PRODUCT MONOGRAPH

NOVO–FLUVOXAMINE

(Fluvoxamine Maleate)

Tablets

Antidepressant/Antiobsessional Agent

Teva Canada Limited
Toronto, Canada

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THERAPEUTIC CLASSIFICATION

Antidepressant/Antiobsessional Agent

ACTION AND CLINICAL PHARMACOLOGY

The antidepressant and antiobsessional actions of fluvoxamine are believed to be related to its selective inhibition of presynaptic serotonin re-uptake in brain neurons.

There is minimum interference with noradrenergic processes and, in common with several other specific inhibitors of serotonin uptake, fluvoxamine has very little in vitro affinity for α_1, α_2, β_1, dopamine$_2$, histamine$_1$, serotonin$_1$,serotonin$_2$ or muscarinic receptors.

Pharmacokinetics

In healthy volunteers, fluvoxamine is well absorbed after oral administration. Following a single 100 mg oral dose, peak plasma levels of 31-87 ng/mL were attained 1.5 to 8 hours post-dose. Peak plasma levels and AUC's (0-72 hours) are directly proportionate to dose after single oral doses of 25, 50, and 100 mg.

Following single doses, the mean plasma half-life is 15 hours, and slightly longer (17-22 hours), during repeated dosing. Steady-state plasma levels are usually achieved within 10-14 days. The pharmacokinetic profile in the elderly is similar to that in younger patients.

Metabolism and Elimination

Fluvoxamine undergoes extensive hepatic transformation, mainly via oxidative demethylation, to at least nine metabolites, which are excreted by the kidney. Ninety-four percent of an oral radioactive dose is recovered in the urine within 48 hours. The two major metabolites showed negligible pharmacological activity. In vitro binding of fluvoxamine to human plasma proteins is about 77% at drug concentrations up to 4000 ng/mL.

A two-way, double-blind, single-dose, comparative, randomized bioavailability study was conducted in sixteen healthy male volunteers between two 100 mg fluvoxamine maleate tablet products under fasting conditions. The pharmacokinetic plasma data calculated for both NOVO-FLUVOXAMINE and Luvox® (Solvay Pharma Inc., Canada) tablets are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
FLUVOXAMINE MALEATE
(1 X 100 mg)
From measured data

	Geometric Mean Arithmetic Mean (C.V.%)		
	NOVO-FLUVOXAMINE	Luvox®*	Ratio of Geometric Means
AUC_T (ng□h/ml)	774.87 848.00 (54.03)	765.54 866.14 (62.27)	101
AUC_I (ng□h/ml)	819.66 892.40 (53.33)	833.52 893.70 (62.90)	98
C_{max} (ng/ml)	32.46 33.28 (28.64)	32.12 33.36 (35.05)	101
T_{max}** (h)	6.03 (29.11)	7.09 (31.44)	--
$T_{1/2}$** (h)	14.04 (18.52)	16.18 (19.36)	--

* Luvox® manufactured by Solvay Pharma Inc., Scarborough, ON, Canada.
**For T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

INDICATIONS

Depression

NOVO-FLUVOXAMINE may be indicated for the symptomatic relief of depressive illness.

The effectiveness of fluvoxamine in long-term use (i.e., for more than 5 to 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use fluvoxamine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Obsessive-Compulsive Disorder

Fluvoxamine has been shown to significantly reduce the symptoms of obsessive-compulsive disorder. 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 fluvoxamine has been studied in double-blind, placebo-controlled clinical trials conducted in obsessive-compulsive outpatients. The usefulness of fluvoxamine for long-term use (i.e. for more than 10 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use fluvoxamine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

NOVO-FLUVOXAMINE (fluvoxamine) is contraindicated in patients with known hypersensitivity to the drug.

Fluvoxamine should not be administered together with monoamine oxidase (MAO) inhibitors. At least two weeks should elapse after discontinuation of MAO inhibitor therapy before fluvoxamine treatment is initiated. MAO inhibitors should not be introduced within 2 weeks of cessation of therapy with NOVO-FLUVOXAMINE.

PRECAUTIONS

Seizures

Convulsions have been reported rarely during fluvoxamine administration. Caution is recommended when the drug is administered to patients with a history of seizures. If seizures occur during fluvoxamine administration, the drug should be discontinued.

ECT

Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area.

Hepatic Enzymes

Treatment with fluvoxamine has been rarely associated with increases in hepatic enzymes, usually accompanied by symptoms. Fluvoxamine administration should be discontinued in such cases.

Combination with Alcohol

Fluvoxamine may potentiate the effects of alcohol and increase the level of psychomotor impairment.

Cognitive and Motor Disturbances

Sedation may occur in some patients. Therefore, patients should be cautioned about participating in activities requiring complete mental alertness, judgement, and physical co-ordination - such as driving an automobile or performing hazardous tasks - until they are reasonably certain that treatment with NOVO-FLUVOXAMINE does not affect them adversely.

Suicide

The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high-risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for NOVO-FLUVOXAMINE should be written for the smallest quantity of drug consistent with good patient management.

Concomitant Illness

Fluvoxamine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies.

Use in Pregnancy and Lactation

Safe use of fluvoxamine during pregnancy and lactation has not been established. Therefore, it should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient outweigh the possible hazards to the child or fetus.

Use in Children

Safety and efficacy in children under 18 years of age have not been established.

