

NEW ZEALAND DATA SHEET

1. FLUOXETINE – AFT

Fluoxetine hydrochloride equivalent to Fluoxetine 20mg/5mL Oral Liquid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluoxetine 20mg/5mL: contains fluoxetine hydrochloride equivalent to fluoxetine 20mg per 5mL of solution.

Excipients with known effect:

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral liquid.

Fluoxetine-AFT oral liquid is a clear, colourless, mint flavoured solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FOR ADULTS USE ONLY

- Depression and its associated anxiety
- Bulimia nervosa
- Obsessive-Compulsive disorder
- Premenstrual dysphoric disorder - a severe form of PMS.

Diagnosis of PMDD: The essential features of PMDD are clear and established cyclicality of symptoms (occurring during the last week of the luteal phase in most menstrual cycles) such as depressed mood, anxiety, affective lability, and physical symptoms such as breast tenderness or swelling, headaches, joint or muscle pain, bloating, and weight gain. PMDD is a severe clinical entity and is distinguished from the broader premenstrual syndrome by the intensity of its symptoms (particularly mood symptoms) and the extent to which it interferes with social and/or occupational function.

4.2 Dose and method of administration

Depression

20 mg per day is the recommended initial dose.

Bulimia Nervosa

60 mg per day is the recommended dose.

Obsessive-Compulsive Disorder

20 mg to 60 mg per day is the recommended dose.

Premenstrual Dysphoric Disorder

20 mg per day is recommended continuously throughout the menstrual cycle. Initial treatment should be limited to six months, after which patients should be reassessed regarding the benefit of continued therapy.

All Indications

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

Age

There are no data to suggest that alternative dosing is required on the basis of age alone.

Use in Children and Adolescents (<18 years)

The safety and efficacy of fluoxetine for the treatment of children and adolescents less than 18 years of age has not been established.

Administration with Food

Fluoxetine-AFT may be administered with or without food.

Concurrent Disease and/or Concomitant Medication

A lower or less frequent dose should be considered in patients with hepatic impairment, with concurrent diseases, or who are taking multiple medications.

4.3 Contraindications

- Hypersensitivity to fluoxetine
- Fluoxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or less than 14 days after discontinuing treatment with a MAOI. At least five weeks should elapse between discontinuation of Fluoxetine-AFT and initiation of therapy with a MAOI. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with fluoxetine and a MAOI in close temporal proximity.

4.4 Special warnings and precautions for use

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.

Cardiac Disease

Clinical experience in acute cardiac disease is limited; therefore caution is advisable.

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 maybe detrimental.

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.

Serotonin Syndrome

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 combination with other serotonergic and/or neuroleptic medicines. As this syndrome 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 confusions, irritability, extreme agitation, progressing to delirium and coma) occur and supportive treatment should be initiated.

Cerebral Vasoconstriction Syndrome: Reversible cerebral vasoconstriction syndrome (thunderclap headache) has been associated with serotonergic agents such as SSRIs or triptans.

Mydriasis

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

Haemorrhage

There have been reports of cutaneous bleeding abnormalities, such as ecchymosis and purpura with SSRIs. Ecchymosis has been reported as an infrequent event. Other haemorrhagic manifestations (e.g. gynaecological haemorrhages, gastro-intestinal bleeding and other cutaneous or mucous bleeding) have been reported rarely. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, drugs known to affect platelet function or other drugs that may increase the risk of bleeding, as well as in patients with a history of bleeding disorders.

Bone Fractures

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

Alcohol

As with other psychotropic drugs patients should be advised to avoid alcohol use while taking paroxetine.

Hyponatraemia

Hyponatraemia has been reported rarely, predominantly in the elderly. Caution should be exercised in those patients at risk of hyponatraemia e.g. from concomitant medicines and cirrhosis.

