PRODUCT MONOGRAPH

BCI FLUVOXAMINE TABLETS
(fluvoxamine maleate tablets, mfr. std)

50 mg & 100 mg Film Coated Tablets

Antidepressant

Antiobsessional Agent

Manufacturer:
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ACTION

The antidepressant and antiobsessional actions of BCI Fluvoxamine Tablets (fluvoxamine maleate) are believed to be related to its selective inhibition of presynaptic serotonin re-uptake in brain neurones.

There is minimum interference with noradrenergic processes, and, in common with several other specific inhibitors of serotonin uptake, fluvoxamine maleate 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 maleate 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.

In a dose proportionality study involving fluvoxamine maleate at 100, 200 and 300 mg/day for 10 consecutive days in 30 normal volunteers, steady state was achieved after about a week of dosing. Maximum plasma concentrations at steady state occurred within 3-8 hours of dosing and reached concentrations averaging 88, 283 and 546 ng/mL, respectively. Thus, fluvoxamine maleate had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

A biostudy was conducted to establish the equivalence of BCI FLUVOXAMINE TABLETS (fluvoxamine maleate tablets) against Solvay Pharma Luvox® (fluvoxamine maleate tablets). The biostudy was an open-label, comparative, randomized, single-dose, fasted, two-way cross-over design, comparing a single 100 mg dose of BCI FLUVOXAMINE TABLETS (fluvoxamine maleate tablets) against Solvay Pharma Luvox®. Twenty subjects completed the study. Blood samples were collected pre-dose and at 10, 20, 30, 40 and 50 minutes post-dose as well as 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 36, 48 and 72 hours post-dose. The wash-out was two weeks. Fluvoaxmine was measured by a validated bioanalytical method. The pharmacokinetic parameters are tabulated in the table below. On the basis of this study, BCI FLUVOXAMINE TABLETS (fluvoxamine maleate tablets) and Solvay Pharma Luvox® are judged to be bioequivalent.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA Fluvoxamine Maleate Tablets (IVAX) vs Luvox (Solvay Pharma, Canada) (1 X 100 mg) From measured data Geometric Mean Arithmetic Mean (CV %)			
Parameter	**Test - BCI**	**Reference - Solvay Pharma, Canada**	**% Ratio of Geometric Means**
AUC_T (ng.h/mL)	886.67 76.3 ± 754.01 (70.1)	915.68 1094.7 ± 744.44 (68.0)	96.8 (91.6, 102.4)
AUC_I (ng.h/mL)	955.02 1246.7 ± 1063.69 (85.3)	915.68 1094.7 ± 744.44 (68.0)	97.6 (91.9, 103.8)
C_{MAX} (ng/mL)	37.88 40.03 ± 14.29 (35.7)	39.13 41.64 ± 15.89 (38.2)	96.8 (92.3, 101.5)
T_{MAX}^{*} (h)	6.389 ± 1.72 (26.9)	5.778 ± 1.26 (21.9)	
$T_{½}^{*}$ (h)	15.94 ± 10.07 (63.1)	15.137 ± 9.08 (60.0)	

* expressed as arithmetic mean (CV%) only.

METABOLISM AND ELIMINATION

Fluvoxamine maleate 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 maleate to human plasma proteins is about 77% at drug concentrations up to 4000 ng/mL.

INDICATIONS

DEPRESSION

BCI Fluvoxamine Tablets (fluvoxamine maleate) may be indicated for the symptomatic relief of depressive illness.

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

OBSESSIVE-COMPULSIVE DISORDER

BCI Fluvoxamine Tablets (fluvoxamine maleate) 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 BCI Fluvoxamine Tablets (fluvoxamine maleate) has been studied in double-blind, placebo-controlled clinical trials conducted in obsessive-compulsive outpatients. The usefulness of BCI Fluvoxamine Tablets (fluvoxamine maleate) 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 BCI Fluvoxamine Tablets (fluvoxamine maleate) for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

BCI Fluvoxamine Tablets (fluvoxamine maleate) is contraindicated in patients with known hypersensitivity to the drug.

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

Co-administration of thioridazine, mesoridazine, terfenadine, astemizole, or cisapride with BCI Fluvoxamine Tablets (fluvoxamine maleate) is contraindicated (see WARNINGS and PRECAUTIONS).

