PRODUCT MONOGRAPH

RIVA-FLUOXETINE

(FLUOXETINE hydrochloride)

Capsules

Antidepressant/Antiobsessional/Antibulimic

Laboratoire Riva Inc.
Blainville, Canada

Control # 091102

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THERAPEUTIC CLASSIFICATION

Antidepressant/Antiobsessional/Antibulimic Agent

ACTION AND CLINICAL PHARMACOLOGY

The antidepressant, antiobsessional, and antibulimic actions of FLUOXETINE are presumed to be linked to its ability to selectively inhibit the neuronal reuptake of serotonin. At clinically relevant doses FLUOXETINE blocks the uptake of serotonin into human platelets. Antagonism of muscarinic, histaminergic and α_1-adrenergic receptors has been hypothesised to be associated with various anticholinergic, sedative and cardiovascular effects of classical tricyclic antidepressant drugs. *In vitro* receptor binding studies have demonstrated that FLUOXETINE binds to these and other membrane receptors [opiate, serotonergic (5-HT_1, 5-HT_2), adrenergic (α_1, α_2, β and dopaminergic] much less potently than do the tricyclic drugs.

Pharmacokinetics:

FLUOXETINE is well absorbed after oral administration. 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. 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.

FLUOXETINE is extensively metabolised in the liver to norFLUOXETINE, and other unidentified metabolites. The pharmacological activity of norFLUOXETINE, which is formed by demethylation of FLUOXETINE appears to be similar to that of the parent drug. NorFLUOXETINE contributes to the long duration of action of FLUOXETINE. 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 that may potentially affect its 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 4 to 16 days after acute and chronic administration) results in significant accumulation during chronic use. After 30 days of dosing at 20 mg/day, mean plasma concentrations of FLUOXETINE 79.1± 33.4 ng/mL and of norFLUOXETINE 129 ±42.0 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.

Steady state plasma levels are attained after 4 to 5 weeks of continuous drug administration. 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 to 5 weeks.

Similarly, because of the long half-lives of FLUOXETINE and norFLUOXETINE, it may take up to 1 to 2 months for the active drug substance to disappear from the body. This is of potential consequence in the withdrawal of FLUOXETINE (see WARNINGS).

Age:

The disposition of single doses of FLUOXETINE in healthy elderly subjects (greater than 65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and non-linear disposition of the drug, a single-dose study is not adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases.

The effects of age upon the metabolism of FLUOXETINE have been investigated in a subset of 260 elderly, but otherwise healthy, depressed patients (mean age: 67.4 years, range 60 to 85 years) who received 20 mg FLUOXETINE for 6 weeks. Mean plasma concentrations were found to be 89.5±53.6 ng/mL for FLUOXETINE and 119±51.3 ng/mL for norFLUOXETINE.

Protein Binding:

Approximately 94% of FLUOXETINE are protein bound. The interaction between FLUOXETINE and other highly protein bound drugs has not been fully evaluated, but may be important (see PRECAUTIONS).

Liver Disease:

As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of FLUOXETINE. In patients with cirrhosis, the elimination half-life of FLUOXETINE was prolonged, with a mean of 7.6 days compared to the range of 2 to 3 days seen in subjects without liver disease; norFLUOXETINE elimination half-life was also delayed, with a mean duration of 12 days for cirrhotic patients compared to the range of 7 to 9 days in normal subjects. This suggests that the use of FLUOXETINE in patients with liver disease must be approached with caution (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Disease:

In single dose studies, the pharmacokinetics of FLUOXETINE and norFLUOXETINE were similar among subjects with all levels of impaired renal function including anephric patients on chronic hemodialysis. However, with chronic administration, additional accumulation of FLUOXETINE or its metabolites (possibly including some not yet identified) may occur in patients with severely impaired renal function and use of a lower or less frequent dose is advised (see PRECAUTIONS).

Clinical Trials:

The efficacy of FLUOXETINE was established in 5 and 6 week placebo controlled clinical trials in depressed outpatients (≥18 yrs of age), who meet the DSM-III criteria for major depressive disorder.

Two, 6 week, placebo controlled clinical trials in depressed elderly patients, who met the DSM-III-R criteria for major depressive disorder (mean age 67.4 years, range 60 to 85 years) have shown FLUOXETINE, 20 mg/day to be effective.

A comparative two-way, crossover, bioavailability study was performed on two 20 mg FLUOXETINE capsule products, RIVA-FLUOXETINE 20 mg capsules and PROZAC® 20 mg capsules, in 12 normal healthy male volunteers. The pharmacokinetic plasma data for FLUOXETINE and norFLUOXETINE are tabulated below.

Pharmacokinetic Indices for FLUOXETINE:

	Geometric Mean Arithmetic Mean (C.V.)		
Parameter	RIVA-FLUOXETINE (2 x 20 mg)	PROZAC®** (2 x 20 mg)	Percentage of PROZAC®
$AUC_{0\text{-}72\ hr}$ (ng•hr/mL)	745.6 753.9 (16)	696.5 702.8 (14)	107%
AUC_T (ng•hr/mL)	828.8 856.9 (27)	772.8 810.3 (35)	107%
AUC_I (ng•hr/mL)	992.3 1024 (25)	934.5 974.9 (34)	106%
C_{max} (ng/mL)	20.49 20.89 (18)	19.89 20.21 (16)	103%
T_{max}* (hr.)	8.33 (2)	8.67 (2)	–
$t_{1/2}$* (hr.)	36.3 (13)	37.5 (22)	–

*For the T_{max} and $t_{1/2}$ parameters these are the arithmetic means (standard deviation).
**PROZAC® Manufactured by Eli Lilly Canada Inc.