Drug Interactions

Combined use of NOVO-FLUVOXAMINE and MAO inhibitors is contraindicated (see CONTRAINDICATIONS).

An increase in tricyclic antidepressant blood levels has also been reported in patients taking fluvoxamine concomitantly.

Lithium, and possibly tryptophan, may enhance the serotonergic effects of fluvoxamine; these combinations should therefore be used with caution.

Fluvoxamine may prolong the elimination of drugs which are metabolized by oxidation in the liver, and a clinically significant interaction is more likely when the second agent has a narrow therapeutic index, as is the case with warfarin, phenytoin, and theophylline. Such combinations should therefore be administered with caution, and consideration be given to lowering the dose of the second agent. In interaction studies, a 5-fold increase in plasma levels of propranolol and a 65% increase in warfarin plasma levels were seen during concurrent administration of fluvoxamine. An absence of pharmacokinetic interaction has been seen with digoxin and atenolol, which are not significantly metabolized in the liver.

Cytochrome P450 Isozyme (IID6)

Like other selective serotonin reuptake inhibitors, fluvoxamine 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 metabolized by this

isozyme. Drugs metabolized by cytochrome P450IID6 include the tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (e.g., perphenazine and thioridazine), and Type lC antiarrhythmics (e.g., propafenone and flecainide).

ADVERSE REACTIONS

Commonly Observed

In clinical trials, the most commonly observed adverse events associated with fluvoxamine administration, and not seen at an equivalent incidence among placebo-treated patients, were gastrointestinal complaints, including nausea (sometimes accompanied by vomiting), constipation, anorexia, diarrhea and dyspepsia; central nervous system complaints, including somnolence, dry mouth, nervousness, insomnia, dizziness, tremor and agitation; and asthenia. Abnormal (mostly delayed) ejaculation was frequently reported by patients with obsessive-compulsive disorder, primarily at doses over 150 mg/day.

Adverse Events Leading to Discontinuation of Treatment

Approximately 14% (14.4%) of 34,587 patients who received fluvoxamine in clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials included nausea and vomiting, insomnia, agitation, headache, abdominal pain, somnolence, dizziness, asthenia and anorexia. The most common events causing discontinuation in patients suffering from obsessive-compulsive disorder included insomnia, asthenia and somnolence.

Incidence of Adverse Experiences

Adverse events with an incidence of ≥ 5% reported in double-blind, placebo-controlled clinical trials in depression and in obsessive-compulsive disorder are presented in the following table for each indication.

Treatment-Emergent Adverse Experience Incidence (≥ 5%) in Placebo-Controlled Clinical Trials for Depression and Obsessive-Compulsive Disorder†

PERCENTAGE OF PATIENTS REPORTING EVENT				
	Depression		OCD	
Body System/Adverse Event	Fluvoxamine (N=222)	Placebo (N=192)	Fluvoxamine (N=160)	Placebo (N=160)
Nervous System				
Somnolence	26.2	9.0	26.9	9.4
Agitation	15.7	8.9	3.8	0
Insomnia	14.4	10.4	31.3	15.0
Dizziness	14.8	13.5	9.4	4.4
Tremor	10.8	4.7	8.1	0.6
Hypokinesia	8.1	3.6	--	--
Hyperkinesia	6.7	8.9	--	--
Depression	4.0	4.2	6.3	4.4
Nervousness	2.2	1.6	15.6	5.0
Anxiety	2.3	2.1	9.4	6.9
Libido Decreased	--	--	7.5	1.9
Thinking Abnormal	--	--	6.9	3.8
Digestive System				
Nausea	36.5	10.9	28.8	6.9
Dry Mouth	25.7	23.9	11.9	3.1
Constipation	18.0	6.8	14.4	8.8
Anorexia	14.9	6.3	5.0	3.1
Diarrhea	5.9	6.3	11.9	8.8
Dyspepsia	3.2	0	13.8	9.4
Body as a Whole				
Headache	21.6	18.7	20.0	23.8
Pain	5.9	3.7	4.4	1.3
Asthenia	4.9	3.2	28.8	9.4
Infection	--	--	11.3	9.4
Abdominal Pain	3.6	3.6	5.6	8.1
Flu Syndrome	--	--	5.0	3.8
Skin				
Sweating Increased	11.2	12.5	6.9	1.9
Respiratory System				
Pharyngitis	--	--	6.3	5.0
Rhinitis	1.3	2.6	5.6	1.9
Special Senses				
Accommodation Abnormal	6.3	6.3	--	--
Taste Perversion	3.2	3.1	5.0	0
Urogenital				
Urinary Frequency	2.2	1.6	5.0	1.3
Abnormal Ejaculation	1.4	0	17.9*	0

†Dosage titration at study initiation varied between the depression and OCD trials. In depression, fluvoxamine was administered: Day 1, 50 mg hs; Day 2, 100 mg; Day 3, 150 mg then titrated to response. In OCD, fluvoxamine was administered: Days 1-4, 50 mg; Days 5-8, 100 mg, Days 9-14, 150 mg then titrated to response.

*Corrected for gender (males: n=78).

