ¹⁴	Sexual dysfunction	Galactorrhoea
	Erectile dysfunction		Hyperprolactinemia
	Ejaculation disorder ¹⁵		Priapism
<i>General disorders and administration site conditions</i>			
Fatigue ¹⁶	Feeling jittery	Malaise	Mucosal haemorrhage
	Chills	Feeling abnormal	
		Feeling cold	
		Feeling hot	
<i>Investigations</i>			
	Weight decreased	Abnormal liver function tests	

¹ Includes anorexia

² Includes early morning awakening, initial insomnia, middle insomnia

³ Includes loss of libido

⁴ Includes nightmares

⁵ Includes anorgasmia

⁶ Includes completed suicide, depression suicidal, intentional self-injury, self-injurious ideation, suicidal behaviour, suicidal ideation, suicide attempt, morbid thoughts, self-injurious behaviour. These symptoms may be due to underlying disease.

⁷ Includes hypersomnia, sedation

⁸ Includes hot flush

⁹ Includes atelectasis, interstitial lung disease, pneumonitis.

¹⁰ Includes most frequently gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea haemorrhagic, melaena, and gastric ulcer haemorrhage.

¹¹ Includes erythema, exfoliative rash, heat rash, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash macular-papular, rash morbilliform, rash papular, rash pruritic, rash vesicular, umbilical erythema rash.

¹² Could progress to Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (Lyell Syndrome).

¹³ Includes pollakiuria.

¹⁴ Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhoea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage.

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

¹⁶ Includes asthenia

c. Description of selected adverse reactions

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

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

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

d. Paediatric population (see sections 4.4 and 5.1)

Additional adverse reactions have been observed specifically in this population and are described below.

In paediatric clinical trials, suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility were more frequently observed among children and adolescents treated with antidepressants compared to those treated with placebo. Manic reactions, including mania and hypomania, were reported (2.6% of fluoxetine-treated patients vs. 0% in placebo-controls), leading to

discontinuation in the majority of cases. These patients had no prior episodes of hypomania/mania.

After 19 weeks of treatment, paediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height ($p=0.004$) and 1.1 kg less in weight ($p=0.008$) than subjects treated with placebo. Isolated cases of growth retardation have also been reported from clinical use.

In paediatric clinical trials, epistaxis was commonly reported, and fluoxetine treatment was 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard.

4.9 Overdose

The fatal dose is not known. The effects will be potentiated by alcohol taken at the same time. Toxicity is also potentiated by tricyclic antidepressants and MAOIs.

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 arrhythmias (including nodal rhythm and ventricular arrhythmias), or ECG changes indicative of QTc prolongation to cardiac arrest, (including very rare cases of Torsade de Pointes), pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of 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 drug 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Fluoxetine is a selective inhibitor of serotonin reuptake, and this probably accounts for the mechanism of action. Fluoxetine has practically no affinity to other receptors such as α_1 -, α_2 -, and β -adrenergic; serotonergic; dopaminergic; histaminergic₁; muscarinic; and GABA receptors.

Clinical efficacy and safety

Major depressive episodes: Clinical trials in patients with major depressive episodes have been conducted versus placebo and active controls. Fluoxetine has been shown to be significantly more effective than placebo, as measured by the Hamilton Depression Rating Scale (HAM-D). In these studies, Fluoxetine produced a significantly higher rate of response (defined by a 50% decrease in the HAM-D score) and remission compared to placebo.

Dose response: In the fixed-dose studies of patients with major depression there is a flat dose response curve, providing no suggestion of advantage in terms of efficacy for using higher than the recommended doses. However, it is clinical experience that uptitrating might be beneficial for some patients.

Obsessive-compulsive disorder: In short-term trials (under 24 weeks), fluoxetine was shown to be significantly more effective than placebo. There was a therapeutic effect at 20mg/day, but higher doses (40 or 60mg/day) showed a higher response rate. In long-term studies (three short-term studies extension phase and a relapse prevention study), efficacy has not been shown.

Bulimia nervosa: In short-term trials (under 16 weeks), in out-patients fulfilling DSM-III-R-criteria for bulimia nervosa, fluoxetine 60mg/day was shown to be significantly more effective than placebo for the reduction of bingeing, vomiting and purging activities. However, for long-term efficacy no conclusion can be drawn.

