20 243 S 021 rsp

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

NDA 20-243/S-021

Solvay Pharmaceuticals
Attention: J. Greg Perkins, Ph.D.
Vice President Regulatory Science
901 Sawyer Road
Marietta, Georgia 30062

SEP 2 8 2000

Dear Dr. Perkins:

Please refer to your supplemental new drug application dated and received December 2, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Luvox (fluvoxamine maleate) 25 mg, 50 mg, and 100 mg Tablets.

Additionally, we acknowledge receipt of your submissions dated May 31, and June 30, 2000.

Reference is also made to an Agency letter dated March 25, 1997, providing for the approval of supplemental application S-006 to use Luvox to treat obsessive compulsive disorder in the pediatric population. This letter also committed that Solvay explore further the effects of Luvox in obsessive compulsive disorder (OCD) patients between the ages of 12 – 17 years old as a Phase 4 commitment.

We additionally refer to a series of faxes dated September 21, 24, and 26, 2000 in which labeling for this supplemental application, S-021, was agreed upon by Solvay and the Agency.

This supplemental new drug application provides for revised labeling of Luvox based upon the results of a long-term, open-label safety study and a pharmacokinetic study in children and adolescents with OCD.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

Additionally, this data completely fulfills your Phase 4 commitment for S-006 as enumerated in our March 25, 1997, Agency letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 paper copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-243/S-021". Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

/S/

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 20-243
HFD-120/Div. File
HFD-120/P.David
HFD-120/R.Katz/T.Laughren
HFD-120/A.Mosholder/G.Dubitsky
HFD-860/R.Baweja/E.Fadiran/V.Sekar
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-42/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT
HFD-093/DDMS-IST (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

9/14/00pd
filename:

APPROVAL (AP)
(AC) ACKNOWLEDGMENT OF FULFILLMENT OF PHASE 4 COMMITMENT
(Phase 4 Commitments)

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 13, 2000

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Luvox (fluvoxamine) Supplement for Pediatric Exclusivity

TO: File NDA 20-243/S-021
[**Note:** This overview should be filed with the 12-2-99 original submission.]

1.0 BACKGROUND

Luvox (fluvoxamine) is a selective serotonin reuptake inhibitor that was approved for the treatment of obsessive compulsive disorder (OCD) 12-5-94 (NDA 20-243). Supplement S-006, including data from a single clinical trial supporting the use of fluvoxamine in the treatment of OCD in pediatric patients with this condition, in a dose range of 50-200 mg/day, was approved 3-25-97. On 11-7-97, we added standard language to Luvox labeling regarding uncertainties about possible effects of psychotropic drugs on long term growth and development.

At the time of the approval of S-006, we requested that the sponsor commit to addressing the finding that the positive results in the pediatric study were derived entirely from the preadolescent subjects, and the sponsor did agree to this request. While it was suspected adolescent subjects might have been underdosed, there were no pharmacokinetic data to support this hypothesis.

S-021 includes data from 2 studies to address the above 2 issues. Study RH.114.02.01 was a one year, open extension from the double blind pediatric study, to assess long-term safety and efficacy. Study S.114.11.02 was a pediatric PK study. These 2 studies were the subject of a Written Request issued 11-30-00, and S-021 is in response to that WR. Dr. Woodcock granted a waiver of the AIP to permit this review, and Solvay has been granted 6 months exclusivity for submission of S-021.

The sponsor has proposed changes in several sections of labeling based on the results of these 2 studies, in particular, Pharmacokinetics and Clinical Trials (under Clinical Pharmacology), Indications, Pediatric Use (under Precautions), and Dosage and Administration.

Since the proposal is to use the currently approved Luvox formulations for these modified claims, there was no need for chemistry or pharmacology reviews of this supplement. Consequently, the focus was on clinical and pharmacokinetic data. The primary review of the efficacy and safety data was done by Andrew Mosholder, M.D. from the clinical group. Vanitha Sekar, Ph.D. from Biopharmaceutics has reviewed the pharmacokinetic data.