WARNINGS

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

Pediatrics: <u>Placebo-Controlled Clinical Trial Data</u>

- **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 suicide-related events 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 ~~in the class~~.**

<u>Adults and Pediatrics: Additional data</u>

- **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 severe 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 indictors 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 current taking BCI Fluvoxamine Tablets should NOT be discontinued abruptly, due to risk of discontinuation symptoms. At the time that a medical decision is made to discontinue an SSRI or other newer anti-depressant drug, a gradual reduction in the dose rather than an abrupt cessation is recommended.

Potential Interaction with Thioridazine and Mesoridazine:

The effect of fluvoxamine (25 mg bid for one week) on thioridazine steady-state concentrations was evaluated in 10 male inpatients with schizophrenia. Concentrations of thioridazine and its two active metabolites, mesoridazine and sulforidazine, increased threefold following coadministration of fluvoxamine.

Thioridazine and mesoridazine administration produces a dose-related prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. It is likely that this experience underestimates the degree of risk that might occur with higher doses of thioridazine. Moreover, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Therefore BCI Fluoxamine Tablets (fluvoxamine maleate) and thioriadzine or mesoridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

Terfenadine, astemizole, and cisapride are all metabolized by the cytochrome P450 IIIA4 isozyme. Since fluvoxamine maleate is known to inhibit the CYP IIIA4 isozyme, theoretically, there may be a potential interaction with terfenadine, astemizole, orcisapride. Consequently, it is recommended that fluvoxamine maleate not be used in combination with either terfenadine, astemizole, or cisapride.

PRECAUTIONS

SEIZURES

Convulsions have been reported rarely during BCI Fluvoxamine Tablets (fluvoxamine maleate) administration. Caution is recommended when the drug is administered to patients with a history of seizures. If seizures occur during fluvoxamine maleate 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 maleate has been rarely associated with increases in hepatic enzymes, usually accompanied by symptoms. Fluvoxamine maleate administration should be discontinued in such cases.

COMBINATION WITH ALCOHOL

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

SEROTONIN SYNDROME

On rare occasions development of a serotonin syndrome has been reported in association with treatment of fluvoxamine, particularly when given in combination with other serotonergic drugs, and appeared to be reversible upon discontinuation and/or symptomatic treatment.

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 BCI Fluvoxamine Tablets (fluvoxamine maleate) 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 BCI Fluvoxamine Tablets (fluvoxamine maleate) should be written for the smallest quantity of drug consistent with good patient management **(see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**.

CONCOMITANT ILLNESS

BCI Fluvoxamine Tablets (fluvoxamine maleate) 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.

HAEMORRHAGE

There have been reports of cutaneous bleeding abnormalities such as ecchymoses and purpura with SSRI's. Caution is advised in patients taking SSRI's, particularly in concomitant use with drugs known to affect platelet function (e.g. atypical antipsychotics and phenothiazines, most tricyclic antidepressants (TCA's), aspirin, NSAID's) as well as in patients with a history of bleeding disorders.

USE IN PREGNANCY AND LACTATION

Safe use of fluvoxamine maleate during pregnancy and lactation has not been established. Like other antidepressants, fluvoxamine maleate is excreted via human milk in small quantities. 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

BCI Fluovoxamine tablets (fluvoxamine maleate) are contraindicated in combined use with either MAO inhibitors, thioridazine or mesoridazine. (see CONTRAINDICATIONS and WARNINGS).

Isolated cases of cardiac toxicity have been reported when fluvoxamine was combined with thioridazine (See CONTRAINDICATIONS and WARNINGS).

An increase in previously stable plasma levels of those tricyclic antidepressants and neuroleptics which are largely metabolized through cytochrome P450 IA2, has been reported in patients taking fluvoxamine maleate concomitantly. Thus, the combination of these drugs with fluvoxamine is not recommended.

Lithium, and possibly tryptophan, may enhance the serotonergic effects of fluvoxamine maleate; these combinations should therefore be used with caution. The serotonergic effects may also be enhanced when fluvoxamine maleate and other agents, including sumatriptan and SSRI's, are used in combination. This may, on rare occasions, result in a serotonergic syndrome.