Pharmacokinetic Parameters for NorFLUOXETINE:

	Geometric Mean Arithmetic Mean (C.V.)		
Parameter	RIVA-FLUOXETINE (2 x 20 mg)	PROZAC®** (2 x 20 mg)	Percentage of PROZAC®
$AUC_{0\text{-}72\ hr}$ (ng•hr/mL)	827.3 877.6 (35)	842.5 904.4 (38)	98.2%
AUC_T (ng•hr/mL)	3944 4093 (29)	3789 4006 (34)	104%
AUC_I (ng•hr/mL)	4628 4739 (25)	4628 4789 (28)	100%
C_{max} (ng/mL)	15.03 15.82 (32)	14.88 15.61 (33)	101%
T_{max}* (hr.)	72.0 (25)	63.3 (31)	–

$t_{1/2}$* (hr.)	152.0 (44)	162.0 (47)	–

*For the T_{max} and $t_{1/2}$ parameters these are the arithmetic means (standard deviation).
**PROZAC® Manufactured by Eli Lilly Canada Inc.

INDICATIONS AND CLINICAL USE

DEPRESSION:

RIVA-FLUOXETINE (FLUOXETINE hydrochloride) is indicated for the symptomatic relief of depressive illness.

BULIMIA NERVOSA:

FLUOXETINE has been shown to significantly reduce binge-eating and purging activity when compared with placebo treatment.

OBSESSIVE-COMPULSIVE DISORDER:

FLUOXETINE has been shown to significantly reduce the symptoms of obsessive-compulsive disorder in double-blind, placebo-controlled clinical trials.
The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning.

The efficacy of FLUOXETINE in hospitalised patients has not been adequately studied.

The effectiveness of FLUOXETINE in long-term use (i.e. for more than 5 to 6 weeks in depression, for more than 16 weeks in bulimia nervosa, or for more than 13 weeks in obsessive compulsive disorder), has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use RIVA-FLUOXETINE for

extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

RIVA-FLUOXETINE (FLUOXETINE hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

Monoamine Oxidase Inhibitors (MAOI): There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving FLUOXETINE in combination with a monoamine oxidase inhibitor, and in patients who have recently discontinued FLUOXETINE and then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, RIVA-FLUOXETINE should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI. Since FLUOXETINE and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping FLUOXETINE before starting an MAOI. Limited reports suggest that intravenously administered dantrolene (Dantrium®) or orally administered cyproheptadine (Periactin®) may benefit patients experiencing such reactions.

WARNINGS

POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM.

Pediatrics: Placebo-Controlled Clinical Trial Data

- **Recent analyses of placebo-controlled clinical trial safety databases from SSRIs and other newer anti-depressants suggests that use of these drugs in patients under the age of 18 may be associated with behavioural and emotional changes, including an increased risk of suicidal ideation and behaviour over that of placebo.**

- **The small denominators in the clinical trial database, as well as the variability in placebo rates, preclude reliable conclusions on the relative safety profiles among these drugs.**

Adults and Pediatrics: Additional data

- **There are clinical trial and post-marketing reports with SSRIs and other newer anti-depressants, in both pediatrics and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, depersonalization. In some cases, the events occurred within several weeks of starting treatment.**

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type emotional and behavioural changes.

Discontinuation Symptoms

Patients currently taking a newer anti-depressant should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue treatment, a gradual

reduction in the dose rather than an abrupt cessation, except for fluoxetine, is recommended (see WARNINGS: IMPLICATIONS OF THE LONG ELIMINATION HALF-LIFE OF FLUOXETINE).

Allergic Reactions (Rash and Accompanying Events):

During premarketing testing of more than 5,600 patients given FLUOXETINE, about 4% developed rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Other symptoms reported in association with these allergic reactions were fever, leukocytosis, arthralgias, oedema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and a mild increase in transaminase. Most patients improved promptly with discontinuation of FLUOXETINE and/or adjunctive therapy with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

Two patients involved in these premarketing trials developed a serious cutaneous systemic illness. In neither case was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness.

Since the introduction of FLUOXETINE, systemic effects which are possibly related to vasculitis have developed in patients with rash. Although these events occur

rarely, they could be serious and involve the lung, kidney or liver. Death, has been reported to occur in association with these systemic events.

Anaphylactoid events including bronchospasm, angioedema, and urticaria alone and in combination have been reported. Pulmonary events such as inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

It is not known whether these systemic events and rash have a common underlying cause or are due to different aetiologies or pathogenic processes. In addition, a specific underlying immunologic cause for these events has not been found. If a rash or other possibly allergic phenomena appear for which there is no alternative explanation, RIVA-FLUOXETINE should be discontinued. Particular caution should be exercised in patients with a history of allergic reactions.

Implications of the Long Elimination Half-Life of FLUOXETINE:

Due to the long elimination half-lives of FLUOXETINE and its major active metabolite, norFLUOXETINE, alterations in dosage will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and discontinuation of therapy (see ACTIONS AND DOSAGE AND ADMINISTRATION). Even when treatment is withdrawn, the active drug will remain in the body for weeks because of the long elimination half-lives of FLUOXETINE and norFLUOXETINE. This is of potential consequence when discontinuation is desired or when drugs are to be administered which may interact with either FLUOXETINE or the active metabolite following discontinuation of RIVA-FLUOXETINE.

PRECAUTIONS

Anxiety and Insomnia:

In premarketing investigations, anxiety, nervousness and insomnia occurred in 10 to 15% of the patients treated with FLUOXETINE. These effects required discontinuation of the drug in 5% of the patients.

Weight Change:

Significant weight loss, especially in underweight depressed patients and the elderly, may be an undesirable result of treatment with FLUOXETINE.

Mania/Hypomania:

In the premarketing trials carried out in a patient population composed mainly of unipolar depressives, hypomania or mania occurred in about 1% of patients given FLUOXETINE. The frequency of these events in a general patient population which might include bipolar depressives is unknown. The possibility of hypomanic or manic episodes may be greater with higher doses. Such reactions require a reduction in dosage or discontinuation of the drug.