The 2 studies noted above were conducted [redacted] The original supplement (S-021) was submitted 12-2-99.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

2.0 CHEMISTRY

Luvox is a marketed product, and there were no chemistry issues requiring review for this supplement.

3.0 PHARMACOLOGY

There were no pharmacology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

S-021 included the results of Study S1141102, a pediatric PK study. After excluding premature dropouts and subjects from a site failing to meet GCP standards, there were n=34 subjects with evaluable data. Doses were titrated up to 100 mg bid in children (total exposure time of 36 days) and up to 150 mg bid in adolescents (total exposure time of 43 days). The sponsor concluded that the data showed clearances in children about half that observed in adolescents, with female children having lower clearances than male children. They also compared the adolescent data to adult data (at the same doses), and concluded that the adolescent clearances were about 50% higher than in adults. On the basis of these findings, they recommended dosage adjustments in adolescents up to 150 mg bid, and possibly lower doses in female children compared to male children.

Dr. Sekar and the biopharm group did not agree with the sponsor's approach to PK analysis, although they did agree with the overall conclusions of higher plasma exposures in children, and female children in particular. They felt that the data were not sufficient for calculation of clearance and half-life. and so, they focused only on Cmax, Cmin, and AUC values. They also disagreed with

the assumption of linear kinetics underlying Solvay's calculations, and alternatively, used a population PK approach. These analyses revealed nonlinear PK. They argued that the data revealed a nonlinearity, not for oral clearance, but rather, for bioavailibility. Thus, weight dependent differences in bioavailability explain the differences in plasma exposures in children vs adolescents and female children vs male children.

The bottom line, however, regarding dosing recommendations is the same. Dr. Sekar and the biopharm group have proposed a different summary description of the results of the PK study, but agree with the dosing recommendations.

5.0 CLINICAL DATA

5.1 Efficacy Data

Summary of Efficacy Data for Open Extension of Study RH.114.02.01

The only efficacy data submitted in S-021 were open extension data (1 year) for the RCT that was the basis for the original claim in pediatric OCD. On the basis of these efficacy data, the sponsor has proposed adding language to labeling suggesting that the short-term benefits are maintained for up to 1 year. Dr. Mosholder has reviewed these data, concluding that they are not interpretable regarding longer-term efficacy, and I agree.

5.2 Safety Data

Summary of Safety Data for Open Extension of Study RH.114.02.01

The only safety data submitted in S-021 were open extension data (1 year) for the RCT that was the basis for the original claim in pediatric OCD. On the basis of these safety data, the sponsor has proposed deleting language from labeling suggesting that the effects of fluvoxamine on growth and development are unknown. Dr. Mosholder has reviewed these data, concluding that they are not sufficient to justify removing the standard cautionary language regarding possibble effects on growth and development, and I agree. We agree that these data support general language regarding a finding of a similar adverse event profile to that observed in adults.

5.3 Clinical Sections of Labeling

We have made several changes in the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling. I will briefly note here several of the more critical issues needing modification:

-A different description of the pediatric PK study.

-An explanation in the Clinical Trials summary of the lack of efficacy in adolescents in the pediatric OCD study.

-Omission of language suggesting longer-term efficacy based on open extension data.

-Retention of standard language regarding the possibility of effects on growth and development under Pediatric Use.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take S-021 to the PDAC.

7.0 DSI INSPECTIONS

There was a for cause inspection of one site in the PK study, resulting in data from the small number of patients at that site being excluded from the analyses. No other sites have been inspected at this time. We have inquired of DSI whether or not any of the other investigators in this study have been inspected recently and the outcome of those inspections.

8.0 LABELING AND APPROVABLE LETTER

8.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made several changes to the sponsor's draft dated 12-2-99.

8.2 Approvable Letter

The approvable letter includes draft labeling.