The plasma levels of oxidatively metabolized benzodiazepines (e.g., alprazolam, diazepam) are likely to be increased during co-administration of fluvoxamine maleate.

The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine maleate.

An absence of pharmacokinetic interaction has been seen with digoxin and atenolol, which are not significantly metabolized in the liver.

CYTOCHROME P450 ISOZYMES

Fluvoxamine maleate has been shown to be a potent inhibitor of CYP IA2 activity in human hepatic microsomes. Therefore, it may cause a drug interaction with CYP IA2 substrates like propranolol. A clinically significant interaction is possible with CYP IA2 substrates that have a narrow therapeutic index such as clozapine, theophylline, tacrine, and warfarin. 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 maleate. When a single 40 mg dose of tacrine was added to fluvoxamine maleate 100 mg/day administered at steady-state, an associated five and eight fold increase in tacrine Cmax and AUC, respectively, were observed.

Fluvoxamine maleate is also known to inhibit the CYP IIIA4 isozyme and thus may interact with CYP IIIA4 substrates like diltiazem and alprazolam. A clinically significant interaction is possible with CYP IIIA4 substrates that have a narrow therapeutic index such as carbamazepine, methadone, and cyclosporin. Such combinations should therefore be administered with caution, and consideration be given to lowering the dose of the concomitant agent. A significantly increased methadone plasma level/dose ratio was seen during concurrent administration of fluvoxamine maleate. When fluvoxamine maleate and alprazolam were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, Cmax, $T_{1/2}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; clearance was reduced by about 50%. Since terfenadine, astemizole, and cisapride, are metabolized by the CYP IIIA4 isozyme, theoretically there may be a potential interaction with fluvoxamine maleate. Thus, it is recommended that fluvoxamine maleate not be used in combination with either terfenadine, astemizole, or cisapride (see CONTRAINDICATIONS).

Fluvoxamine maleate is also believed to inhibit CYP IIC isozymes and thus may interact with CYP IIC substrates like diazepam. A clinically significant interaction is possible with CYP IIC substrates that have a narrow therapeutic index such as phenytoin. Clearance of both diazepam and its active metabolite N-desmethyldiazepam were reduced with concurrent administration of fluvoxamine maleate.

Cytochrome P450 isozyme (IID6) is responsible for the metabolism of substrates such as debrisoquine, sparteine, tricyclic antidepressants (e.g., nortriptyline, amitriptyline,imipramine, and desipramine), phenothiazine neuroleptics (e.g.,perphenazine and thioridazine), and Type 1Cantiarrhythmics (e.g., propafenone and flecainide). In vitro data suggest that fluvoxamine maleate is a relatively weak inhibitor of the IID6 isozyme, and hence the potential for interactions with compounds metabolized by this isoenzyme is low.

The specific CYP isoenzymes involved in the metabolism of fluvoxamine maleate remains to be identified.

ADVERSE REACTIONS

COMMONLY OBSERVED

In clinical trials, the most commonly observed adverse events associated with Fluvoxamine tablets (fluvoxamine maleate) 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 tablets (fluvoxamine maleate) 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

Body System / Adverse Event	Depression		OCD	
	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	-	-

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE (≥ 5%) IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR DEPRESSION AND OBSESSIVE COMPULSIVE DISORDER* Percentage of Patients Reporting Event				
Body System / Adverse Event	**Depression**		**OCD**	
	Fluvoxamine (N=222)	**Placebo (N=192)**	**Fluvoxamine (N=160)**	**Placebo (N=160)**
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

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE (≥ 5%) IN PLACEBO-CONTROLLED CLINICAL TRIALS FOR DEPRESSION AND OBSESSIVE COMPULSIVE DISORDER* Percentage of Patients Reporting Event				
Body System / Adverse Event	**Depression**		**OCD**	
	Fluvoxamine (N=222)	**Placebo (N=192)**	**Fluvoxamine (N=160)**	**Placebo (N=160)**
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, 50mg; Days 5-8, 100mg, Days 9-14, 150mg then titrated to response.

\+ Corrected for gender (males: n=78)

During premarketing and postmarketing studies, multiple doses of fluvoxamine tablets (fluvoxamine maleate) 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 tablets (fluvoxamine maleate), they were not necessarily caused by it.

NERVOUS SYSTEM

Frequent: Agitation, anxiety, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, vertigo.