Seizures:

RIVA-FLUOXETINE (FLUOXETINE hydrochloride) should be used with caution in patients with a history of convulsive disorders. The frequency of seizures occurring during clinical trials of FLUOXETINE was not different from that reported with other

marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials.

Simultaneous administration of FLUOXETINE with electroshock therapy should be avoided due to the lack of experience in this area. Prolonged seizures have occurred rarely in patients taking FLUOXETINE and receiving ECT treatment.

Hypokalemia:

Self-induced vomiting often leads to hypokalemia which may lower seizure threshold and/or may lead to cardiac conduction abnormalities. Electrolyte levels of bulimic patients should be assessed prior to initiation of treatment.

Suicide:

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Thus, those patients with a greater probability for attempting suicide should be watched closely while on therapy and the possible requirement for hospitalisation should be considered. In order to minimise the opportunity for overdose, the smallest amount of drug necessary for good patient management should be prescribed at any one time. **(**see **WARNINGS**: **POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**

Concomitant Illness:

RIVA-FLUOXETINE should be used cautiously in patients with systemic illness especially those with diseases or conditions affecting metabolism or hemodynamic responses since clinical data regarding these patients is limited.

RIVA-FLUOXETINE has not been tested or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Such patients were systematically excluded from premarketing clinical trials. Retrospective analysis of EKG's in some of these trials found no conduction abnormalities that resulted in heart block. The mean heart rate was lowered by about 3 beats/minute.

FLUOXETINE should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (eg. co-morbid depression) markedly outweigh the potential weight reducing effect of the drug.

In diabetic patients, FLUOXETINE could affect glycemic control. Hypoglycaemia has been reported during FLUOXETINE treatment and hyperglycaemia has developed following termination of treatment. As with many other types of drugs, insulin and/or oral hypoglycaemic dosage adjustment may be necessary in diabetic patients when FLUOXETINE therapy is begun or terminated.

FLUOXETINE is extensively metabolised, excretion of unchanged drug in urine is a minor route of elimination. Until sufficient data has been collected from patients with severe renal impairment receiving chronic FLUOXETINE therapy, the drug should be used cautiously in such patients.
Since clearances of FLUOXETINE and norFLUOXETINE may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients.

<u>Hyponatremia:</u>

Several instances of hyponatremia have occurred (some with serum sodium levels less than 110 mmol/L). The hyponatremia appears to be reversible upon termination of FLUOXETINE treatment. Although these cases were complex with many different possible aetiologies, it is possible that some were due to the syndrome of inappropriate

antidiuretic hormone secretion (SIADH). Most of these cases have been in older patients and in patients receiving diuretics or who were otherwise volume depleted.

In a placebo-controlled, double-blind trial in elderly patients, 10 of 313 FLUOXETINE-treated patients and 6 of 320 placebo-treated patients had a lowering of serum sodium below the reference range. The lowest observed concentration of sodium in a FLUOXETINE treated patient was 129 mmol/L.

Platelet Function:

Rare cases of altered platelet function and/or abnormal results from laboratory studies have been reported in patients receiving FLUOXETINE. Though abnormal bleeding has been reported in several patients taking FLUOXETINE it is not certain whether this was due to FLUOXETINE.

Cognitive and Motor Performance:

Patients should be advised against driving automobiles or performing hazardous tasks until they are quite sure that RIVA-FLUOXETINE does not cause any adverse effects.

Use in Pregnancy and Lactation:

The safe use of FLUOXETINE in pregnant or lactating women has not been determined. Thus, FLUOXETINE should be avoided by women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the foetus or child.

In a sample of breast milk, the concentration of FLUOXETINE plus norFLUOXETINE was measured to be 70.4 ng/mL. The concentration in the mother's plasma was 295.0

ng/mL. No adverse effects on the infant were noted. In another case , a 6 week infant, nursed by a mother on FLUOXETINE , developed crying, decreased sleep, vomiting and watery stools. The breast milk showed concentrations of 69 ng/mL for FLUOXETINE and 90 ng/mL for norFLUOXETINE. In the infant's plasma, the concentrations of FLUOXETINE and norFLUOXETINE were 340 and 208 ng/mL, respectively.

Use in Children:

The safe and effective use of FLUOXETINE in patients under 18 years of age has not been determined.

Use in the Elderly:

Evaluation of patients over the age of 60 who received FLUOXETINE 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are however insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs.

Drug Interactions:

The concomitant use of RIVA-FLUOXETINE and MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

There have been greater than 2 fold increases of previously stable plasma levels of other antidepressants when FLUOXETINE has been administered in combination with these agents.

There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with FLUOXETINE. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Five patients receiving FLUOXETINE in combination with tryptophan experienced adverse reactions including agitation, restlessness and gastrointestinal distress.

The half-life of concurrently administered diazepam may be prolonged in some patients. Experience with the use of FLUOXETINE in combination with other CNS-active drugs is limited and caution is advised if such concomitant medication is required (see WARNINGS).

Phenytoin: In patients on stable, maintenance doses of phenytoin, plasma phenytoin concentrations increased substantially and symptoms of phenytoin toxicity appeared (nystagmus, diplopia, ataxia, and CNS depression) following initiation of concomitant FLUOXETINE treatment.

Drugs tightly bound to plasma protein: FLUOXETINE is highly plasma protein bound and thus the concomitant use of FLUOXETINE with another drug which is tightly bound to protein (e.g. warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound FLUOXETINE by other tightly bound drugs.

P450 Isozyme (IID6):

Like other selective serotonin reuptake inhibitors, FLUOXETINE inhibits the specific hepatic cytochrome P450 isozyme (IID6) which is responsible for the metabolism of

debrisoquine and sparteine. Although the clinical significance of this effect has not been established, inhibition of IID6 may lead to elevated plasma levels of co-administered drugs which are metabolised by this isozyme. Drugs metabolised by cytochrome P450IID6 include the tricyclic antidepressants (eg. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (eg. perphenazine and thioridazine), and Type IC antiarrhythmics (eg. propafenone and flecainide).

