

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Norzac 20 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 22.4 mg of fluoxetine hydrochloride equivalent to 20.0 mg fluoxetine base.

Excipients - Contains Lactose Monohydrate 146.6mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Light green, opaque capsules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:

Major depressive episodes.

Obsessive-compulsive disorder.

Bulimia nervosa: Norzac is indicated as a complement of psychotherapy for the reduction of binge-eating and purging activity.

Children and adolescents aged 8 years and above:

Moderate to severe major depressive episode, if depression is unresponsive to psychological therapy after 4-6 sessions. Antidepressant medication should be offered to a child or young person with moderate to severe depression only in combination with a concurrent psychological therapy.

4.2 Posology and method of administration

For oral administration to adults only.

Major depressive episodes

Adults and the elderly: 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 for undesirable effects at higher doses, a dose increase may be considered after three weeks if there is no response.

In agreement with the consensus statement of the WHO, antidepressant medication should be continued for at least 6 months.

Obsessive-compulsive disorder - Adults and the elderly: 20 mg/day to 60 mg/day. A dose of 20mg/day is recommended as the initial dose. Although there may be an increased potential for side effects at higher doses, a dose increase may be considered after two weeks if there is no response. 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.

Bulimia nervosa - Adults and the elderly: A dose of 60 mg/day is recommended. Long-term efficacy (more than 3 months) has not been demonstrated in bulimia nervosa.

All indications: The recommended dose may be increased or decreased. Doses above 80 mg/day have not been systematically evaluated.

Fluoxetine may be administered as a single or divided dose, during or between meals.

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 and adolescents (under the age of 18) is not recommended, as safety and efficacy have not been established.

Elderly: Caution is recommended when increasing the dose and the daily dose should generally not exceed 40 mg. Maximum recommended dose is 60 mg/day.

A lower or less frequent dose (e.g. 20 mg every second day) should be considered in patients with hepatic impairment (*see section 5.2, Pharmacokinetic Properties*), or in patients where concomitant medication has the potential for interaction with fluoxetine (*See section 4.5, Interaction with other medicinal products and other forms of interactions*).

4.3 Contraindications

Hypersensitivity to fluoxetine or to any of its excipients.

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 a 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 contra-indicated 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, methylthionium chloride (also called methylene blue; a reversible non-selective MAOI indicated for the treatment of methaemoglobinaemia)) 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.

4.4 Special warnings and precautions for use

Warnings

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

Use in children and adolescents under 18 years of age

Norzac should not be used in the treatment of children and adolescents under the age of 18 years. 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 anti-depressants compared to those treated with placebo. 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, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Precautions

Seizures: Seizures are a potential risk with antidepressant drugs. Therefore, as with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures. Treatment should be discontinued in any patient who develops seizures or where there is an increase in seizure frequency. Fluoxetine should be avoided in patients with unstable seizure disorders/epilepsy and patients with controlled epilepsy should be carefully monitored.

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 Function: 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 20 mg/day for 2 months, patients with severe renal failure (GFR <10 ml/min) requiring dialysis showed no difference in plasma levels of fluoxetine or norfluoxetine compared to controls with normal renal function.

Cardiac Disease: No conduction abnormalities that resulted in heart block were observed in the ECG of 312 patients who received fluoxetine in double blind clinical trials. However, clinical experience in acute cardiac disease is limited, therefore caution is advisable.

Weight Loss: Weight loss may occur in patients taking fluoxetine but it is usually proportional to baseline body weight.

Diabetes: In patients with diabetes, treatment with an SSRI 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.

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.

Haemorrhage: There have been reports of cutaneous bleeding abnormalities such as ecchymosis and purpura with SSRI's. Ecchymosis has been reported as an infrequent event during treatment with fluoxetine. Other hemorrhagic manifestations (e.g., gynaecological haemorrhages, gastrointestinal bleedings and other cutaneous or mucous bleedings) have been reported rarely. Caution is advised in patients taking SSRI's, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function (e.g. atypical antipsychotics such as clozapine, phenothiazines, most TCA's, aspirin, NSAID's) or other drugs that may increase risk of bleeding as well as in patients with a history of bleeding disorders.

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

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

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

With reference to the presence of lactose monohydrate in the formulation, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Half-life: 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).

Monoamine oxidase inhibitors: (see Section 4.3).

Not recommended combinations: MAOI-A (see Section 4.3)

Combinations requiring precautions for use: MAOI-B (selegiline): risk of serotonin syndrome. Clinical monitoring is recommended.

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.

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 and tryptophan: There have been reports of serotonin syndrome when SSRIs have been given with lithium or tryptophan and, therefore, the concomitant use of fluoxetine with these drugs should be undertaken with caution. When

fluoxetine is used in combination with lithium, closer and more frequent clinical monitoring is required.

CYP2D6 isoenzyme: Because fluoxetine's metabolism (like tricyclic antidepressants and other selective serotonin antidepressants) involves the hepatic cytochrome CYP2D6 isoenzyme system, concomitant therapy with drugs also metabolised by this enzyme system may lead to drug interactions. Concomitant therapy with drugs predominantly metabolised by this isoenzyme, and which have a narrow therapeutic index (such as flecainide, encainide, 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 interaction between CYP2D6 inhibitors and tamoxifen, showing a 65-75% reduction in plasma levels of one of the more active forms of the tamoxifen, i.e. endoxifen, has been reported in the literature. Reduced efficacy of tamoxifen has been reported with concomitant usage of some SSRI antidepressants in some studies. As a reduced effect of tamoxifen cannot be excluded, co-administration with potent CYP2D6 inhibitors (including fluoxetine) should whenever possible be avoided (see section 4.4).