Pre-Menstrual Dysphoric Disorder: Two placebo-controlled studies were conducted in patients meeting pre-menstrual dysphoric disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

Paediatric population

Major depressive episodes: Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Fluoxetine, at a dose of 20mg, has been shown to be significantly more effective than placebo in two short-term pivotal studies, as measured by the reduction of Childhood Depression Rating Scale-Revised (CDRS-R) total scores and Clinical Global Impression of Improvement (CGI-I) scores. In both studies, patients met criteria

for moderate to severe MDD (DSM-III or DSM-IV) at three different evaluations by practising child psychiatrists. Efficacy in the fluoxetine trials may depend on the inclusion of a selective patient population (one that has not spontaneously recovered within a period of 3-5 weeks and whose depression persisted in the face of considerable attention). There is only limited data on safety and efficacy beyond 9 weeks. In general, efficacy of fluoxetine was modest. Response rates (the primary endpoint, defined as a 30% decrease in the CDRS-R score) demonstrated a statistically significant difference in one of the two pivotal studies (58% for fluoxetine versus 32% for placebo, $P = 0.013$; and 65% for fluoxetine versus 54% for placebo, $P = 0.093$). In these two studies, the mean absolute changes in CDRS-R from baseline to endpoint were 20 for fluoxetine versus 11 for placebo, $P = 0.002$; and 22 for fluoxetine versus 15 for placebo, $P < 0.001$.

Effects on growth, see sections 4.4 and 4.8: After 19 weeks of treatment, paediatric subjects treated with fluoxetine in a clinical trial gained an average of 1.1 cm less in height ($p=0.004$) and 1.1 kg less in weight ($p=0.008$) than subjects treated with placebo.

In a retrospective matched control observational study with a mean of 1.8 years of exposure to fluoxetine, paediatric subjects treated with fluoxetine had no difference in growth adjusted for expected growth in height from their matched, untreated controls (0.0 cm, $p=0.9673$).

5.2 Pharmacokinetic properties

Absorption: Fluoxetine is well absorbed from the gastro-intestinal tract after oral administration. The bioavailability is not affected by food intake.

Distribution: Fluoxetine is extensively bound to plasma proteins (about 95%) and it is widely distributed (volume of distribution: 20-40 L/kg). Steady-state plasma concentrations are achieved after dosing for several weeks. Steady-state concentrations after prolonged dosing are similar to concentrations seen at 4 to 5 weeks.

Biotransformation: Fluoxetine has a non-linear pharmacokinetic profile with first-pass liver effect. Maximum plasma concentration is generally achieved 6 to 8 hours after administration. Fluoxetine is extensively metabolised by the polymorphic enzyme CYP2D6. Fluoxetine is primarily metabolised by the liver to the active metabolite norfluoxetine (desmethylfluoxetine), by demethylation.

Elimination: The elimination half-life of fluoxetine is 4 to 6 days and for norfluoxetine 4 to 16 days. These long half-lives are responsible for persistence of the drug for 5-6 weeks after discontinuation. Excretion is mainly (about 60%) via the kidney. Fluoxetine is secreted into breast milk.

Special populations

Elderly: Kinetic parameters are not altered in healthy elderly when compared to younger subjects.

Paediatric population: The mean fluoxetine concentration in children is approximately 2-fold higher than that observed in adolescents and the mean norfluoxetine concentration 1.5-fold higher. Steady-state plasma concentrations are dependent on body weight and are higher in lower-weight children (see section 4.2). As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

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

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

5.3. Preclinical safety data

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

Adult animal studies.

In a 2-generation rat reproduction study, fluoxetine did not produce adverse effects on the mating or fertility of rats, was not teratogenic, and did not affect growth, development, or reproductive parameters of the offspring the concentrations in the diet provided doses approximately equivalent to the 1.5, 3.9 and 9.7 mg fluoxetine/kg body weight.

Male mice treated daily for 3 months with fluoxetine in the diet at a dose approximately equivalent to 31 mg/kg showed a decrease in testis weight and hypospermatogenesis. However, this dose level exceeds the maximum-tolerated dose (MTD) as significant signs of toxicity were seen.

Juvenile animal studies

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. A study in juvenile mice has indicated that inhibition of the serotonin transporter prevents the accrual of bone formation. This finding would appear to be supported by clinical findings. The reversibility of this effect has not been established.

Another study in juvenile mice (treated on postnatal days 4 to 21) has demonstrated that inhibition of the serotonin transporter had long-lasting effects on the behaviour of the mice. There is no information on whether the effect was reversible. The clinical relevance of this finding has not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The capsule also contains: pregelatinised maize starch, anhydrous colloidal silica, magnesium stearate and talc.

The capsule shell contains: quinoline yellow E104, erythrosine E127, indigo carmine E132, titanium dioxide E171 and gelatin.

The printing ink contains: shellac (E904), black iron oxide (E172), soya lecithin (E322), antifoam DC 1510.

6.2 Incompatibilities

None known.

6.3 Shelf Life

Blister Pack- 3 years

HDPE Bottle – 2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

28 capsule pack: 14 capsules packed in a blister (PVC / Aluminium) and 2 such blisters packed in a carton

30 capsule pack: 10 capsule packed in a blister (PVC / Aluminium) and 3 such blisters packed in a carton

Round HDPE capsule container and white LDPE snap on cap with PP liner containing 28 or 30 capsules.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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Tolpits Lane

Watford

Hertfordshire

WD18 9SS

United Kingdom

Trading as: Co-pharma

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