9.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Solvay has adequately responded to the question of differential effectivenss on the basis of age in the pediatric population, although we differ with them somewhat regarding how best to characterize the results of the PK study and the open extension in labeling. I recommend that we issue the attached approvable letter with our labeling proposal.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig NDA
HFD-120
HFD-120/TLaughren/RKatz/AMosholder/PDavid

DOC: MEMLV021.AE1

MEMORANDUM

DATE: September 27, 2000

FROM: Director
Division of Neuropharmacoiogical Drug Products/HFD-120

TO: File, NDA 20-243/S-021

SUBJECT: Action Memo for NDA 20-243/S-021, for the use of Luvox (fluvoxamine maleate) in adolescents with obsessive compulsive disorder

NDA 20-243, for the use of Luvox (fluvoxamine maleate) was approved for the treatment of adults with obsessive-compulsive disorder (OCD) on 12/5/94. On 3/25/97, Supplement S-006, which included data from a single controlled trial in pediatric patients, was approved, and language describing this study and dosing recommendations in this population were added to labeling. However. it was noted at that time that the evidence of effectiveness seen in that single trial was largely due to an effect in pre-adolescent children, with no appreciable effect seen in adolescents, and labeling included language that noted this difference. As a Phase 4 commitment, the sponsor agreed to further explore the effectiveness of the drug in adolescents.

In fulfillment of this Phase 4 commitment, Solvay Pharmaceuticals submitted S-021 on 12/2/99. This supplement included the results of open extension data from the original controlled trial on which pediatric approval was granted (referred to as Study RH.114.02.01), as well as a pharmacokinetic study evaluating the kinetics in children and adolescents (Study S.114.11.02). In addition, the sponsor compared the kinetics in adolescents derived from this study to kinetic data in adults.

This supplement has been reviewed by Dr. Andrew Mosholder, medical reviewer (review dated 8/8/00), Dr. Vanitha Sekar, Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/7/00), and Dr. Thomas Laughren, Psychiatric Drugs Team Leader (memo dated 9/13/00). All reviewers recommend that the application be considered approvable. All reviewers have concluded that the sponsor has adequately addressed the issue of efficacy in adolescents, but also all agreed that the sponsor's initially proposed labeling was inadequate.

I will briefly review the results of the studies submitted, and offer the basis for the division's action.

Pharmacokinetic evaluation

The results of Study S.114.02.01 demonstrate that, for a given dose, AUC, mean plasma concentrations, Cmax, and Cmin are all considerably greater in children

from ages 6-11 than in adolescents. For example, as can be seen in Dr. Sekar's Figure 3 (page 5 of her review), the mean plasma concentration in children over 12 hours after a 100 mg single dose (during a 100 mg BID regimen) was on the order of twice that seen in adolescents (about 400 ng/ml compared to about 200 ng/ml). Her Tables 3 and 4 (page 6) provide quantitative comparisons for Cmin, Cmax, and AUC (0-12). Fluvoxamine was seen to demonstrate non-linear kinetics, which Dr. Sekar has concluded is related to non-linear bioavailability (as the dose increases, the oral bioavailability increases), and not non-linearity of clearance, as the sponsor has suggested.

Importantly, the kinetics of fluvoxamine in adolescents, as derived from this study, were compared to the kinetics in adults, using data in this latter population derived from Study CR100.0059, which was previously submitted. This comparison demonstrated that mean plasma concentrations did not materially differ between the groups (see Dr. Sekar's Figure 8, page 11). Further, there were no significant differences noted between adults and adolescents in Cmin, Cmax, AUC, or clearance (see Dr. Sekar's Table 9, page 11), although it is worth noting that adolescents consistently demonstrated numerically lower point estimates for Cmin, Cmax, and AUC and a higher estimate for CL/F than adults (for example, as can be seen in Table 9, the ratio of adolescent AUC/adult AUC was about 69, and the ratio for CL/F was about 150).

Clinical evaluation

As noted above, the sponsor submitted the results of a safety and efficacy analysis of the open, uncontrolled extension data of the controlled trial. As noted by both Drs. Mosholder and Laughren, the lack of a concurrent control makes it impossible to make reliable conclusions about long term effectiveness. As noted by Dr. Mosholder, there does not appear to be any unique adverse event that is of particular concern. Further, as pointed out by Dr. Mosholder, the sponsor's analysis of fluvoxamine's effect on growth was inadequate, and probably by itself does not support their conclusion that there is no adverse effect on growth (although there does not appear to be any obvious, large negative effect).