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

Rare: Akinesia, CNS neoplasia, CNS stimulation, coma, convulsion, delirium, delusions, dysarthria, dyskinesia, dystonia, extrapyramidal syndrome, hemiplegia, hyperesthesia, hypotonia, hysteria, myoclonus, neuralgia, neuropathy, paralysis, paranoid reaction, psychosis, reflexes decreased, schizophrenic reaction, screaming syndrome, torticollis, trismus.

DIGESTIVE SYSTEM

Frequent: Anorexia, constipation, diarrhea, dry mouth, dyspepsia, nausea, vomiting.

Infrequent: Colitis, dysphagia, eructation, flatulence, gastritis, gastroenteritis, increased appetite, thirst.

Rare: Biliary pain, esophagitis, fecal incontinence, gastrointestinal carcinoma, gastrointestinal hemorrhage, gingivitis, glossitis, hematemesis, hepatitis, jaundice, liver function tests abnormal, melena, mouth ulceration, rectal hemorrhage, stomatitis,

tenesmus, tongue discoloration, tongue edema, tooth disorder.

CARDIOVASCULAR SYSTEM

Frequent: Palpitation.

Infrequent: Angina pectoris, hypertension, hypotension, migraine, postural hypotension, syncope, tachycardia.

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

BODY AS A WHOLE

Frequent: Abdominal pain, asthenia, headache, malaise.

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

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

SKIN

Frequent: Sweating increased.

Infrequent: Pruritus, rash.

Rare: Acne, alopecia, dry skin, eczema, furunculosis, Herpes simplex, Herpes zoster, maculopapular rash, psoriasis, urticaria.

RESPIRATORY SYSTEM

Infrequent: Dyspnea, pharyngitis, rhinitis.

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

SPECIAL SENSES

Infrequent: Abnormal vision, amblyopia, hyperacusis, taste perversion, tinnitus.

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

MUSCULOSKELETAL SYSTEM

Infrequent: Arthralgia, arthrosis, myalgia, myasthenia, tetany.

Rare: Arthritis, bone pain, leg cramps, pathological fracture, rheumatoid arthritis.

UROGENITAL SYSTEM

Infrequent: Abnormal ejaculation, dysuria, impotence, metrorrhagia, urinary frequency, urinary incontinence.

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

METABOLIC AND NUTRITIONAL SYSTEM

Frequent: Weight gain.

Infrequent: Peripheral edema, weight loss.

Rare: Alcohol intolerance, dehydration, edema, obesity.

HEMATIC AND LYMPH SYSTEMS

Rare: Anemia, cyanosis, ecchymosis, lymphadenopathy, thrombocytopenia.

HYPONATREMIA

As with other SSRIs, hyponatraemia has been rarely reported, and appeared to be reversible when fluvoxamine was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion. The majority of reports were associated with older patients.

HAEMORRAHAGE

See " precautions".

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. These are usually mild and self-limiting, and do not necessarily imply dependence. Before stopping treatment, gradual dosage reduction may be considered.

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 500 cases of overdosage with fluvoxamine maleate, alone or in combination with other compounds, have been reported. The most common symptoms of overdosage include gastrointestinal complaints (nausea, vomiting, and diarrhoea), somnolence, and dizziness. Cardiac events (tachycardia, bradycardia, hypotension), liver function disturbances, convulsions, and coma have also been reported. Among

more than 490 patients reported to have taken deliberate overdoses of fluvoxamine maleate, there have been 44 deaths, all but six 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 maleate. 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 maleate, forced diuresis or dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION

BCI Fluvoxamine Tablets (fluvoxamine maleate) is not indicated for use in children under 18 years of age (see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

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 BCI Fluvoxamine Tablets (fluvoxamine maleate) 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. Fluvoxamine Tablets (fluvoxamine maleate) 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 maleate in children under 18 years of age have not been established **(see WARNINGS: POTENTIAL ASSOCIATION WITH BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).**

USE IN GERIATRICS

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

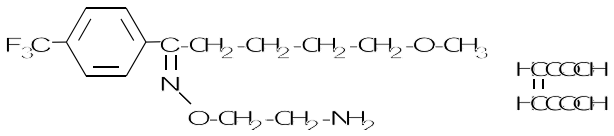
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Fluvoxamine maleate

Chemical Name: 5-methoxy-4'-(trifluoromethyl) valerophenone(E)-0-(2-aminoethyl) oxime maleate (1:1)

Structural Formula:



Molecular Weight: 434.4

Description: White, odorless, crystalline powder, sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

STORAGE CONDITIONS

Preserve in well-closed containers. Store at controlled room temperature (15°C - 30°C).