Dependence Liability:

The potential for abuse, tolerance or physical dependence to FLUOXETINE has not been investigated in animals or humans. Therefore, physicians should carefully evaluate patients for history of drug abuse and monitor these patients closely, checking for signs of misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

ADVERSE REACTIONS

In clinical trials, the most frequently observed adverse effects related to the use of FLUOXETINE and occurring at a higher incidence than with the use of placebo were: central nervous system effects such as headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or light-headedness; gastrointestinal effects such as nausea, diarrhoea, dry mouth and anorexia; and excessive sweating. FLUOXETINE treatment had to be terminated in 15% of about 4000 patients in North American clinical trials because of adverse effects. The most common causes for withdrawing treatment were: psychiatric (5.3%), mainly nervousness, anxiety, and insomnia; digestive (3.0%), mainly nausea; nervous system (1.6%), mainly dizziness, asthenia, and headaches; skin (1.4%), mainly rash and pruritis.

In obsessive compulsive disorder studies, 12.1% of FLUOXETINE treated patients discontinued treatment early because of adverse events. Anxiety, and rash, at incidences of less than 2%, were the most frequently reported events. In bulimia nervosa studies, 10.2% of FLUOXETINE treated patients discontinued treatment early because of adverse events. Insomnia, anxiety and rash, at incidences of less than 2%, were the most frequently reported events.

Serious Adverse Reactions:

Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double blind clinical trials in patients with major depressive disorder compared FLUOXETINE (n=1765) with a tricyclic antidepressant

(n=731) or placebo (n=569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for FLUOXETINE, 2.6% for placebo, and 3.6% for tricyclic antidepressants. In countries where the drug is presently marketed, the following potentially serious adverse effects have been observed; interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life threatening effects have been linked to some of these reactions, though a definite association with FLUOXETINE has not been determined.

Adverse Experience Reports:

The pattern of treatment-emergent adverse experience incidence (≥5%) for both FLUOXETINE and placebo was somewhat different in bulimia and obsessive compulsive disorder trials than in the adult and elderly depression studies, and is summarised below:

	Percentage of Patients Reporting Event							
	DEPRESSION (Adults)		DEPRESSION (Elderly)		OCD		BULIMIA	
Body System/ Adverse Event	Fluoxetin (N=1730)	Placebo (N=799)	FLUOXETINE (N=335)	Placebo (N=336)	FLUOXETINE (N=264)	Placebo (N=89)	FLUOXETINE (N=418)	Placebo (N=210)
Nervous								
Headache	20.3	15.5	27.5	23.8	32.6	23.6	30.1	26.9
Nervousness	14.9	8.5	12.2	7.4	14.4	14.6	10.8	5.2
Insomnia	13.8	7.1	18.2	12.5	29.6	22.5	33.1	15.0
Somnolence	11.6	6.3	9.3	5.7	17.1	6.7	12.7	7.1
Anxiety	9.4	5.5	13.1	8.0	13.6	6.7	16.3	11.1
Tremor	7.9	2.4	7.8	3.9	9.1	1.1	13.7	2.0
Dizziness	5.7	3.3	11.0	10.1	13.3	11.2	11.4	5.4
Libido, decreased	1.6	–	–	–	11.4	2.3	5.9	0.9
Depression	–	–	–	–	8.0	14.6	10.1	16.4
Emotional lability	–	–	–	–	–	–	2.7	7.8
Digestive								
Nausea	21.1	10.1	16.7	7.4	26.5	13.5	29.7	13.5
Diarrhoea	12.3	7.0	14.3	8.9	18.2	13.5	7.5	6.7
Dry mouth	9.5	6.0	6.6	4.8	12.1	3.4	9.9	8.6
Anorexia	8.7	1.5	10.7	1.8	16.7	10.1	8.8	4.4
Dyspepsia	6.4	4.3	11.0	5.1	9.9	4.5	10.7	6.7
Gastrointestinal disorder	–	–	–	–	5.7	1.1	5.7	5.9
Constipation	–	–	6.9	6.3	4.2	6.7	4.8	4.6
Flatulence	–	–	7.2	2.4	3.4	5.6	–	–
Skin and Appendages								
Sweating, excessive	8.4	3.8	7.2	3.3	7.2	–	8.9	1.6
Rash	–	–	–	–	6.4	3.4	5.1	4.9
Body as a Whole								
Asthenia	4.4	1.9	12.8	10.1	15.2	10.1	21.7	9.6
Flu syndrome	–	–	–	–	9.9	6.7	10.1	5.9

Back Pain	–	–	6.9	8.6	2.7	5.6	3.9	7.0
Infection	–	–	–	–	–	–	6.2	6.2
Abdominal Pain	–	–	6.0	5.7	4.9	11.2	9.6	6.5
Myalgia	–	–	3.3	5.4	–	–	4.7	9.4
Respiratory								
Upper respiratory infection	7.6	6.0	–	–	–	–	–	–
Rhinitis	–	–	9.0	14.3	22.7	23.6	23.0	29.1
Pharyngitis	–	–	–	–	10.6	9.0	11.1	5.5
Sinusitis	–	–	3.3	6.8	–	–	5.7	6.9
Yawn	–	–	–	–	7.2	–	11.1	0.8
Cardiovascular								
Vasodilatation	–	–	–	–	5.3	–	–	–
Urogenital								
Menstrual disorder	–	–	–	–	3.4	5.6	8.3	4.8
Dysmenorrhea	–	–	–	–	3.4	5.6	6.1	7.8
Urinary frequency	–	–	–	–	–	–	6.2	1.6
Urinary tract infection	–	–	–	–	–	–	5.1	2.0

The following adverse reactions, were reported on at least one occasion by patients during treatment with FLUOXETINE either during clinical trials or after marketing. All reported events are included except those where a drug cause was remote or the event term so general as to be unhelpful. Multiple events may have been reported by a single patient and related to a single condition, which may have pre-existed. Therefore, while the following events occurred during treatment with FLUOXETINE, they were not necessarily caused by it.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 but at least 1/1000 patients, rare events are those occurring in less than 1/1000 patients.