During premarketing and postmarketing studies, multiple doses of fluvoxamine were administered to approximately 34,587 patients. All events with an incidence of >0.01% are listed, regardless of relation to drug, except those in terms so general as to be uninformative. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent (occurring on 1 or more occasions in at least 1/100 patients), infrequent (occurring in less than 1/100, but at least 1/1000 patients), or rare (occurring in less than 1/1000 but at least in 1/10,000 patients). Multiple events may have been reported by a single patient. It is important to emphasize that although the events reported did occur during treatment with fluvoxamine, they were not necessarily caused by it.

Nervous System

Frequent: Somnolence, insomnia, dizziness, nervousness, tremor, vertigo, thinking abnormal, agitation, anxiety.

Infrequent: Abnormal dreams, paraesthesia, amnesia, depression, vasodilatation, libido decreased, depersonalization, drug dependence, psychotic depression, akathisia, hallucinations, hypertonia, confusion, apathy, emotional lability, ataxia, abnormal gait, hostility, hyperkinesia, libido increased, hypokinesia, euphoria, manic reaction, neurosis, stupor, incoordination, hypesthesia, twitching, increased salivation.

Rare: Screaming syndrome, hypotonia, hemiplegia, myoclonus, delirium, convulsion, neuralgia, dysarthria, paranoid reaction, extrapyramidal syndrome, neuropathy, CNS neoplasia, akinesia, dyskinesia, paralysis, psychosis, CNS stimulation, coma, delusions, hyperesthesia,

hysteria, schizophrenic reaction, torticollis, trismus, dystonia, reflexes decreased.

Digestive System

Frequent: Nausea, vomiting, dyspepsia, constipation, diarrhea, anorexia, dry mouth.

Infrequent: Flatulence, dysphagia, increased appetite, eructation, gastroenteritis, gastritis, thirst, colitis.

Rare: Stomatitis, glossitis, hepatitis, esophagitis, fecal incontinence, gingivitis, jaundice, mouth ulceration, rectal hemorrhage, melena, tongue discoloration, tooth disorder, biliary pain, gastrointestinal carcinoma, gastrointestinal hemorrhage, hematemesis, liver function tests abnormal, tenesmus, tongue edema.

Cardiovascular System

Frequent: Palpitation

Infrequent: Syncope, angina pectoris, tachycardia, postural hypotension, hypotension, migraine, hypertension.

Rare: Arrhythmia, myocardial infarct, pallor, bradycardia, extrasystoles, hemorrhage, peripheral vascular disorder, cerebrovascular accident, shock.

Body as a Whole

Frequent: Asthenia, headache, abdominal pain, malaise.

Infrequent: Back pain, chills, chest pain, suicide attempt, fever, neck pain, infection, allergic reaction, accidental injury, pain, flu syndrome.

Rare: Overdose, face edema, hangover effect, abdomen enlarged, halitosis, neck rigidity, pelvic pain, hernia, chills and fever.

Skin

Frequent: Sweating increased.

Infrequent: Pruritus, rash.

Rare: Urticaria, acne, eczema, dry skin, alopecia, psoriasis, furunculosis, Herpes simplex, Herpes zoster, maculopapular rash.

Respiratory System

Infrequent: Dyspnea, pharyngitis, rhinitis.

Rare: Cough increased, yawn, epistaxis, hyperventilation, sinusitis, bronchitis, laryngismus, hiccup, pneumonia, asthma, laryngitis, voice alternation.

Special Senses

Infrequent: Taste perversion, tinnitus, amblyopia, abnormal vision, hyperacusis.

Rare: Conjunctivitis, abnormality of accommodation, taste loss, eye pain, lacrimation disorder, diplopia, dry eyes, mydriasis, ear pain, parosmia, deafness, photophobia, blepharitis.

Musculoskeletal System

Infrequent: Myalgia, arthralgia, myasthenia, tetany, arthrosis.

Rare: Leg cramps, rheumatoid arthritis, arthritis, bone pain, pathological fracture.

Urogenital System

Infrequent: Urinary frequency, impotence, dysuria, metrorrhagia, abnormal ejaculation, urinary incontinence.

Rare: Breast pain, urinary retention, urinary urgency, cystitis, nocturia, menorrhagia, anorgasmia, female lactation, vaginitis, amenorrhea, dysmenorrhea, urinary tract infection, hematuria, kidney pain, prostatic disorder, polyuria, leukorrhea.

Metabolic and Nutritional System

Frequent: Weight gain.

Infrequent: Weight loss, peripheral edema.

Rare: Alcohol intolerance, dehydration, obesity, edema.

Hematic and Lymph Systems

Rare: Ecchymosis, cyanosis, anemia, lymphadenopathy, thrombocytopenia.

Adverse Effects Following Discontinuation of Treatment

Symptoms, including headache, nausea, dizziness and anxiety, have been reported after discontinuation of other antidepressants, though rarely after abrupt discontinuation of fluvoxamine maleate.

Anecdotal spontaneous reports, from the marketplace, but not from clinical trials, have been collected for the following adverse experiences: angioedema, galactorrhoea, and photosensitivity.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

More than 300 cases of overdosage with fluvoxamine, alone or in combination with other compounds, have been reported. The most common symptoms of overdosage include gastrointestinal complaints (nausea, vomiting, and diarrhea), somnolence, and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions, and coma have also been reported. Among more than 300 patients reported to have taken deliberate overdoses of fluvoxamine, there have been 30 deaths, all but one of which occurred in patients who were confirmed to have taken multiple medications. The highest documented dose of fluvoxamine maleate ingested by a patient is 12 g; this patient recovered completely with symptomatic treatment only.