AVAILABILITY

Each white, round-shaped, deep scored, film-coated 50 mg tablet, debossed "Ɪ","7206" on one side and plain scored on the other, contains 50 mg fluvoxamine maleate. Non-medicinal ingredients: mannitol powder, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, sodium stearyl fumarate, and Opadry II white (polydextrose, titanium dioxide, hydroxypropyl methylcellulose 2910, polyethylene glycol 400, carnuba wax, and iron oxide yellow). Bottles of 100, 250, 500 and 1000.

Each white, elliptical-shaped, film-coated 100 mg tablet, debossed "Ɪ","7207" on one

side and plain scored on the other, contains 100 mg fluvoxamine maleate. Non-medicinal ingredients: mannitol powder, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, sodium stearyl fumarate, and Opadry II white (polydextrose, titanium dioxide, hydroxypropyl methylcellulose 2910, polyethylene glycol 400, carnuba wax, and iron oxide yellow). Bottles of 100, 250, 500 and 1000.

Fluvoxamine maleate is a Schedule F drug.

BCI Fluvoxamine Tablets: Patient Information

Your doctor has chosen BCI Fluvoxamine Tablets (fluvoxamine maleate) as the best medication to help you with your condition. This summary provides basic information about using BCI Fluvoxamine Tablets and is intended only to supplement the advice of your doctor. Be sure to follow your doctor's advice as he or she best understands your medical condition.

What are BCI Fluvoxamine Tablets?

BCI Fluvoxamine Tablets are a prescription medication containing the active ingredient, fluvoxamine maleate. BCI Fluvoxamine Tablets are intended for the relief of symptoms of depression, or the reduction of symptoms associated with obsessive-compulsive disorder (OCD). **Treatment with these types of medications is most safe and effective when you and your doctor have good communication about how you are feeling.**

How do they work?

BCI Fluvoxamine Tablets are believed to work by enhancing the availability of serotonin, one of the chemical transmitters in the brain. Depression and OCD have been associated with a decrease in the flow of serotonin between certain brain cells.

Before taking BCI Fluvoxamine Tablets your doctor needs to know:

- Any other medical condition that you may have including a history of seizures, heart or liver disease;
- How much alcohol you consume;
- Whether you are planning to get pregnant, are currently pregnant or are nursing an infant;
- Any other prescription or over-the-counter medication that you are currently taking. Of particular importance are monoamine oxidase inhibitors (MAOIs), other antidepressants, thioridazine, mesoridazine, neuroleptics, warfarin, propranolol, phenytoin, theophylline, lithium, trytophan, terfenadine, astemizole, and cisapride.

When not to use BCI Fluvoxamine Tablets:

- Stop taking the drug and contact your doctor immediately if you experience any severe or unusual side effects, or if you experience an allergic reaction.

How to take BCI Fluvoxamine Tablets:

- It is very important that you take BCI Fluvoxamine Tablets exactly as your doctor has instructed. BCI Fluvoxamine Tablets should be taken at bedtime. Swallow the tablet(s) with water and without chewing.
- Establishing an effective dosage level will vary from one person to another. For this reason, your doctor may increase your dosage gradually during treatment.
- Never change the amount of BCI Fluvoxamine Tablets you are taking unless instructed to do so by your doctor.
- Never double up on your next dose to make up for a missed dose.

What to expect with BCI Fluvoxamine Tablets:

- As with all antidepressants, improvement with BCI Fluvoxamine Tablets is gradual.
- You may experience some side effects such as nausea (sometimes with vomiting), constipation, diarrhea, loss of appetite, upset stomach, sleepiness,

sleeplessness, dry mouth, tremor, dizziness, or headache. Some side effects may be temporary. Consult your doctor if you experience these or other side effects, as the dose may have to be adjusted.