Allergic or Toxic:

Frequent: rash, pruritus.

Infrequent: chills and fever, urticaria, maculopapular rash.

Rare: allergic reaction, erythema multiforme, vesiculobullous rash, serum sickness, contact dermatitis, erythema nodosum, purpuric rash, leukocytoclastic vasculitis, leukopenia, thrombocytopenia, arthralgia, angioedema, bronchospasm, lung fibrosis, allergic alveolitis, larynx oedema, respiratory distress.

Neurologic:

Frequent: headache, tremor, dizziness or light-headedness, asthenia.

Infrequent: abnormal gait, ataxia, akathisia, buccoglossal syndrome, hyperkinesia, hypertonia, incoordination, neck rigidity, extrapyramidal syndrome, convulsions,

photophobia, myoclonus, vertigo, migraine, tinnitus, hypesthesia, neuralgia, neuropathy, acute brain syndrome.

Rare: dysarthria, dystonia, torticollis, decreased reflexes, nystagmus, paralysis, paresthesia, carpal tunnel syndrome, stupor, coma, abnormal electroencephalogram, chronic brain syndrome, dyskinesia and other movement disorders (including worsening of pre-existing conditions or appearance in patients with risk factors [eg. Parkinson's disease, treatment with neuroleptics or other drugs known to be associated with movement disorders]), neuroleptic malignant syndrome-like events.

Behavioural:

Frequent: insomnia, anxiety, nervousness, agitation, abnormal dreams, drowsiness and fatigue.

Infrequent: confusion, delusions, hallucinations, manic reaction, paranoid reaction, psychosis, depersonalisation, apathy, emotional lability, euphoria, hostility, amnesia, increased libido.

Rare: antisocial reaction, hysteria, suicidal ideation, and violent behaviours.

Autonomic:

Frequent: excessive sweating

Infrequent: dry mouth, constipation, urinary retention, vision disturbance, diplopia, mydriasis, hot flushes.

Cardiovascular:

Infrequent: chest pain, hypertension, syncope, hypotension (including postural hypotension), angina pectoris, arrhythmia, tachycardia.

Rare: bradycardia, ventricular arrhythmia, first degree AV block, bundle branch block, myocardial infarct, cerebral ischemia, cerebral vascular accident, thrombophlebitis.

Gastrointestinal:

Frequent: nausea, disturbances of appetite, diarrhoea.

Infrequent: vomiting, stomatitis, dysphagia, eructation, esophagitis, gastritis, gingivitis, glossitis, melena, thirst, abnormal liver function tests.

Rare: bloody diarrhoea, hematemesis, g.i. haemorrhage, duodenal ulcer, stomach ulcer, mouth ulceration, hyperchlorhydria, colitis, enteritis, cholecystitis, cholelithiasis, hepatitis, hepatomegaly, liver tenderness, jaundice, increased salivation, salivary gland enlargement, tongue discoloration, faecal incontinence, pancreatitis.

Respiratory:

Frequent: bronchitis, rhinitis, yawn.

Infrequent: asthma, dyspnea, hyperventilation, pneumonia, hiccups, epistaxis.

Rare: apnea, lung oedema, hypoxia, pleural effusion, hemoptysis.

Endocrine:

Frequent: weight loss

Infrequent: generalised oedema, peripheral oedema, face oedema, tongue oedema, hypoglycaemia, hypothyroidism, weight gain.

Rare: dehydration, gout, goitre, hyperthyroidism, hypercholesterolemia, hyperglycaemia, hyperlipidemia, hyperprolactinemia, hypokalemia, hyponatremia, iron deficiency anaemia, syndrome of inappropriate ADH secretion.

Haematological:

Infrequent: anaemia, lymphadenopathy, haemorrhage.

Rare: bleeding time increased, leukocytosis, lymphocytosis, thrombocytopenia, thrombocytopenic purpura, thrombocythemia, retinal haemorrhage, petechia, purpura, sedimentation rate increased, aplastic anaemia, pancytopenia, immune-related haemolytic anaemia.

Dermatological:

Infrequent: acne, alopecia, dry skin, herpes simplex.

Rare: excema, psoriasis, seborrhea, skin hypertrophy, skin discoloration, herpes zoster, fungal dermatitis, hirsutism, ecchymoses.

Musculoskeletal:

Frequent: muscle pain, back pain, joint pain.

Infrequent: arthritis, bone pain, bursitis, tenosynovitis, twitching.

Rare: bone necrosis, osteoporosis, pathological fracture, chondrodystrophy, myositis, rheumatoid arthritis, muscle haemorrhage.

Urogenital:

Frequent: painful menstruation, sexual dysfunction, impotence, urinary tract infection, frequent micturition.

Infrequent: abnormal ejaculation, menopause, amenorrhea, menorrhagia, ovarian disorder, vaginitis, leukorrhea, fibrocystic breast, breast pain, cystitis, dysuria, urinary urgency, urinary incontinence.

Rare: breast enlargement, galactorrhea, abortion, dyspareunia, uterine spasm, vaginal haemorrhage, metrorrhagia, hematuria, albuminuria, polyuria, pyuria, epididymitis, orchitis, pyelonephritis, salpingitis, urethritis, kidney calculus, urethral pain, urolithiasis.

Miscellaneous:

Frequent: chills, abnormal vision.

Infrequent: amblyopia, conjunctivitis, cyst, ear pain, eye pain, jaw pain, neck pain, pelvic pain, hangover effect, malaise.