Treatment

There is no specific antidote to fluvoxamine. In situations of overdosage, the stomach should be emptied as soon as possible after tablet ingestion and symptomatic treatment initiated. The repeated use of medicinal charcoal is also recommended. Due to the large distribution volume of fluvoxamine, forced diuresis or dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

Depression

Adult Dosage: Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime, and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 200 mg, and should be adjusted

gradually according to the individual response of the patient, up to a maximum of 300 mg. Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. Tablets should be swallowed with water and without chewing.

Obsessive-Compulsive Disorder

Treatment should be initiated at the lowest possible dose (50 mg) given once daily at bedtime, and then increased to 100 mg daily at bedtime after a few days, as tolerated. The effective daily dose usually lies between 100 mg and 300 mg, and should be adjusted gradually according to the individual response of the patient, up to a maximum of 300 mg. If no improvement is observed within 10 weeks, treatment with NOVO-FLUVOXAMINE (fluvoxamine) should be reconsidered.

Dosage increases should be made in 50 mg increments. Doses above 150 mg should be divided so that a maximum of 150 mg is given in the bedtime dose. NOVO-FLUVOXAMINE (fluvoxamine) should be swallowed with water and without chewing.

Use in Hepatic or Renal Insufficiency:

Patients with hepatic or renal insufficiency should begin treatment with a low dose and be carefully monitored.

Use in Children:

The safety and effectiveness of fluvoxamine in children under 18 years of age have not been established.

Use in Geriatrics:

Since there is limited clinical experience in the geriatric age group, caution is recommended when administering fluvoxamine to elderly patients.

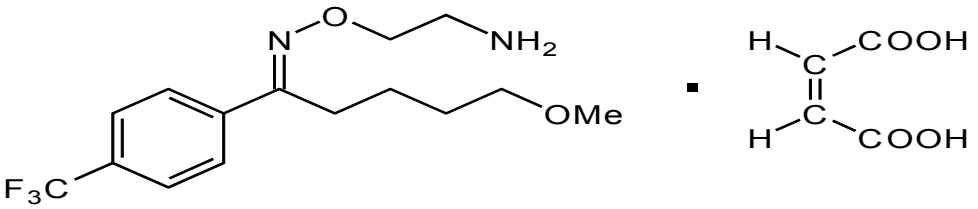
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Fluvoxamine Maleate

Chemical Name: 5-methoxy-4'-(trifluoromethyl)valerophenone(E)-O-(2-aminoethyl) oxime maleate (1:1)

Structural Formula:



Molecular Formula: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ Molecular Weight: 434.4

Description: White, odourless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether. The pKa is 8.7 and the pH is 4.5 in 0.1% aqueous solutions. The melting point is approximately 121°C.

COMPOSITION

Mannitol, corn starch, povidone, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methycellulose, polyethylene glycol, titanium dioxide, hydroxypropyl cellulose, talc, triethyl citrate, carnauba wax.

STABILITY AND STORAGE RECOMMENDATION

Store tablets in tightly closed containers between 15°C-30°C and protected from humidity.

AVAILABILITY OF DOSAGE FORMS

NOVO-FLUVOXAMINE is available as:

50 mg	-round, scored, white film-coated tablets, engraved '5|0' on the scored side and 'N' on the other side.
100 mg	-oval, scored, white film-coated tablets, engraved 'N|N' on the scored side and '100' of the other side.
Supplied:	Bottles of 100, 500 and 1 000 tablets.

PHARMACOLOGY

In a series of in vitro and animal in vivo experiments, fluvoxamine maleate demonstrated as its primary pharmacological effect, serotonin potentiating properties due to blockade of the membrane pump mechanism responsible for neuronal serotonin reuptake. Fluvoxamine was effective in inhibiting serotonin uptake by blood platelets and brain synaptosomes. The drug prevented serotonin depletion by tyramine derivatives through its membrane-pump inhibiting properties. As a result of this interference with the neuronal serotonin reuptake mechanism, fluvoxamine produced a decreased serotonin turnover in the brain. The effects of 5-hydroxytryptophan in mice and rabbits were potentiated. Fluvoxamine, in combination with MAO inhibitors (in rats together with tryptophan), induced serotonin-like behaviour in mice and rats. In receptor binding studies, fluvoxamine is practically devoid of affinity towards cholinergic, histaminergic, adrenergic, dopaminergic and serotonergic receptors.

In contrast with tricyclic antidepressants, fluvoxamine had no antihistaminic, sedative, MAO inhibiting or amphetamine-like stimulating activities in rats and cats. The drug had little effects on noradrenaline reuptake processes, and reserpine effects such as ptosis and hypothermia were only affected at high doses. Also, no stimulating effects were found when reserpine-like compounds were given after a dose of fluvoxamine.

Further indication of the serotonin potentiating properties of fluvoxamine was evidenced by its pharmacological effects in other animal studies. Fluvoxamine decreased REM sleep in rats and cats and reduced food consumption in rats. Intraperitoneal administration of 10 mg/kg to solitary cats did not induce a lysergic acid diethylamide (LSD)-type syndrome, but increased

activated behaviour.