Oral anticoagulants: Altered anti-coagulant 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).

Electroconvulsive Therapy (ECT): There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment, 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.

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

St. John's Wort: In common with other SSRIs, pharmacodynamic interactions between fluoxetine and the herbal remedy St. John's Wort (*Hypericum perforatum*) may occur, which may result in an increase of undesirable effects.

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, particular 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.

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).

Lactation: 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 SSRIs have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

4.7 Effects on ability to drive and use machines

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

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.

The table below gives the adverse reactions observed in clinical trials (n = 9297) and from spontaneous reporting. Some of these adverse reactions are in common with other SSRIs.

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 rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very Common	Common	Uncommon	Rare	Very Rare	Frequency Not Known
<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	Depersonalisation Elevated mood Euphoric mood Thinking abnormal	Hypomania Mania Hallucinations Agitation		Suicidal thoughts and behaviour ¹⁴

	Tension Libido decreased ⁴ Sleep disorder Abnormal dreams ³	Orgasm abnormal ⁵ Bruxism	Panic attacks		Confusion Dysphemia
<i>Nervous system disorders</i>					
Headache	Disturbance in attention Dizziness Dysgeusia Lethargy Somnolence ⁶ Tremor	Psychomotor hyperactivity Dyskinesia Ataxia Balance disorder Myoclonus	Convulsion Akathisia Buccoglossal syndrome		Serotonin syndrome Memory impairment
<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 ⁷	Hypotension	Vasculitis Vasodilatation		
<i>Respiratory, thoracic and mediastinal disorders</i>					
	Yawning	Dyspnoea	Pharyngitis		Pulmonary events (inflammatory processes of varying histopathology and/or fibrosis) Epistaxis
<i>Gastrointestinal disorders</i>					
Diarrhoea Nausea	Vomiting Dyspepsia Dry mouth	Dysphagia	Oesophageal pain		Gastrointestinal haemorrhage ¹⁵
<i>Hepato-biliary disorders</i>					
					Very rare idiosyncratic hepatitis

<i>Skin and subcutaneous tissue disorders</i>					
	Rash ⁸ Urticaria Pruritus Hyperhidrosis	Alopecia Increased tendency to bruise Cold sweat	Angioedema Ecchymosis Photosensitivity reaction Purpura		Erythema multiforme ¹³
<i>Musculoskeletal, connective tissue and bone disorders</i>					
	Arthralgia	Muscle twitching			Myalgia
<i>Renal and urinary disorders</i>					
	Frequent urination ⁹	Dysuria	Urinary retention		Micturition disorder
<i>Reproductive system and breast disorders</i>					
	Gynaecological bleeding ¹¹ Erectile dysfunction Ejaculation disorder ¹⁰	Sexual dysfunction	Galactorrhoea Hyperprolactinemia		Priapism
<i>General disorders and administration site conditions</i>					
Fatigue ¹²	Feeling jittery Chills	Malaise Feeling abnormal Feeling cold Feeling hot			Mucosal haemorrhage
<i>Investigations</i>					
	Weight decrease				Abnormal liver function tests

¹ Includes anorexia

² Includes early morning awakening, initial insomnia, middle insomnia

³ Includes nightmares

⁴ Includes loss of libido

⁵ Includes anorgasmia

⁶ Includes hypersomnia, sedation

⁷ Includes hot flush

⁸ 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

⁹ Includes pollakiuria

¹⁰ Includes ejaculation failure, ejaculation dysfunction, premature ejaculation, ejaculation delayed, retrograde ejaculation

¹¹ Includes cervix haemorrhage, uterine dysfunction, uterine bleeding, genital haemorrhage, menometrorrhagia, menorrhagia, metrorrhagia, polymenorrhoea, postmenopausal haemorrhage, uterine haemorrhage, vaginal haemorrhage

¹² Includes asthenia

¹³ Could progress to Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (Lyell Syndrome)

¹⁴ These symptoms may be due to underlying disease.

¹⁵ Includes most frequent gingival bleeding, haematemesis, haematochezia, rectal haemorrhage, diarrhoea

haemorrhagic, melaena, and gastric ulcerhaemorrhage.

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 fluoxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Children and adolescents (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 versus 0% in placebo-controls), leading to discontinuation in the majority of cases. These patients had no prior episodes of hypomania/mania.

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

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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'. Alternatively, the traditional post-paid 'yellow card' option may also continue to be used.

FREEPOST

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4.9 Overdose

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. 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 overdose, 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: NO6 AB03

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.

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 up-titrating 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 20 mg/day, but higher doses (40 or 60 mg/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 60 mg/day was shown to be significantly more effective than placebo for the reduction of bingeing and purging activities. However, for long-term efficacy no conclusion can be drawn.

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 20 mg 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 (20 mg 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.

Major depressive episodes (children and adolescents): Clinical trials in children and adolescents aged 8 years and above have been conducted versus placebo. Fluoxetine, at a dose of 20 mg, 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 (children and adolescents), 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 of 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 gastrointestinal 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.

Metabolism:

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 (demethylfluoxetine), by desmethylation.

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.

At-risk populations

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

Children and adolescents: 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 1.5, 3.9, and 9.7 mg fluoxetine/kg bodyweight.

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 exceeded 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**

Lactose Monohydrate
Microcrystalline Cellulose
Magnesium Stearate
Colloidal Anhydrous Silica

Capsule Shell:

Gelatin
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)
Quinoline Yellow (E104)
Indigo Carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

The capsules are placed in thermoformed PVC/PVdC foil laminated with aluminium. The blister pack sizes are 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112 and 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Norton Healthcare Limited
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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