Conclusions

The sponsor has submitted kinetic data that demonstrates that children have considerably greater exposure to fluvoxamine for a given dose than do adolescents. Further, they have demonstrated, from a cross-study comparison, that adolescents and adults treated with 150 mg BID have similar exposures, although the exposure seems to be somewhat less in adolescents. We have clinical evidence from a controlled trial that the drug is effective in the pediatric population, but an exploratory analysis of that trial revealed no demonstrable effect in adolescents. The data in this current supplement are intended to establish an effective dose range in adolescents.

I agree with Drs. Mosholder and Laughren that the open, uncontrolled extension data cannot serve as support for either the effectiveness, or any proposed dosing recommendations, in adolescents. Therefore, the effectiveness in adolescents can only be answered (if at all) with the kinetic analyses presented.

In this regard, we know that for any given dose, children have greater plasma levels of fluvoxamine than adolescents. The problem that arises from this fact (with regard to identifying an effective dose in adolescents) is that if the data in the controlled trial demonstrate that efficacy in children is associated only with high plasma levels of fluvoxamine, these levels may be greater than levels known to be achievable at the doses examined to date in adolescents. Were this to be the case, we would have no data on which to base a dosing recommendation for adolescents, because we could not know with confidence 1) what dose to administer to adolescents to achieve these higher plasma levels, and 2) that the lower levels known to be achieved in adolescents (at the doses studied) were effective in adolescents. On the other hand, if it can be shown that there is considerable overlap in the plasma levels achieved with doses shown to be effective in children and adults, then it will be 1) reasonable to assume that these levels will also be effective in adolescents, and 2) possible to write dosing recommendations for adolescents (because the kinetics are essentially the same as in adults).

The current dosing recommendations for children are 50-200 mg/day (25-100 mg BID). From the kinetic study submitted in this supplement, the mean Cmin plasma levels achieved in children at these doses range from about 40 ng/ml – 400 ng/ml. The recommended effective dose range in adults is 100-300 mg/day. Given that (at least at 300 mg/day) the kinetics in adults are essentially the same as in adolescents, this dose range can be considered to yield plasma levels in adults in the range of 50-300 ng/ml (based in part on the kinetic data in adolescents). It can be seen that these plasma level ranges exhibit considerable overlap between children and adults, supporting the view that similar plasma levels are effective in both children and adults. Based on this finding, it is reasonable to conclude that this range will also be effective in adolescents. Further, the similarity in kinetics between adults and adolescents permit dosing recommendations to be written in adolescents to achieve these plasma levels.

Other issues

It should be noted that there was an additional Phase 4 commitment contained in the 3/25/97 Approval letter; namely, that the sponsor would eventually market the approved 25 mg tablet. In a submission dated 4/21/97, the sponsor honored that commitment (acknowledged in division letter of 5/23/97).

Finally, the review team has recommended that an Approvable letter issue, given their concerns about the sponsor's proposed labeling. However, since those reviews have been completed, the team has negotiated labeling with the

sponsor, and the sponsor and review team have agreed to a version of labeling. For this reason, and for the reasons stated above, I will issue the attached Approval letter.

/S/

Russell Katz, M.D.

Cc:
NDA 20-243/S-021
HFD-120
HFD-120/Katz/Laughren/Mosholder/David
HFD-860/Sekar/Fadiran

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT
NDA 20-243/S-021

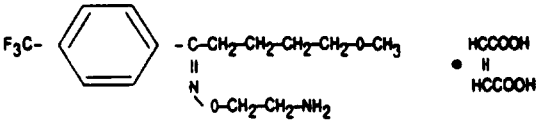
[Note: Below is the labeling for Luvox. This labeling was agreed upon by Solvay and the Agency in a series of faxes dated September 21, 24, and 26, 2000. The labeling is identical to your last approved labeling supplement, S-022, which was approved in an Agency letter dated August 9, 2000, except for the highlighted revisions. These revisions to labeling are based on the labeling changes proposed in your December 2, 1999 submission (S-021) as well as labeling revisions requested in an Agency letter dated June 1, 2000 (S-017). Double underline font denotes additions to the labeling, and strikeout font denotes deletions to the labeling.]