Investigation of the parasympatholytic activity of fluvoxamine showed that the drug possesses very low affinity for muscarinic receptors in brain. The drug showed only a weak spasmolytic activity against carbachol-induced contraction of isolated guinea pig ileum, very little effect on pupil diameter and intestinal motility in mice, and did not antagonize oxotremorine-induced analgesia or pilocarpine-induced behavioural effects in mice, confirming that fluvoxamine is unlikely to cause anticholinergic effects at peripheral or central sites.

The ability of fluvoxamine maleate and other antidepressants to evoke epileptogenic electrographic signs (spindles and spikes) was evaluated in recordings taken from various regions of the brain of freely moving rats. Intravenous fluvoxamine, in doses up to 60 mg/kg, showed no tendency to induce seizures. In contrast, reference compounds including amitriptyline HCl and imipramine HCl produced serious epileptogenic responses at 10 mg/kg and seizures at 50 mg/kg.

The physical dependence liability of fluvoxamine was assessed and compared with diazepam following two 28-day periods of oral administration in monkeys. The results indicated that fluvoxamine at dose levels of 90 mg/kg twice daily has no physical dependence liability whereas diazepam in doses up to 20 mg/kg produced intermediate to severe dependence liability.

No serious effects on cardiovascular (and respiratory) parameters were observed after administration of fluvoxamine.

Oral fluvoxamine (25 mg/kg) did not affect blood pressure in hypertensive rats. Following an i.v. bolus injection in cats, a dose-dependent, transient blood pressure reduction was observed; infusions of fluvoxamine over 2 minutes did not influence blood pressure. On isolated rabbit hearts fluvoxamine caused coronary dilatation. Fluvoxamine affected contractility of guinea pig atria in vitro markedly less than tricyclic agents.

In conscious rabbits, ECG disturbances were only observed at nearly lethal doses. In dogs, the only ECG abnormality that was seen after intravenous fluvoxamine was a slight prolongation of the QT interval due to a reduction in heart rate at doses of 10 mg/kg or higher.

Combined administration of fluvoxamine with an MAO inhibitor (tranylcypromine sulfate) exacerbated serotonergic symptoms, and a potentiation of the depressant activity of benzodiazepines and butabarbital was found when these drugs were given in combination with fluvoxamine. With amphetamine, the interactions of fluvoxamine were variable depending upon test conditions. However, the drug did not have any effect upon the sympathetic blocking properties of guanethidine and did not potentiate the hypotensive activity of a-methyldopa.

Pharmacokinetics: Fluvoxamine is rapidly absorbed following oral administration. In dogs, peak plasma levels were reached in 2 to 4 hours; in rats and hamsters in 1 hour. The drug is completely absorbed but the bioavailability of orally administered fluvoxamine in dogs was restricted to 60% at 1 mg/kg by firstpass metabolism.

The elimination rate varied from species to species. In the dog, the half-life was estimated at 3 hours after 1 mg/kg and appeared to increase with increasing dose. In rats the half-life was shorter than in dogs, and in hamsters it was shorter than in rats.

The excretion rates were in accordance with the plasma half-lives. In dogs, about 70% of the urinary excretion occurred within 24 hours after 1 mg/kg, but only 50% after 25 mg/kg. In mice and hamsters, excretion was rapid; 90% took place within 24 hours. The main metabolic pathway was similar in the rat, dog, hamster, rabbit and man and consisted of elimination of the methoxyl group leading to the corresponding carboxylic acid as the main metabolite. However, in the mouse, the intermediate alcohol in conjugated form is a major metabolite.

The two main metabolites of fluvoxamine maleate in man were tested for antidepressant activity in four relevant test models. The results indicate that these metabolites are not pharmacologically active in serotonergic or noradrenergic processes.

TOXICOLOGY

Acute Toxicity

The following table presents the results of the acute toxicity studies in mice, rats and dogs:

Species	Sex	Route	LD_{50} (mg/kg)	95% Confidence Interval
Mouse	M	Oral	1100	550-2200
	F	Oral	1330	737-2410
	M & F	i.v.	61	46-80

Species	Sex	Route	LD_{50} (mg/kg)	95% Confidence Interval
Rat	M	Oral	2000	1370-2910
	F	Oral	1470	862-2500
	M	i.v.	43.0	29.5-62.6
	F	i.v.	68.1	46.4-100.0
Dog	M & F	Oral	≥464	

The main acute toxic symptoms noted in mice and rats following oral administration of fluvoxamine occurred at lethal or near lethal dose levels and included convulsions, bradypnea, mydriasis and ataxia with increased muscle tone. In dogs, ataxia was associated with rhythmic side-to-side head movements and mydriasis. Fluvoxamine also induced emesis in the dog at dose levels of 25 mg/kg and higher, and autopsy of rats which succumbed to the treatment revealed marked erosion and haemorrhage of the intestinal mucosa. All symptoms were completely reversible in surviving animals.

The signs observed in rats given the drug intravenously were indicative of an effect on the central and autonomic nervous systems, muscle tone and awareness. Haemoglobinuria at concentrations of ≥10 mg/mL was indicative of an haemolytic effect. Mice given the drug intravenously showed signs of dyspnea.

Subacute Toxicity

Tolerance was evaluated in hamsters and mice with particular attention to lipid parameters.