Clinical Worsening and Suicide Risk

The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. This risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviours (suicidality) whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more

of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with co-morbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analyses of 24 short-term (4 to 16 weeks), placebo-controlled trials of nine antidepressant medicines [selective serotonin reuptake inhibitors (SSRIs) and others] in 4400 children and adolescents with major depressive disorder (16 trials), obsessive compulsive disorder (4 trials), or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4%, compared with 2% of patients given placebo. There was considerable variation in risk among the antidepressants, but there was a tendency towards an increase for almost all antidepressants studied. The risk of suicidality was most consistently observed in the major depressive disorder trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established, there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of children and adolescents being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour, and other symptoms described above, as well as the emergence of suicidality, and to report such symptoms to health care providers immediately. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

Prescriptions for Fluoxetine-AFT should be written for the smallest quantity of medicine consistent with good patient management, in order to reduce the risk of overdose.

Rash

Rash, anaphylactoid events, and progressive systemic events, sometimes serious and involving skin, kidney, liver or lung has been reported in patients taking Fluoxetine-AFT. Upon the appearance of rash, or of other possible allergic phenomena for which an alternative aetiology cannot be identified Fluoxetine-AFT should be discontinued.

Mania and Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with any antidepressant alone may increase the likelihood of a mixed/manic episode in patients at risk for bipolar disorder. Prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. It should be noted that fluoxetine is not approved for use in treating bipolar depression.

Seizures

As with other antidepressants, fluoxetine should be introduced cautiously in patients who have a history of seizures.

Hyponatraemia

Cases of hyponatraemia (some with serum sodium lower than 110 mmol/L) have been reported. The majority of these cases occurred in elderly patients and in patients treated with diuretics or otherwise volume-depleted.

Glycaemic Control

In patients with diabetes, hypoglycaemia has occurred during therapy with fluoxetine and hyperglycaemia has developed following discontinuation. Insulin and/or oral hypoglycaemic dosage may need to be adjusted when fluoxetine therapy is initiated or discontinued.

Mydriasis

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

Withdrawal Reactions

Discontinuation symptoms have been reported in association with selective serotonin reuptake inhibitors (SSRIs). Because of the long elimination half-life of fluoxetine, and its active metabolite norfluoxetine, plasma fluoxetine and norfluoxetine concentrations decrease gradually at the conclusion of therapy, which reduces greatly the likelihood of developing discontinuation symptoms and makes dosage tapering unnecessary in most patients. Common symptoms associated with withdrawal of SSRIs include dizziness, paraesthesia, headache, anxiety and nausea. Onset of symptoms can occur within a day of discontinuation but may be delayed, particularly in the case of fluoxetine, due to its long half-life. The majority of symptoms experienced on withdrawal of SSRIs are non-serious, self-limiting and have varying durations. Fluoxetine has been only rarely associated with such symptoms.

4.5 Interaction with other medicines and other forms of interaction

Lithium and tryptophan

There have been reports of serotonin syndrome when SSRs have been given with lithium or tryptophan, 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.

Tamoxifen

Pharmacokinetic interaction between CYP2D6 inhibitors and tamoxifen showing a 65-75% reduction in plasma levels of one of the more active forms of tamoxifen (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 be avoided when possible.

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, mainly serotonergic, effects.

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 available.

Monoamine Oxidase Inhibitors

Fluoxetine should not be used in combination with a monoamine oxidase inhibitor (MAOI) or less than 14 days after discontinuing treatment with a MAOI. At least five weeks should elapse between discontinuation of Fluoxetine-AFT and initiation of therapy with a MAOI. If fluoxetine has been prescribed chronically and/or at a high dose, a longer interval should be considered. Serious and fatal cases of serotonin syndrome (which may resemble and be diagnosed as neuroleptic malignant syndrome) have been reported in patients treated with fluoxetine and a MAOI in close temporal proximity.

Medicines Metabolised by Cytochrome P450IID6 Isoenzyme

Because fluoxetine has the potential to inhibit the cytochrome P450IID6 isoenzyme, therapy with medications that are predominantly metabolised by the P450IID6 system and that have a relatively narrow therapeutic index, should be initiated at the low end of the dose range if a patient is receiving Fluoxetine-AFT concurrently or has taken it in the previous five weeks. If Fluoxetine-AFT is added to the treatment range of a patient already receiving such a medicine, the need for decreased dose of the original medication should be considered.