LUVOX®
(Fluvoxamine Maleate) Tablets
25 mg, 50 mg and 100 mg

DESCRIPTION

Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl)valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1) and has the empirical formula $C_{15}H_{21}O_2N_2F_3 \cdot C_4H_4O_4$. Its molecular weight is 434.4.

The structural formula is:



Fluvoxamine maleate is a white or off white, odorless, crystalline powder which is sparingly soluble in water, freely soluble in ethanol and chloroform and practically insoluble in diethyl ether.

LUVOX® (Fluvoxamine Maleate) Tablets are available in 25 mg, 50 mg and 100 mg strengths for oral administration. In addition to the active ingredient, fluvoxamine maleate, each tablet contains the following inactive ingredients: carnauba wax, hydroxypropyl methylcellulose, mannitol, polyethylene glycol, polysorbate 80, pregelatinized starch (potato), silicon dioxide, sodium stearyl fumarate, starch (corn), and titanium dioxide. The 50 mg and 100 mg tablets also contain synthetic iron oxides.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons. In preclinical studies, it was found that fluvoxamine inhibited neuronal uptake of serotonin.

In *in vitro* studies fluvoxamine maleate had no significant affinity for histaminergic, alpha or beta adrenergic, muscarinic, or dopaminergic receptors. Antagonism of some of these receptors is thought to be associated with various

sedative, cardiovascular, anticholinergic, and extrapyramidal effects of some psychotropic drugs.

Pharmacokinetics

Bioavailability: The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food.

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 had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose.

Distribution/Protein Binding: The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution.

Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL.

Metabolism: Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. (See **PRECAUTIONS - Drug Interactions**)

Elimination: Following a ^{14}C-labelled oral dose of fluvoxamine maleate (5 mg), an average of 94% of drug-related products was recovered in the urine within 71 hours.

The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

Elderly Subjects: In a study of LUVOX® Tablets at 50 and 100 mg comparing elderly (ages 66-73) and young subjects (ages 19-35), mean maximum plasma concentrations in the elderly were 40% higher. The multiple dose elimination half-life of fluvoxamine was 17.4 and 25.9 hours in the elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX® Tablets should be slowly titrated during initiation of therapy.

Pediatric Subjects: The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents (see table

below). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of LUVOX® Tablets may produce therapeutic benefit (see table below). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (see table below). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between children, adolescents and adults

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)		Dose = 300 mg/day (150 mg bid)	
	Children (n=10)	Adolescent (n=17)	Adolescents (n= 13)	Adults (n=16)
AUC0-12 (ng.h/ml/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
Cmax (ng/ml/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
Cmin (ng/ml/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between male and female children (6-11 years)

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)	
	Male Children (n=7)	Female children (n= 3)
AUC0-12 (ng.h/ml/kg)	95.8 (83.9)	293.5 (233.0)
Cmax (ng/ml/kg)	9.1 (7.6)	28.1 (21.1)
Cmin (ng/ml/kg)	6.6 (6.1)	21.2 (17.6)

Hepatic and Renal Disease: A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable to each other, suggesting no accumulation of fluvoxamine in these patients. (See **PRECAUTIONS - *Use in Patients with Concomitant Illness***)

Clinical Trials

Adult OCD Studies: The effectiveness of LUVOX® Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the

Clinical Global Impressions (CGI) scale for both studies combined.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO ADULT OCD STUDIES		
Outcome Classification	**Fluvoxamine (N = 120)**	**Placebo (N = 134)**
Very Much Improved	13%	2%
Much Improved	30%	10%
Minimally Improved	22%	32%
No Change	31%	51%
Worse	4%	6%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