Rare: abdomen enlarged, blepharitis, cataract, corneal lesion, glaucoma, iritis, ptosis, strabismus, deafness, taste loss, moniliasis, hydrocephalus, LE syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSE

During clinical trials, there were two deaths among approximately 38 reports of acute overdose with FLUOXETINE, either alone or in combination with other drugs and/or

alcohol. One death involved a combined overdose with approximately 1800 mg of FLUOXETINE and an undetermined amount of maprotiline. Plasma concentrations of FLUOXETINE and maprotiline were 4.57 mg/L and 4.18 mg/L, respectively.

A second death involved 3 drugs yielding plasma concentrations as follows: FLUOXETINE, 1.93 mg/L; norFLUOXETINE, 1.10 mg/L; codeine, 1.80 mg/L; temazepam, 3.80 mg/L.

One other patient who reportedly took up to 3000 mg of FLUOXETINE experienced two grand mal seizures that remitted spontaneously without specific treatment. Since vomiting occurred, the amount of drug absorbed may have been less than that ingested.

In the postmarketing phase, there have been 16 confirmed reports of overdose of FLUOXETINE taken alone. The amount of drug ingested has varied from 80 mg to 2000 mg and the patients have ranged in age from 13 to 51 years. There have been no deaths in this group of patients, some of whom were treated vigorously with activated charcoal in the acute phase. Furthermore, patient recoveries were remarkable in the absence of serious adverse events with the exception of a 13 year old male who ingested 1880 mg and experienced two brief seizures but thereafter had an uneventful recovery.

Since introduction, reports of death attributed to overdose of FLUOXETINE alone have been rare.

Symptoms: Nausea and vomiting were prominent in overdoses involving higher FLUOXETINE doses. Other prominent symptoms of overdose included agitation, restlessness, hypomania, and other signs of CNS excitation, including seizures.

Treatment: Establish and maintain an airway; insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Based on experience in animals, which may not be relevant to humans, FLUOXETINE-induced seizures which fail to remit spontaneously may respond to diazepam.

There are no specific antidotes for FLUOXETINE.

Due to large volume of distribution of FLUOXETINE, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit.
In managing overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

RIVA-FLUOXETINE (fluoxetine) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)

Since it may take up to four or five weeks to reach steady-state plasma levels of RIVA-FLUOXETINE (FLUOXETINE hydrochloride), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions.

DEPRESSION:

Initial Adult Dosage: The usual initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited.

Use in the Elderly: FLUOXETINE was evaluated in depressed elderly patients only at a dosage of 20 mg/day. A lower or less frequent dosage may be effective and should be considered in elderly patients with concurrent disease or on multiple medications.

Use in Children: The safety and effectiveness of RIVA-FLUOXETINE in patients below the age of 18 years have not been established.

BULIMIA NERVOSA:

Adult Dosage: The recommended dosage is 60 mg per day, although studies show that lower doses may also be efficacious. Electrolyte levels should be assessed prior to initiation of treatment.

OBSESSIVE-COMPULSIVE DISORDER:

A dose range of 20 mg/day to 60 mg/day is recommended for the treatment of obsessive compulsive disorder.

For any indication, the total FLUOXETINE dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited.

During maintenance therapy, the dosage should be kept at the lowest effective level.

Children:

(see **WARNINGS** :**POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM**).

A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications.

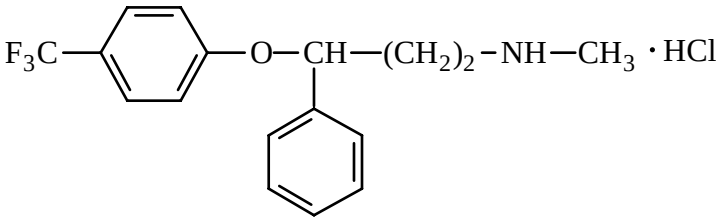
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: FLUOXETINE Hydrochloride

Chemical Name: (±)–N–methyl–3–phenyl–3–[(□,□,□–trifluoro–p–tolyl)–oxy]–propylamine hydrochloride.

Structural Formula:



Molecular Formula: $C_{17}H_{18}F_3NO$•HCl Molecular Weight: 345.79

Description: FLUOXETINE hydrochloride is a white to off–white almost odourless powder. It is freely soluble in methanol and in ethanol; soluble in chloroform; sparingly soluble in isopropanol; slightly soluble in water; practically insoluble in toluene, benzene and ethyl acetate. It has a melting point ranging from 153–159°C. pH=5.0-7.0 (0.5% solution)

NONMEDICINAL INGREDIENTS:

10 mg capsules: starch, sodium carboxymethyl starch, colloidal silicon dioxide, and magnesium stearate. The capsule shell contains gelatin, sodium lauryl sulphate, silicon dioxide, titanium dioxide, FD&C yellow #6, FD&C blue #1, and D&C yellow #10.

20 mg capsules: starch, sodium carboxymethyl starch, colloidal silicon dioxide, and magnesium stearate. The capsule shell contains gelatin, sodium lauryl sulphate, silicon dioxide, titanium dioxide, FD&C yellow #6, and D&C yellow #10.

STABILITY AND STORAGE RECOMMENDATIONS:

Bottles should be stored between 15–30°C and protected from light. Unit dose boxes should be kept between 15–25°C and protected from high humidity and light.

AVAILABILITY OF DOSAGE FORMS

RIVA-FLUOXETINE (FLUOXETINE hydrochloride) is available as:

10 mg: hard gelatin capsules with opaque green cap and opaque green body, imprinted with black ink **RIVA** on cap and **10** on body containing 10 mg of FLUOXETINE. Bottles of 100, 500, and 1000 and boxes of 100 as unit dose strips.