- **Particularly in the first few weeks or when doses are adjusted, a small number of patients taking drugs of this type feel worse instead of better; for example, they may experience unusual feelings of agitation, hostility or anxiety, or have impulse or disturbing thoughts such as thoughts of self-harm or harm to others. Should this happen to you, consult your doctor immediately; do not discontinue your medication on your own.**
- Refrain from potentially hazardous tasks, such as driving a car or operating dangerous machines, until you are certain that this medication does not affect your mental alertness or physical coordination.

What to do in case of an overdose:

Contact your doctor or nearest hospital emergency department even though you may not feel sick.

What do BCI Fluvoxamine Tablets contain?

The 50 mg tablets contain 50 mg fluvoxamine maleate and the following non-medicinal ingredients: mannitol powder, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate and sodium stearyl fumarate.

The 100 mg tablets contain 100 mg fluvoxamine maleate and the following non-medicinal ingredients:mannitol powder, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate and sodium stearyl fumarate.

What do BCI Fluvoxamine Tablets look like?

The 50 mg tablets are white, round-shaped, deep scored,debossed “⧖”,“7206” on one side and plain scored on the other.

The 100 mg tablets are white, elliptical-shaped, debossed “⧖”,“7207” on one side and

plain scored on the other.

How to store BCI Fluvoxamine Tablets:

Keep your BCI Fluvoxamine Tablets in a tightly closed container, in a dry place, at temperatures between 15^{o}C and 30^{o}C. **Keep BCI Fluvoxamine Tablets out of reach of children.**

Reminder: This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your doctor or pharmacist.

Keep this summary handy for future reference.

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 α-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 first-pass 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 limites)
Mouse	M	Oral	1100 (550-2200)
	F	Oral	1330 (737-2410)
	M & F	I.V.	61 (46-80)
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	$\geq$ 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-ß 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.

In 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 2-1/2 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 were 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.

BIBLIOGRAPHY

1. Anon. Fluvoxamine (Faverin): Another Antidepressive Drug. Drug Ther Bull 1988; 26(3):11-2.

2. Baldessarini RJ. Current Status of Antidepressants: Clinical Pharmacology and Therapy. J Clin Psychiatry 1989; 50(4):117-126.

3. Becquemont L., Ragueneau I., Le Bot M., Riche C., Funck-Brentano C., Jaillon P. Pharmacokinetics and Drug Disposition. Influence of the CYP1A2 Inhibitor Fluvoxamine on Tacrine Pharmacokinetics in Humans. Clinical Pharmacology and Therapeutics 1997; 61 (6): 619-627.

4. Benfield P, Ward A. Fluvoxamine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressed illness. Drugs 1986; 32:313-34.

5. Bertschy G., Baumann P., Eap C. B., Baettig D. Probable metabolic interaction between methadone and fluvoxamine in addict patients. Therapeutic Drug Monitoring 1994; 16: 42-45.

6. Berwish, NJ, Amsterdam JD. An Overview of Investigational Antidepressants. Psychosomatics 1989; 30(1):1-18.

7. Blumhardt C. Advances in the Diagnosis and Management of Depression. Am Pharm, Part II 1988; NS28(2):33-7.

8. Brosen K., Skjelbo E., Rasmussen B.B., Poulsen H.E., Loft S. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. Biochemical Pharmacology 1993; 45 (6): 1211-1214.

9. Burrows GD, McIntyre IM, Judd FK, Norman TR. Clinical Effects of Serotonin Reuptake Inhibitors in the Treatment of Depressive Illness. J Clin Psychiatry 1988; 49(8):18-22.

10. Carillo JA, et al. Pharmacokinetic Interaction of Fluvoxamine and Thioridazine in Schizophrenic Patients. J Clin Psychopharmacol 1999;19:494-499.

11. Claassen V. Review of the animal pharmacology and pharmacokinetics of fluvoxamine. Br J Clin Pharmacol 1983; 15:349S-55S.

12. Crewe H.K., Lennard M.S., Tucker G.T., Woods F.R., Haddock R.E. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. British Journal of Clinical Pharmacology 1992; 34: 262-265.

13. Dallaire S. Thioridazine (Mellaril) and mesoridazine (Serentil): prolongation of the QTc interval. Canadian ADR Newsletter, Jan 2001; Vol. 11, No. 1.