Pediatric OCD Study: The effectiveness of LUVOX® Tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17). Patients in this study were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50-200 mg/day (on a bid schedule) on the basis of response and tolerance. All patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score of 24. Patients receiving fluvoxamine maleate experienced mean reductions of approximately six units on the CY-BOCS total score, compared to a three-unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impression (CGI) scale for the pediatric study.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN PEDIATRIC STUDY		
Outcome Classification	**Fluvoxamine (N= 38)**	**Placebo (N= 36)**
Very Much Improved	21%	11%
Much Improved	18%	17%
Minimally Improved	37%	22%
No Change	16%	44%
Worse	8%	6%

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8-11 age group and

essentially no effect in the 12-17 age group. While the significance of these results is not clear, the 2-3 fold higher steady state plasma fluvoxamine concentrations in children compared to adolescents (see Pharmacokinetics) is suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

INDICATIONS AND USAGE

LUVOX® Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX® Tablets was established in three 10-week trials with obsessive compulsive outpatients with the diagnosis of Obsessive Compulsive Disorder as defined in DSM-III-R. (See **Clinical Trials** under **CLINICAL PHARMACOLOGY**.)

Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of LUVOX® Tablets for long-term use, i.e., for more than 10 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use LUVOX® Tablets for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. (See **DOSAGE AND ADMINISTRATION**)

CONTRAINDICATIONS

Co-administration of thioridazine, terfenadine, astemizole, cisapride, or pimozide with LUVOX® Tablets is contraindicated (see **WARNINGS** and **PRECAUTIONS**).

LUVOX® Tablets are contraindicated in patients with a history of hypersensitivity to fluvoxamine maleate.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with monoamine oxidase inhibitors (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have discontinued that drug and have been started on a MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that LUVOX® Tablets not be used in combination with a MAOI, or within 14 days of discontinuing treatment with a MAOI. After stopping LUVOX® Tablets, at least 2 weeks should be allowed before starting a MAOI.

Potential Interaction with Thioridazine

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 co-administration of fluvoxamine.

Thioridazine 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 be even more pronounced when it is administered at higher doses.

Therefore, fluvoxamine and thioridazine should not be co-administered (see CONTRAINDICATIONS and PRECAUTIONS).

Potential Terfenadine, Astemizole, Cisapride, and Pimozide Interactions

Terfenadine, astemizole, cisapride, and pimozide are all metabolized by the cytochrome P450IIIA4 isozyme, and it has been demonstrated that ketoconazole, a potent inhibitor of IIIA4, blocks the metabolism of these drugs, resulting in increased plasma concentrations of parent drug. Increased plasma concentrations of terfenadine, astemizole, cisapride, and pimozide cause QT prolongation and have been associated with torsades de pointes-type ventricular tachycardia, sometimes fatal. As noted below, a substantial pharmacokinetic interaction has been observed for fluvoxamine in combination with alprazolam, a drug that is known to be metabolized by the IIIA4 isozyme. Although it has not been definitively demonstrated that fluvoxamine is a potent IIIA4 inhibitor, it is likely to be, given the substantial interaction of fluvoxamine with alprazolam. Consequently, it is recommended that fluvoxamine not be used in combination with either terfenadine, astemizole, cisapride, or pimozide (see CONTRAINDICATIONS and PRECAUTIONS).

Other Potentially Important Drug Interactions
(Also see **PRECAUTIONS - Drug Interactions**)

Benzodiazepines: Benzodiazepines metabolized by hepatic oxidation (e.g., alprazolam, midazolam, triazolam, etc.) should be used with caution because the clearance of these drugs is likely to be reduced by fluvoxamine. The clearance of benzodiazepines metabolized by glucuronidation (e.g., lorazepam, oxazepam, temazepam) is unlikely to be affected by fluvoxamine.