20 mg: hard gelatin capsules with opaque ivory cap and opaque ivory body, imprinted with black ink **RIVA** on cap, **20** on body, containing 20 mg of FLUOXETINE. Bottles of 100, 500 and 1000 and boxes of 100 as unit dose strips.

PHARMACOLOGY

In vitro and *in vivo* studies have shown FLUOXETINE and norFLUOXETINE (the active, primary metabolite) to be potent and selective neuronal pre–synaptic reuptake blockers of serotonin. The main mechanism of deactivation of serotonin released into the synaptic cleft by a nerve impulse is reuptake into the presynaptic nerve ending where it is metabolised or retained in storage granules. FLUOXETINE specifically blocks reuptake, thus allowing serotonin to be present in the synaptic cleft for a longer period and enhancing the activity of the neurotransmitter on post-synaptic receptors. FLUOXETINE has a low affinity for various receptor systems in receptor binding studies.

Several behavioural, neuroendocrinologic, and other pharmacological effects of FLUOXETINE in experimental animals have been credited to its potentiation of serotonergic function by inhibition of serotonin uptake. FLUOXETINE restored the capacity for acquisition of passive avoidance task in olfactory bulbectomized rats and enhanced 5–HT–induced head twitch in mice. FLUOXETINE suppressed REM sleep in rats and cats, and reduced the amount or changed the composition of dietary intake in rats. It also selectively decreased non–protein caloric intake in rats.

Few pharmacological actions of FLUOXETINE other than blockade of serotonin uptake and consequences of that inhibition have been demonstrated. FLUOXETINE does not antagonise reserpine– or apomorphine–induced hypothermia in mice nor does it decrease the immobility in the forced swimming test in rats.

Pharmacokinetics:

FLUOXETINE was well absorbed orally and the oral bioavailability of FLUOXETINE in dogs was 72%. In dogs given oral doses of 1 to 10 mg/kg FLUOXETINE for one year, dose dependent increases in FLUOXETINE and norFLUOXETINE concentrations were observed in liver, adrenal, and lung.

NorFLUOXETINE concentrations exceeded FLUOXETINE concentrations in the tissues, and persisted for a longer period in plasma.

In rats, after a single i.p. dose of 10 mg/kg, the plasma half-life of FLUOXETINE was 26 hours and that of norFLUOXETINE, 40 hours. The plasma half-life in dogs dosed orally at 5 to 10 mg/kg for 15 days, was 1 day for FLUOXETINE and 2.1 to 5.4 days for norFLUOXETINE.

In vitro FLUOXETINE was N-demethylated to norFLUOXETINE by rat, guinea pig, and rabbit liver microsomes. *In vivo,* FLUOXETINE was N-demethylated to norFLUOXETINE by rat, guinea pig, and rabbit liver microsomes. *In vivo* FLUOXETINE was metabolised mainly by N-demethylation in mice, rats, guinea pigs, rabbits, and dogs. The other major metabolite was p-trifluoromethylphenol, formed by O-dealkylation, which was excreted as a sulphate or glucuronide conjugate by rats, guinea pigs, and dogs.

FLUOXETINE and norFLUOXETINE were also excreted in the urine unchanged in guinea pigs, rabbits, and dogs. In rats, FLUOXETINE and norFLUOXETINE were both further metabolised, so that neither FLUOXETINE nor its N-demethylated

metabolite was found in the urine. Rats eliminated 16 to 42 percent of the dose in urine as p-trifluoromethylphenol and 8 percent of the dose as hippuric acid in 24 hours.

TOXICOLOGY

Acute Toxicity:

Species	Route of NorFLUOXETINE Administration	Sex	FLUOXETINE LD_{50} (mg/kg)	LD_{50} (mg/kg)
Mouse	p.o.	F	248	361
	i.v.	F	45	42
Rat	p.o.	M	467	
		F	437	
	i.v.	M	35	
		F	35	37
Guinea Pig	p.o.	M	> 250	
Cat	p.o.	M/F	> 50	
Dog	p.o.	M/F	> 100	
Monkey	p.o.	M/F	> 50	

Signs of toxicity included vomiting, anorexia, mydriasis, salivation, tremors, clonic convulsions and hyperirritability and cachexia.

Long-Term Toxicity:

Mice (5/sex/dose) were given diets containing 25, 59 and 204 mg/kg/day FLUOXETINE for 15 days. Thirty and 100% mortality were observed with the mid– and high dose, respectively. Other significant effects occurring at the two highest

doses were hyperactivity and body weight loss, reduction in spleen weights and phospholipidosis.

In another study, mice (5/sex/group) were kept on diets containing equivalent to 2, 7 or 31 mg/kg/day FLUOXETINE for 3 months. Significant effects occurred in the high dose group including mortality, persistent hyperactivity, reduced body weight gain, slight and reversible increases in alkaline phosphatase and alanine transaminase, hypospermatogenesis, and pulmonary phospholipidosis.

In rats fed a diet which contained average doses of approximately 9, 25 or 74 mg/kg/day for 3 months, the main pathological observation was pulmonary histocytosis (phospholipidosis). All animals at 74 mg/kg/day died by week 8. Reduced food consumption, weight loss, and hyperirritability were observed in the 25 mg/kg/day dose group.

Dogs given 5 to 50 mg/kg/day p.o. for two weeks experienced anorexia, mydriasis and vomiting. Dogs in the 50 mg/kg/day group displayed ataxia, tremors and a convulsion in one dog.

Dogs survived oral doses up to 20 mg/kg/day for three months. The main effect noted was anorexia. Significant accumulation of both FLUOXETINE and norFLUOXETINE occurred in the plasma and tissues. Mydriasis and tremors were observed during the first month.

Monkeys given 10 or 25 mg/kg/day FLUOXETINE orally for 2 weeks were seen to experience anorexia and weight loss. One monkey receiving the high dose experienced clonic convulsions after six doses. A reduction in erythrocyte and white blood cell count was also demonstrated.