In one of two studies involving hamsters, the effects of fluvoxamine, imipramine and amitriptyline on serum and liver lipids were compared. Drug was administered daily for two weeks at dose levels of 100 and 200 mg/kg for fluvoxamine, and 25, 50 and 100 mg/kg for imipramine and amitriptyline. Fluvoxamine caused a slight decrease in serum lipids and an increase in liver lipids at 200 mg/kg whereas amitriptyline 100 mg/kg caused a rise in serum cholesterol and a decrease in the relative weights of the spleen. Other effects seen with all three compounds included a

decrease in body weight gain and food consumption and minor histological changes (cloudy swelling) in the liver. With fluvoxamine, these occurred at the 200 mg/kg dose level.

The second study, in which hamsters were administered oral doses of 0, 9, 36, 142 and 432 mg/kg/day fluvoxamine, was of 30 days duration. Body weight gain and food consumption were significantly lower in the high-dose group and in male hamsters receiving 142 mg/kg/day. There was a significant treatment-related decrease in serum lipid levels in all treatment groups. However, after the 30-day recovery period, no treatment-related differences were evident except for a lower phospholipid level in the males of the high-dose group.

Analysis of liver lipids revealed a significant decrease in cholesterol levels in all treatment groups except the high-dose group and a significant increase in phospholipids and total lipids in the high-dose group. Histopathological examination of the kidneys revealed a significant increase in the incidence of renal tubular changes in the treated groups, and in the liver, traces of fat droplets were observed in a proportion of both treated and control groups.

The effects of fluvoxamine (100, 200 mg/kg), imipramine and amitriptyline (25, 50, 100 mg/kg) on serum lipids were also compared in groups of mice given daily oral doses of each drug for two weeks. All three drugs exerted similar effects, with amitriptyline showing the strongest and fluvoxamine the mildest. In mice treated with 200 mg/kg fluvoxamine, there was a dose-related decrease in body weight gain and food consumption, and an increase in the weights of the liver and spleen. Slight histological changes were observed in the liver, lung, spleen and mesenteric lymph nodes. In addition, a dose-related hypolipidemia and, in the high-dose group, a significant increase in liver lipids were found. However, there was no evidence of phospholipidosis.

Fluvoxamine was administered to mice in two separate studies at dose levels of 0, 75, 150, 300 and 600 mg/kg/day for four weeks.

In the first study, there was a significant increase in body weight gain in females in the 150 mg/kg group and males in the 300 mg/kg group. In

addition, there was a reduction in water intake at 300 mg/kg in female mice and at 600 mg/kg in both sexes. Packed cell volume and hemoglobin content were significantly reduced in females at all dose levels and liver weight was also significantly increased in both sexes in the 150, 300 and 600 mg/kg groups. Histopathological examination of the liver indicated hypertrophy of the centrilobular hepatocytes in males in the 300 mg/kg group and in mice of both sexes receiving 600 mg/kg. There was fine vacuolation of the cytoplasm in one male mouse at the 300 and 600 mg/kg dose levels, and vacuolation and distension of the hepatocytes at 600 mg/kg.

Similar changes were observed in the second mouse study involving another mouse strain. There was a significant increase in body weight gain in males in the 75, 150 and 300 mg/kg groups, and a reduction in water consumption in males in the 300 and 600 mg/kg groups. Packed cell volume was significantly reduced in males in the 300 and 600 mg/kg groups and liver weight was significantly increased in males in the 300 mg/kg group, and in mice of both sexes in the 600 mg/kg group. Histopathological examination of the liver revealed hypertrophy of the centrilobular hepatocytes and vacuolation and/or distension of hepatocytes in the 300 and 600 mg/kg groups.

The toxic effects of orally administered fluvoxamine was further evaluated in mice in two additional 4-week studies involving doses ranging from 200 to 1600 mg/kg/day.

In one study, mice received 0, 200, 300 or 400 mg/kg/day. Changes observed were a decrease in the body weight gain in male mice of the high-dose group and a dose-related accentuation of hepatic lobular pattern.

Daily doses of 0, 400, 600, 800 or 1600 mg/kg were administered to mice in the other study of 4-weeks duration. Poor general body condition, piloerection, lethargy and body tremors were observed at the highest dose level, and 1 male mouse died during week 4. Examination at necropsy revealed only autolytic changes. There was an increase in body weight gain in the 800 and 1600 mg/kg groups and a decrease in food consumption in the 1600 mg/kg group.

At necropsy, there were generalized discolouration of the liver and an increase in the absolute and relative weights of the liver in all treatment groups except for the absolute weight of the liver in the 1600 mg/kg group. Also, all increases were dose-related except for animals receiving the highest dosage. In addition, there was a decrease in the absolute and relative weights of the thymus in the highest dose group and treatment-related lesions were found in hepatic sections of all drug groups, possibly reflective of intra-cellular lipid accumulation.

Long Term Toxicity

The long-term toxicological effects of orally administered fluvoxamine maleate were investigated in seven studies involving hamsters, rats, and dogs, for treatment periods ranging from 13 weeks to 2 years.

During the 13-week evaluation in hamsters, fluvoxamine was administered in the diet in doses of 0 or 233 mg/kg/day. Fluvoxamine treatment significantly reduced body weight gain and increased water consumption. Also, there was a reduction in plasma lipid concentration in male hamsters only, and an increase in liver lipid concentration with a corresponding increase in fat droplets in the hepatocytes in both sexes.