CNS active medicines

Changes in the blood levels of phenytoin, carbamazepine, haloperidol, clozapine, diazepam, alprazolam, lithium, imipramine and desipramine, and in some cases, clinical manifestations of toxicity have been observed. Consideration should be given to using conservative titration schedules of the concomitant medicine and monitoring of clinical status.

Protein binding

Because fluoxetine is tightly bound to plasma protein, the administration of Fluoxetine-AFT to a patient taking another medicine that is tightly bound to protein may cause a shift in plasma concentrations of either medicine.

Warfarin

Altered anti-coagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but increased bleeding, have been reported uncommonly when fluoxetine is co-administered with warfarin. As is prudent in concomitant use of warfarin with many other medicines, patients receiving warfarin therapy should receive careful monitoring when Fluoxetine-AFT is initiated or stopped.

Electroconvulsive therapy (ECT)

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

Elimination half-life

The long elimination half-lives of fluoxetine and its principal metabolite, norfluoxetine, are of potential consequence when medicines are prescribed which might interact with either substance following the discontinuation of Fluoxetine-AFT.

4.6 Fertility, pregnancy and lactation

Category C

Fluoxetine use should be considered during pregnancy only if the potential benefit justifies the potential risk to the foetus, taking into account the risks of untreated depression.

Experimental animal studies do not indicate direct or indirect harmful effects, with respect to the development of the embryo or foetus or the course of gestation. Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if clearly needed.

Results of a number of epidemiological studies assessing the risk of fluoxetine exposure in early pregnancy have been inconsistent and have not provided conclusive evidence of an increased risk of congenital malformations. However, one meta-analysis suggests a potential risk of cardiovascular defects in infants of women

exposed to fluoxetine during the first trimester of pregnancy compared to infants of women who were not exposed to fluoxetine.

Fluoxetine may increase risks of congenital anomalies, persistent pulmonary hypertension, neonatal behavioral syndrome, and pre-term birth. Epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

Recent data suggests the use of SSRIs, including Fluoxetine, after the first 20 weeks of pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The data shows the absolute risk among those who used SSRIs late in pregnancy was reported to be about 6 to 12 per 1000 women, compared to 1 to 2 per 1000 women in the United States general population. These findings should be taken into account by the physician when making decisions whether to continue the use of SSRIs during pregnancy.

This drug crosses the placenta.

At the end of pregnancy, caution should be exercised, as transitory withdrawal symptoms (eg. transient jitteriness, difficulty feeding, tachypnea and irritability) have been reported rarely in the neonate after maternal use near term.

Neonates exposed to fluoxetine and other SSRIs or serotonin and noradrenaline reuptake inhibitors (SNRIs), late in the third trimester have been uncommonly reported to have clinical findings of respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. Such events can arise immediately upon delivery and are usually transient. These features could be consistent with either a direct effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. When treating a pregnant woman with fluoxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Teratogenic effects:

Reproduction studies have been performed in rats and rabbits at doses of up to 12.5 and 15 mg/kg/day and have revealed no evidence of harm to the foetus due to fluoxetine hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labour and delivery:

The effect of fluoxetine on labour and delivery in humans is unknown.

Lactation:

Because fluoxetine is excreted in human milk, breastfeeding while on Lovan is not recommended. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant breastfed by a mother on fluoxetine developed crying, sleep disturbance, vomiting and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

4.7 Effects on ability to drive and use machines

Psychoactive medicines may impair judgement, thinking, or motor skills. Patients should be advised to avoid driving a car or operating machinery until they are reasonably certain that their performance is not affected.

Information for Patients and Families

Physicians are advised to discuss the following issues with patients for whom they prescribe fluoxetine:

- Because fluoxetine may impair judgement, thinking, or motor 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.
- Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter medicines, or alcohol.
- Patients should be advised to inform their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should be advised to notify their physician if they are breast feeding an infant.
- Patients should be advised to notify their physician if they develop a rash or hives.