14. Daniel D.G. et al. Coadministration of fluvoxamine increases serum concentrations of haloperidol. Journal of Clinical Psychopharmacology 1994; 14(5): 340-343.

15. Daniel W.A., Syrek M., Haduch A., Wojcikowski J. The influence of selective serotonin reuptake inhibitors (SSRIs) on the pharmacokinetics of thioridazine and its metabolites: *in vivo* and *in vitro* studies. Exp. Toxic Pathol. 1999; 51: 309-314.

16. De Bree H, Van Der Schoot JB, Post LC. Fluvoxamine maleate; Disposition in man. Eur J Drug Metab Pharmacokinet 1983; 8(2):175-9.

17. Dick P, Ferrero E. A double-blind comparative study of the clinical efficacy of fluvoxamine and chlorimipramine. Br J Clin Pharmacol 1983; 15:419S-25S.

18. Dillenkoffer RL, et al. Electrocardiographic Evaluation of Mesoridazine (Serentil). Current Therapeutic Research 1972;14(2):71-72.

19. Dominguez RA, Goldstein BJ, Jacobson AF, Steinbook RM. A double-blind placebo-controlled study of fluvoxamine and imipramine in depression. J Clin Psychiatry 1985; 46:84-7.

20. Ereshefsky L, Riesenman C., Lam Y.W.F. Antidepressant drug interactions and the cytochrome P450 system. The role of cytochrome P450 2D6. Clinical Pharmacokinetics 1995; 29, supp.1: 10-19.

21. Fleishaker J.C., Hulst L.K. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. European Journal of Clinical Pharmacology 1994; 46: 35-39.

22. Fritze J., Unsorg B., Lanczik M. Interaction between carbamazepine and fluvoxamine. Acta Psychiatr. Scand. 1991; 84 (6): 583-584.

23. Guelfi JD, Dreyfus JF, Pichot P. Fluvoxamine and imipramine: Results of a long-term controlled trial. Int Clin Psychopharmacol 1987; 2:103-9.

24. Guy W, Wilson WH, Ban TA, King DL, Manov G, Fjetland OK. A double-blind clinical trial of fluvoxamine and imipramine in patients with primary depression. Drug Dev Res 1984; 4:143-53.

25. Hartigan-Go K, et al. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. Clin Pharmacol Ther 1996;60:543-553.

26. Hiemke C. et al. Elevated Levels of Clozapine in Serum After Addition of

Fluvoxamine. J Clin Pyschopharmacol 1994; 14 (4): 279-281.

27. Lapierre YD, Browne M, Horn E, Oyewumi LK, Sarantidis D, Roberts N, Badoe K, Tessier P. Treatment of major affective disorder with fluvoxamine. J Clin Psychiatry 1987; 48(2):65-8.

28. Lapierre YD, Oyewumi LK, Coleman B. The efficacy of fluvoxamine as an antidepressant. Clin Trials J 1981; 18(5):313-20.

29. Lydiard RB, Laird LK, Morton WA, Steele TE, Kellner C, Laraia MT, Ballenger JC. Fluvoxamine, Imipramine, and Placebo in the Treatment of Depressed Outpatients: Effects on Depression. Psychopharmacol Bull 1989; 25(1):68-70.

30. Mallya, G, White, K, Gunderson, C. Is There a Serotonergic Withdrawal Syndrome? Biol Psychiatry 1996; 33:851-852.

31. Marrs-Simon PA, et al. Cardiotoxic manifestations of mesoridazine overdose. Ann Emerg Med 1988;17(10):1984-90.

32. Martin AJ, Tebbs VM, Ashford JJ. Affective disorders in general practice. Treatment of 6000 patients with fluvoxamine. Pharmatherapeutica 1987; 5(1):40-9.

33. Martin AJ, Wakelin J. Fluvoxamine - a baseline study of clinical response, long term tolerance and safety in a general practice population. Br J Clin Pract 1986; 40:95-9.

34. McHardy, KC. Syndrome of inappropriate antidiuretic hormone secretion due to fluvoxamine therapy. Br J Clin Pract 1993; 47(2):62-63.