Organ weight data revealed a significant decrease in the weights of the kidney (both sexes) and liver (males only), and a significant decrease in brain weight in female hamsters.

When fluvoxamine was administered in the diet of mice at dose levels of 0, 10, 80 or 640 mg/kg/day, an increase in body weight gain was noted in the mid-dose group in male mice during the first 12 of the 21 weeks of treatment and in female mice during weeks 8 to 16. Lower body weight gain was recorded throughout the treatment period in the high-dose group.

Blood chemistry results revealed a significant increase in alanine amino-transferase and aspartate amino-transferase activities in the high-dose group and in male mice in the mid-dose group. Serum lipid levels were significantly lower in the high-dose group and cholesterol levels were marginally lower in the mid-dose group. Also, serum lipoprotein electrophoresis revealed an apparent lowering of the pre-b fraction in mice of all

treatment groups. In addition, there was an increase in the absolute and relative weights of the liver in mice of both sexes within the high-dose group and in male mice within the mid-dose group, and an increase in the absolute weights of the liver in female mice in the mid-dose group.

Autopsy of mice sacrificed after 10 or 21 weeks of treatment revealed an increased incidence of hepatic macropathological changes including accentuation of lobular pattern and a generalized pallor sometimes associated with yellow-green colouration. Dose-related changes in the liver of animals within the mid- and high-dose groups included fine fatty vacuolation of periacinal hepatocytes, large fatty vacuolation of centroacinar hepatocytes and pleomorphic cell inflammation.

Histopathological examination of the liver of mice allowed to recover after treatment revealed an almost total loss of the fine fatty vacuolation and loss of centroacinar hepatocytic large fatty vacuolation. However, a dose-related incidence of panacinar hepatocytic large fatty vacuolation had surfaced in the mid- and high-dose groups.

Two hours following autoradiography, radioactivity was detected within the hepatocellular cytoplasm, vascular endothelium, around and within fat vacuoles, cell borders and connective tissue around blood vessels and bile canaliculi in the mid- and high-dose groups. Twelve hours post-dosing, a less distinct pattern was apparent. Significant hepatocytic enlargement was present in male mice from all treatment groups but was virtually absent in female mice.

Analysis of liver specimens showed a significant increase in liver lipids in male animals within the mid- and high-dose groups and an increase in phospholipid levels at 10 mg/kg/day. In female mice there were significantly higher levels of total lipids, triglycerides and cholesterol in the mid- and high-dose groups, and an increase in phospholipids at 80 mg/kg/day.

Daily oral doses of 0, 5, 20 and 80 mg/kg/day fluvoxamine were administered to rats for 6 months, with the 80 mg/kg dose increased to 100 mg/kg after 9 weeks then further increased to 150 mg/kg after 20 weeks. Increased food consumption and body weight gain occurred in female animals at 20 and 80 mg/kg and water consumption was higher in male rats in the 80 mg/kg group. There was an increase in the absolute weights

of the liver in females and in the relative weights of the liver in males at the 80 mg/kg dose level. In addition, the relative weights of the spleen and thymus were reduced in the 80 mg/kg group. The higher liver weights in females and lower spleen weights in males in the 80 mg/kg group appeared to be drug related. However, no histopathological changes were observed in these organs.

Dogs were treated with fluvoxamine 0, 5, 15 or 45 mg/kg/day (capsules) for 7 months, with the high dose increased to 60 mg/kg/day after 7 weeks then maintained throughout the study at this level except during weeks 14 and 15 when the dose was raised to 80 mg/kg/day. Two dogs died while receiving 60 mg/kg or 80 mg/kg. At 45 mg/kg animals displayed frowning, bouts of "coughing" and rhythmic side-to-side head movements. At 80 mg/kg, ataxia, anorexia and weight loss occurred and one dog had convulsions. Mydriasis was noted at all dose levels, persisting for up to 24 hours after dosing and regressing over a period of 6 days after treatment was stopped.

Histopathological examination revealed the presence of foamy macrophages in the spleen, mesenteric, cervical and intestinal lymph nodes. These macrophages were observed only in animals from the high-dose group (45, 60 or 80 mg/kg). The lesions gave the appearance of lipid granulomata in which phagocytosis of lipid material had occurred, and were more evident in the Peyer's patches in comparison to the other lymph organs, indicating an effect on fat metabolism.

In a second study involving beagle dogs, fluvoxamine was administered orally via capsules for 53 weeks at dose levels of 0, 10, 25 or 62.5 mg/kg/day for 53 weeks. Clinical signs following drug treatment included moderate mydriasis at all dose levels, and reduced weight gain and anorexia in the high-dose group, periodic reduction in water and food consumption and slight increase in the incidence of diarrhea in males in the mid- and high-dose groups. In addition, there was an increase in the levels of plasma alkaline phosphatase, an increase in the incidence of glomerular atrophy (also present in the control group) and occasional increases in plasma urea, creatinine and urine volume in the high-dose animals. Kidney weight was increased in male dogs in the mid- and high-dose groups. A foam-cell reaction in the reticuloendothelial system was observed in the mid- and high-dose groups and the lipid content of these cells was predominantly phospholipid.