- The patient has the right to treatment meeting appropriate ethical and professional standards, and the patient needs to be fully informed with frank discussion of risk/benefit issues relating to the medicine's efficacy and safety when used in the treatment regimen proposed.

4.8 Undesirable effects

Very rare < 0.01%; rare > 0.01% and < 0.1%; uncommon > 0.1% and < 1%; common > 1% and < 10%; frequent > 10%

In Clinical trials the following adverse effects were noted:

Body as a whole:

Frequent: Asthenia

Common: Chills, dry mouth, pruritis, rash, sweating, urticaria, vasodilation

Rare: Anaphylactoid reaction, photosensitivity, serum sickness-like reaction, vasculitis

Others: Fatigue, allergic reaction, feeling abnormal

Cardiac System:

Palpitation, hypotension, orthostatic hypotension,

Gastrointestinal Disorders

Frequent: Diarrhoea, nausea

Common: Dyspepsia, taste perversion, vomiting

Uncommon: Dysphagia

Others: gastrointestinal disorder, oesophageal pain,

Blood and lymphatic system disorders

Uncommon: Ecchymosis

Others: Eosinophilia, thrombocytopenic purpura, haemorrhagic manifestations

Hepatobiliary Disorders

Hepatic necrosis, hepatic failure

Immune System:

Malignant hyperthermia, SJS

Nervous system

Frequent: Anxiety, insomnia, nervousness, somnolence, tremor

Common: Abnormal dreams, anorexia, concentration/thought process impairment, dizziness, palpitation, weight loss

Uncommon: Ataxia, depersonalisation, manic reaction, myoclonus, psychomotor, twitching,

Rare: Buccoglossal syndrome

Others: balance disorder, bruxism, dyskinesia, oculogyric crisis, tardive dyskinesia, memory impairment,

Respiratory

Common: Yawn

Skin and subcutaneous tissue disorders

Uncommon: Alopecia, epidermal necrolysis,

Special senses

Common: abnormal vision, taste perversion

Uncommon: Mydriasis

Urogenital and reproductive system disorders

Common: Delayed or absent ejaculation, impotence, decreased libido, urinary frequency

Uncommon: Anorgasmia, priapism/prolonged erection, urination impaired.

Others: sexual dysfunction, enlarged clitoris, gynaecomastia

Musculoskeletal Disorders

Bone fractures

In addition to the above adverse effects which were noted during clinical trials the following additional adverse effects have been reported in clinical practice:

Body as a whole

Very rare: Angioedema, serotonin syndrome, erythema multiforme

Digestive system

Very rare: idiosyncratic hepatitis

Endocrine system

Very rare: Inappropriate secretion of anti-diuretic hormone

Nervous system

Uncommon: seizures

Special populations (Children)

Very rare: Headache. Weight loss and decreased height gain.

As with other SSRIs decreased weight gain has been observed in children and adolescent patients. In trials, paediatric patients treated with fluoxetine gained on average 1.1 cm in height and 1.1 kg less weight than subjects treated with placebo (19 weeks treatment). Fluoxetine treatment was also associated with a decrease in alkaline phosphate levels. The safety of fluoxetine treatment for paediatric patients has not been systematically assessed for chronic treatment longer than several months duration. There are no long term studies that directly evaluate the longer term effects of fluoxetine on the growth, development and maturation of children and adolescent patients. Height and weight should be monitored periodically in paediatric patients receiving fluoxetine.

4.9 Overdose

Symptoms

Cases of overdose of fluoxetine alone usually have a mild course. Symptoms of overdose have included nausea, vomiting, seizures, cardiovascular dysfunction ranging from asymptomatic arrhythmias to cardiac arrest, pulmonary dysfunction, and signs of altered CNS status ranging from excitation to coma. Fatality attributed to overdose of fluoxetine alone has been extremely rare.

Treatment

Cardiac and vital signs monitoring is 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. In managing overdosage, consider the possibility of multiple medicine involvement.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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; histaminergic; muscarinic; and GABA receptors.