35. Mithani, H, Hurwitz, TA. Paroxetine-Induced Angioedema and Tongue Swelling. J Clin Psychiatry 1996; 57(10):486.

36. Niemann JT, et al. Cardiac conduction and rhythm disturbances following suicidal ingestion of mesoridazine. Ann Emerg Med 1981;10(11):585-8.

37. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, Haffmans J. Treatment strategy in depression. Acta Psychiatr Scand 1988; 78:668-75.

38. Norton KRW, Sireling LI, Bhat AV, Rao B, Paykel ES. A double-blind comparison of fluvoxamine, imipramine and placebo in depressed patients. J Affective Disord 1984; 7:297-308.

39. Ochs HR, Greenblatt DJ, Verburg-Ochs B, Labedski L. Chronic Treatment with Fluvoxamine, Clovoxamine, and Placebo: Interaction with Digoxin and Effects on Sleep and Alertness. J Clin Pharmacol 1989; 29:91-5.

40. Ottevanger EA. Controlled study with Fluvoxamine in outdoor psychiatric patients diagnosed of depressive syndrome with somatization. Psiquis Rev Psiquiatr Psicol Psicosom 1988; 9(3):34-40.

41. Overmars H, Scherpenisse PM, Post LC. Fluvoxamine maleate: metabolism in man. Eur J Drug Metab Pharmacokinet 1983; 8(3):269-80.

42. Perucca E., Gatti G., Cipolla G., Spina E., Barel S., Soback S., Gips M., Bialer M. Inhibition of diazepam metabolism by fluvoxamine: A pharmacokinetic study in normal volunteers. Clinical Pharmacology and Therapuetics 1994; 56 (5): 471-476.

43. Rasmussen B.B., Maenpaa J., Pelkonen O., Loft S., Poulsen H., Lykkesfeldt J., Brosen K. Selective serotonin reuptake inhibitors and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. British Journal of Pharmacology 1995; 39: 151-159.

44. Sperber A.D. Toxic interaction between fluvoxamine and sustained release theophylline in an 11-year-old boy. Drug Safety 1991; 6 (6): 460-462.

45. Stevens, I, Gaertner, HJ. Plasma Level Measurement in a Patient With Clozapine Intoxication. J. Clin. Pharmacology 1996; 16(1):86-87.

46. van Harten J. Overview of the pharmacokinetics of fluvoxamine. Clinical Pharmacokinetics 1995; 29, suppl. 1: 1-9.

47. Vella J.P., Mohamed H.S. Interactions between cyclosporine and newer antidepressant medications. American Journal of Kidney Diseases 1998; 31(2): 320-323.

48. Vertees JE and Siebel G. Rapid death resulting from mesoridazine overdose. Vet Hum Toxicol 1987:29(1):65-7.

49. von Bahr C, et al. Plasma levels of thioridazine and metabolites are influenced by the debrisoquin hydroxylation phenotype. Clin Pharmacol Ther 1991;49(3):234-240.

50. von Moltke L.L., Greenblatt D.J., Court M.H., Duan S.X., Harmatz J.S., Shader R.I. Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and fluvoxamine. Comparison with other selective serotonin reuptake inhibitor antidepressants. Journal of Clinical Psychopharmacology 1995; 15 (2): 125-131.

51. Wagner, W, Zaborny, BA, Grat, TE. Fluvoxamine. A review of its safety profile in world-wide studies. International Clinical Psychopharmacology 1994; 9:223-227.

52. Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data 1986. Int Clin Psychopharmacol 1986; 1:221-30.

53. Wakelin JS. A review of the properties of a new specific 5-HT reuptake inhibitor - fluvoxamine maleate. Front Neuropsychiatric Res 1983; 159-73.

54. Weiss E.L., Potenza M.N., McDougle C.J., Epperson C.N. Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors: an open-label case series. J Clin Psychiatry 1999; 60 (8): 524-527.

55. Wright, S, Dawling, S, Ashford, JJ. Excretion of fluvoxamine in breast milk. Br. J. Clin. Pharmacology 1994; 31:209.

56. Yun C., Okerholm R.A., Guengerich F. P. Oxidation of the Antihistaminic Drug Terfenadine in Human Liver Microsomes. Role of Cytochrome P-450 3A(4) in N-Dealkylation and C-Hydroxylation. Drug Metabolism and Disposition 1993; 21 (3): 403-409.