FLUOXETINE was given to rats (25/sex/dose) in a diet containing levels of 0.5, 2.3 and 10.7 mg/kg/day. Physical signs of toxicity were seen only in the females receiving the high dose and included anorexia, chromodacryorrhea and a strange behaviour in which the animals walked on their toes with extended feet and arched backs after they had been handled.

Phospholipidosis was apparent in the lung, liver and adrenal cortex of animals receiving 10 mg/kg/day and in a few rats receiving lower doses. This condition disappeared two months after termination of treatment. Minimal to slight fat deposition in the liver occurred at all dose levels. Minimal reticuloendothelial cell hyperplasia occurred in the lymph nodes of the animals in all dose groups. This effect was also reversible.

Dogs (5/sex/dose) received oral doses of 1, 4.5, or 20 mg/kg/day of FLUOXETINE for one year. The highest dose was reduced to 10 mg/kg/day after 6 months when 3 females died. The toxicity symptoms were similar to those seen in the subchronic study except that phospholipidosis occurred in the lung, liver, adrenals, the inner plexiform layer of the retina, lymph nodes, spleen, and peripheral leukocytes in the animals receiving the high dose. There was also moderate bradycardia and a decrease in adrenal weight.

Phospholipidosis was only observed in the lung and leukocytes in a few of the dogs at the lowest dose level of 1.0 mg/kg/day. No cardiovascular effects were seen apart from a slight decrease in basal heart rate. All treatment-related effects were reversible during the recovery period in surviving animals.

Carcinogenicity:

Rats were kept on diets containing a time–weighted average dose of 0.45, 2 and 9 mg/kg/day FLUOXETINE for two years. Age-related observations such as chromodacryorrhea, alopecia, and poor grooming increased at the high dose, particularly in females. Weight gain and food consumption were decreased in the high dose group and a handling–induced behaviour involving arching of the back and walking on toes was noted mainly in the females of this group. Increased tissue levels of FLUOXETINE and norFLUOXETINE were observed at all doses, and phospholipidosis was noted mainly in the high dose group. The incidence of tumour or animal mortality was not significantly higher at any dose level.

Mice were given diets containing equivalent to 1.2, 4.8, and 12.1 mg/kg/day FLUOXETINE for 2 years. High mortality occurred in females receiving the high dose early in the two year study, necessitating lowering the dose after 30 days. The survival rate of females receiving the high dose was reduced at two years. No major toxicological effects were seen in mice other than a moderate increase in alanine transaminase in males receiving the high dose and slight changes in organ weights. Hepatocellular degeneration, fat deposition in liver, and centrilobular hepatocellular degeneration, fat deposition in liver, and centrilobular hepatocellular degeneration were observed microscopically at the mid and high doses. There was no sign of phospholipid accumulation in the lung, and no oncogenic effects were noted.

Another two–year mouse study using similar doses produced similar results. Survival at two years was reduced in females receiving the high dose. Handling–

induced clonic convulsions occurred at all dose levels. Minimal to moderate alterations of fat in the liver and hepatocellular cytomegaly occurred in mice in the mid and high dose levels. No phospholipid accumulation in the lung and no oncogenic responses were observed.

Mutagenicity:

The mutagenicity of FLUOXETINE and norFLUOXETINE was tested in a series of *in vitro* and *in vivo* tests such as the Ames test, the modified Ames test, DNA repair in rat hepatocytes, sister Chromatid exchange in Chinese hamster bone marrow assays, and mouse lymphoma assay. FLUOXETINE and norFLUOXETINE were negative in all 5 systems.

Teratology Studies:

Virgin female Fisher 344 rats (25/dose) were bred with untreated control males and were given daily oral (gavage) doses of 2, 5, or 12.5 mg/kg/day FLUOXETINE on gestation days 6-15; animals were evaluated on gestation day 20. The high dose group showed a decrease in body weight gain and food consumption. There were no teratogenic effects or reproductive parameters due to FLUOXETINE.

Virgin female Dutch Belted rabbits (15/dose) were artificially inseminated with semen from untreated control males and were given daily oral (gavage) doses of 2.5, 7.5, or 15 mg/kg/day FLUOXETINE on gestation days 6-18. Maternal toxicity was evident in all groups as manifested by a decrease in body weight gain and food consumption. Two rabbits in the high dose group died and 3 aborted. There was also an increased incidence of resorptions in this group. No teratogenic effects were observed.

Reproductive Studies:

Female Wistar rats (30/dose) were given daily doses of 2, 5 or 12.5 mg/kg/day FLUOXETINE p.o. beginning before mating until the end of gestation or lactation. In another study, male Wistar rats were kept on diets containing FLUOXETINE in amounts approximately equivalent to 1.5, 3.9, or 9.7 mg/kg beginning before mating until the end of the breeding trial. These treated males were mated with female Wistar rats (40/dose) administered the same dietary levels beginning before mating until the end of lactation. In both studies, there was decreased survival of the neonates at the high dose level. There were no teratogenic effects or adverse effects on fertility or post–natal development related to FLUOXETINE.

Other Toxicity Studies:

Systemic phospholipidosis was caused by subchronic and/or chronic treatment with FLUOXETINE in mice, rats and dogs. This effect was related to the accumulation of norFLUOXETINE, and to a lesser extent, FLUOXETINE, in affected tissues. Systemic phospholipidosis was not linked with any adverse effects and was demonstrated to be reversible after chronic administration of FLUOXETINE for one year in rats and dogs. This effect has also been observed in animals with several other clinically useful cationic amphiphilic drugs such as antidepressants (e.g. imipramine), chlorphentermine, fenfluramine, amiodarone and ranitidine. The importance of this finding for humans is not known. It is hoped that in the clinical use of FLUOXETINE, the properties of the drug which result in phospholipidosis will not cause any adverse effects.

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