5.2 Pharmacokinetic properties

Absorption:

In man, following a single oral 40 mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours. Fluoxetine is 80 to 95% absorbed following oral administration. There is a linear dose proportionality for the absorption of fluoxetine over the therapeutic dose range.

Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption inconsequentially. Thus, fluoxetine may be administered with or without food.

Distribution:

The volume of distribution for fluoxetine is estimated at 30-40 L/kg.

Protein binding:

Over the concentration range from 200 to 1,000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and a -1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important.

Metabolism:

Fluoxetine is extensively metabolised in the liver to norfluoxetine and a number of other, unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, norfluoxetine's potency and selectivity as a serotonin uptake blocker are essentially equivalent to fluoxetine's.

Multiple cytochrome P450 isoenzymes, including CYP2D6, are responsible for the conversion of fluoxetine to norfluoxetine; thus other nonsaturable oxidative pathways (i.e. non-2D6 pathways) contribute considerably to norfluoxetine formation.

Excretion:

The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical issues related to metabolism/elimination:

The complexity of the metabolism of fluoxetine has several consequences which may potentially affect fluoxetine's clinical use.

Accumulation and slow elimination:

The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of fluoxetine were higher than those predicted by single dose studies, presumably because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days.

Thus, even if patients are given a fixed dose, steady state plasma concentrations are only achieved after continuous dosing for weeks. Nevertheless, plasma concentrations do not appear to increase without limit. Specifically, patients receiving fluoxetine at doses of 40 to 80 mg/day over periods as long as 3 years exhibited, on average, plasma concentrations similar to those seen among patients treated for 4 or 5 weeks.

Clinical Issues Related to Accumulation and Slow Elimination:

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen and length of previous therapy at discontinuation). This is of potential consequence when drug withdrawal is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of fluoxetine hydrochloride.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of carcinogenicity or mutagenicity from in vitro or animal studies. Impairment of fertility in adult animals at doses up to 12.5 mg/kg/day (approximately 1.5 times the MRHD on a mg/m² basis) was not observed.

In a juvenile toxicology study in CD rats, administration of 30 mg/kg of fluoxetine hydrochloride on postnatal days 21 through 90 resulted in increased serum activities of creatine kinase (CK) and aspartate aminotransferase (AST), which were accompanied microscopically by skeletal muscle degeneration, necrosis and regeneration. Other findings in rats administered 30 mg/kg included degeneration and necrosis of seminiferous tubules of the testis, epididymal epithelial vacuolation, and immaturity and inactivity of the female reproductive tract. Plasma levels achieved in these animals at 30 mg/kg were approximately 5 to 8 fold (fluoxetine) and 18 to 20 fold (norfluoxetine), and at 10 mg/kg approximately 2 fold (fluoxetine) and 8 fold (norfluoxetine) higher compared to plasma concentrations usually achieved in paediatric patients. Following an approximate 11-week recovery period, sperm assessments in the 30 mg/kg males only, indicated an approximately 30% decrease in sperm concentrations without affecting sperm morphology or motility. Microscopic evaluation of testes and epididymides of these 30 mg/kg males indicated that testicular degeneration

was irreversible. Delays in sexual maturation occurred in the 10 mg/kg males and in the 30 mg/kg males and females. The significance of these findings in humans is unknown. Femur length at 30 mg/kg increased to a lesser extent compared with control rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Other excipient:

Benzoic acid, ethanol (96%), Glycerol, Hydrochloric acid, peppermint flavour PHL-050834 2.5 microgram/mL, purified water q.s., sodium hydroxide, sucrose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from date of manufacture. Once opened, product should be used in 28 days.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Bottles containing 140mL of product.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription only medicine.

8. SPONSOR

AFT Pharmaceuticals Ltd
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Takapuna
Auckland 0740
Phone: 0800 423 823
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9. DATE OF FIRST APPROVAL

7 October 2010

10. DATE OF REVISION OF THE TEXT

February 2019

SUMMARY TABLE OF CHANGES

Date	Section(s) Changed	Change (s)
February 2019	All	Reformat consistent with new Medsafe Data Sheet Template.