Histopathological signs of adverse effects on the kidney were confined to the high-dose group and included distension of Bowman's capsule, shrinkage of the glomerular tuft and interstitial fibrosis. The relative weights of the liver, spleen (males) and lungs (females) were increased in animals within the high-dose group sacrificed after 53 weeks of treatment. However, these changes were not associated with any unusual histopathological changes and the weight increases were not present in animals sacrificed following withdrawal of treatment.

ln a special study to investigate lipid distribution in the tissues of rats, fluvoxamine was administered for 52 weeks at dose levels of 0, 10, 40 and 160 mg/kg/day, with the high dose increased to 200 mg/kg/day during weeks 40 to 52. There was a dose-related decrease in food and water consumption and a decrease in body weight in animals in the high-dose group. Histopathological changes included a slight increase in the incidence of lipid-containing vacuoles in hepatocytes and a larger number of lamellar cytoplasmic inclusions in the lymphocytes of treated male rats. Further examination of the mesenteric lymph nodes by electron microscopy showed a six-fold increase in the total number of cytoplasmic lamellar inclusions. The inclusions were of the same type as observed for phospholipidosis-inducing drugs suggesting that fluvoxamine induces a mild form of phospholipidosis.

Fluvoxamine was administered to the diet of rats at dose levels of 0, 10, 40, 160 mg/kg/day for 81 weeks with the high-dose level increased to 200 mg/kg at week 40, then further increased to 240 mg/kg at week 47. Drug-related changes were primarily confined to the high-dose group and included decreases in body weight gain (males only), food and water consumption, the absolute weights of the brain and increases in urine concentration, the relative weights of the lung and liver (males only), the relative and absolute weights of the ovaries, lymphocytic infiltrations in the kidneys, the incidence of vacuolation of hepatocytes, and the incidence of macrophage aggregations in the lungs. In the mid-dose group, there was a decrease in body weight gain (females only) and an increase in the incidence of vacuolation of hepatocytes (males only). No drug-related changes were observed in the low-dose group. However, there was a significant decrease in the absolute and relative weights of the thyroid in females in this group. The biological significance of this finding is unclear.

Carcinogenicity

Rats were given fluvoxamine as a day/diet mixture at dosage levels of 0, 10, 40 and 160 to 240 mg/kg/day for two and a half years. Initially, the high-dose level was 160 mg/kg/day, but this was increased to 200 mg/kg/day after 40 weeks and to 240 mg/kg/day after 53 weeks. At 160 to 240 mg/kg/day there was a decrease in weight gain and a dose-related increase in centrilobular hepatocyte degeneration. However, fluvoxamine did not contribute to mortality or tumour incidence.

Fluvoxamine was also given to hamsters in a lifetime study (about 2 years) at dosages of 0, 9, 36, 144/180/240 mg/kg/day (the high dose was raised from 144 to 180 mg/kg/day at week 14, then to 240 mg/kg/day at week 19 of treatment). No drug or dose-related effects on mortality rates or incidence of tumours were found.

Mutagenicity

Fluvoxamine did not have mutagenic activity in the Ames test with five bacterial test strains, the micronucleus test and a cytogenetic test using lymphocytes cultured in vitro.

Teratology

The teratologic effects of fluvoxamine were studied in both rats and rabbits. When fluvoxamine was administered to rats from day 6 to day 15 of gestation in single daily doses of 0, 5, 20 and 80 mg/kg/day, the drug did not affect the general health, pre- and post-implantation loss and fetal morphology of the animals.

In the two rabbit studies, oral doses of 0, 5, 10, and 20 mg/kg/day (first study) and 0, 5, 10 and 40 mg/kg/day (second study) were given during days 6 to 18 of gestation. In the first rabbit study, the incidence of minor visceral and skeletal anomalies was higher among the treatment groups than in the control group. A statistically significant incidence of skeletal variants was observed in the low-dose group but the incidence in the mid- and high-dose groups was comparable to the controls. The rabbit teratology study was repeated and the results of the second study indicated that incidences of malformations, anomalies and skeletal variants appeared essentially unaffected by treatment with fluvoxamine for doses up to

40 mg/kg/day.

Reproductive Studies

The effects of fluvoxamine on fertility and general reproductive performance were evaluated in rats at dosages of 0, 5, 20 and 80 mg/kg/day administered orally. Male rats were treated for 9 weeks prior to mating and females were treated for 2 weeks prior to mating, during gestation, and during rearing of the young up to 21 days post-partum.

Decreased weight gain was evident among males at all dose levels but there was no apparent effect on female weight gain during the shorter pre-mating period, gestation or lactation.

Fluvoxamine did not affect mating performance, duration of gestation or pregnancy rate. However, a slight increase in pup mortality during days 4 to 12 of lactation was noted in the mid- and high-dose groups.

The effects of fluvoxamine on peri- and post-natal development of the rat was assessed in two studies. In one study, the drug was given in single daily doses of 0, 5, 20 and 80 mg/kg from day 15 of pregnancy, through lactation, to 21 days post partum. There was an increase in pup mortality at all dosages leading to a reduction in litter size.

In the second rat study, daily dosages of 0 and 160 mg/kg were administered and a proportion of litters from the test group were cross-fostered with control litters on day 1 post partum to distinguish between direct and indirect (maternally mediated) effects on post-natal development of offspring. Fluvoxamine was found to exert a primary toxic effect on the parent animal, rather than an effect on late fetal development and the immediate peri-natal period. However, weight gain was slightly lower in fostered and non-fostered offspring from test dams during days 8 to 21 of lactation.

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