Alprazolam - When fluvoxamine maleate (100 mg qd) and alprazolam (1 mg qid) were co-administered to steady state, plasma concentrations and other pharmacokinetic parameters (AUC, C_{max}, $T_{½}$) of alprazolam were approximately twice those observed when alprazolam was administered alone; oral clearance was reduced by about 50%. The elevated plasma alprazolam concentrations resulted in decreased psychomotor performance and memory. This interaction, which has not been investigated using higher doses of fluvoxamine, may be more pronounced if a 300 mg daily dose is co-administered, particularly since fluvoxamine exhibits non-linear pharmacokinetics over the dosage range 100-300 mg. If alprazolam is co-administered with LUVOX® Tablets, the initial alprazolam dosage should be at least halved and titration to the lowest effective dose is recommended. No dosage adjustment is required for LUVOX® Tablets.

Diazepam - The co-administration of LUVOX® Tablets and diazepam is generally not advisable. Because fluvoxamine reduces the clearance of both diazepam and its active metabolite, N-desmethyldiazepam, there is a strong likelihood of substantial accumulation of both species during chronic co-administration.

Evidence supporting the conclusion that it is inadvisable to co-administer fluvoxamine and diazepam is derived from a study in which healthy volunteers taking 150 mg/day of fluvoxamine were administered a single oral dose of 10 mg of diazepam. In these subjects (N=8), the clearance of diazepam was reduced by 65% and that of N-desmethyldiazepam to a level that was too low to measure over the course of the 2 week long study.

It is likely that this experience significantly underestimates the degree of accumulation that might occur with repeated diazepam administration. Moreover, as noted with alprazolam, the effect of fluvoxamine may even be more pronounced when it is administered at higher doses.

Accordingly, diazepam and fluvoxamine should not ordinarily be co-administered.

Theophylline: The effect of steady-state fluvoxamine (50 mg bid) on the pharmacokinetics of a single dose of theophylline (375 mg as 442 mg aminophylline) was evaluated in 12 healthy non-smoking, male volunteers. The clearance of theophylline was decreased approximately three-fold. Therefore, if theophylline is co-administered with fluvoxamine maleate, its dose should be reduced to one third of the usual daily maintenance dose and plasma concentrations of theophylline should be monitored. No dosage adjustment is required for LUVOX® Tablets.

Warfarin: When fluvoxamine maleate (50 mg tid) was administered concomitantly with warfarin for two weeks, warfarin plasma concentrations increased by 98% and prothrombin times were prolonged. Thus patients receiving oral anticoagulants and LUVOX® Tablets should have their prothrombin time monitored and their anticoagulant dose adjusted accordingly. No dosage adjustment is required for LUVOX® Tablets.

PRECAUTIONS

General

Activation of Mania/Hypomania: During premarketing studies involving primarily depressed patients, hypomania or mania occurred in approximately 1% of patients treated with fluvoxamine. In a ten week pediatric OCD study, 2 out of 57 patients (4%) treated with fluvoxamine experienced manic reactions, compared to none of 63 placebo patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, LUVOX® Tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing studies, seizures were reported in 0.2% of fluvoxamine-treated patients. LUVOX® Tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Suicide: The possibility of a suicide attempt is inherent in patients with depressive symptoms, whether these occur in primary depression or in association with another primary disorder such as OCD. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for LUVOX® Tablets should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Hyponatremia: Several cases of hyponatremia have been reported. In cases where the outcome was known, the hyponatremia appeared to be reversible when fluvoxamine was discontinued. The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or with concomitant conditions that might cause hyponatremia. In patients receiving LUVOX® Tablets and suffering from Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH), displacement syndromes, edematous states, adrenal disease or conditions of fluid

loss, it is recommended that serum electrolytes, especially sodium as well as BUN and plasma creatinine, be monitored regularly.

Use in Patients with Concomitant Illness: Closely monitored clinical experience with LUVOX® Tablets in patients with concomitant systemic illness is limited. Caution is advised in administering LUVOX® Tablets to patients with diseases or conditions that could affect hemodynamic responses or metabolism.

LUVOX® Tablets have 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 many clinical studies during the product's premarketing testing. Evaluation of the electrocardiograms for patients with depression or OCD who participated in premarketing studies revealed no differences between fluvoxamine and placebo in the emergence of clinically important ECG changes.

In patients with liver dysfunction, fluvoxamine clearance was decreased by approximately 30%. LUVOX® Tablets should be slowly titrated in patients with liver dysfunction during the initiation of treatment.

Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe LUVOX® Tablets:

***Interference with Cognitive or Motor Performance*:** Since any psychoactive drug may impair judgement, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain that LUVOX® Tablets therapy does not adversely affect their ability to engage in such activities.

Pregnancy: Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy with LUVOX® Tablets.

***Nursing*:** Patients receiving LUVOX® Tablets should be advised to notify their physicians if they are breast feeding an infant. (See **PRECAUTIONS - Nursing Mothers**)

***Concomitant Medication*:** Patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for clinically important interactions with LUVOX® Tablets.

Alcohol: As with other psychotropic medications, patients should be advised to avoid alcohol while taking LUVOX® Tablets.

Allergic Reactions: Patients should be advised to notify their physicians if they develop a rash, hives, or a related allergic phenomenon during therapy with LUVOX® Tablets.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
Potential Interactions with Drugs that Inhibit or are Metabolized by Cytochrome P450 Isozymes: Multiple hepatic cytochrome P450 (CYP450) enzymes are involved in the oxidative biotransformation of a large number of structurally

different drugs and endogenous compounds. The available knowledge concerning the relationship of fluvoxamine and the CYP450 enzyme system has been obtained mostly from pharmacokinetic interaction studies conducted in healthy volunteers, but some preliminary *in vitro* data are also available. Based on a finding of substantial interactions of fluvoxamine with certain of these drugs (see later parts of this section and also **WARNINGS** for details) and limited *in vitro* data for the IIIA4 isozyme, it appears that fluvoxamine inhibits the following isozymes that are known to be involved in the metabolism of the listed drugs:

IA2	IIC9	IIIA4
Warfarin	Warfarin	Alprazolam
Theophylline		
Propranolol		

In vitro data suggest that fluvoxamine is a relatively weak inhibitor of the IID6 isozyme.

Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of cytochrome P450IID6 isozyme. Such individuals have been referred to as "poor metabolizers" (PM) of drugs such as debrisoquin, dextromethorphan, and tricyclic antidepressants. While none of the drugs studied for drug interactions significantly affected the pharmacokinetics of fluvoxamine, an *in vivo* study of fluvoxamine single-dose pharmacokinetics in 13 PM subjects demonstrated altered pharmacokinetic properties compared to 16 "extensive metabolizers" (EM): mean Cmax, AUC, and half-life were increased by 52%, 200%, and 62%, respectively, in the PM compared to the EM group. This suggests that fluvoxamine is metabolized, at least in part, by IID6 isozyme. Caution is indicated in patients known to have reduced levels of P450IID6 activity and those receiving concomitant drugs known to inhibit this isozyme (e.g. quinidine).

The metabolism of fluvoxamine has not been fully characterized and the effects of potent P450 isozyme inhibition, such as the ketoconazole inhibition of IIIA4, on fluvoxamine metabolism have not been studied.

A clinically significant fluvoxamine interaction is possible with drugs having a narrow therapeutic ratio such as terfenadine, astemizole, cisapride, or pimozide, warfarin, theophylline, certain benzodiazepines and phenytoin. If LUVOX® Tablets are to be administered together with a drug that is eliminated via oxidative metabolism and has a narrow therapeutic window, plasma levels and/or pharmacodynamic effects of the latter drug should be monitored closely, at least until steady-state conditions are reached (See **CONTRAINDICATIONS** and **WARNINGS**).

CNS Active Drugs:
Monoamine Oxidase Inhibitors: See **WARNINGS**

Alprazolam: See **WARNINGS**

Diazepam: See **WARNINGS**

Alcohol: Studies involving single 40 g doses of ethanol (oral administration in one study and intravenous in the other)

and multiple dosing with fluvoxamine maleate (50 mg bid) revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of the other.

Carbamazepine: Elevated carbamazepine levels and symptoms of toxicity have been reported with the co-administration of fluvoxamine maleate and carbamazepine.

Clozapine: Elevated serum levels of clozapine have been reported in patients taking fluvoxamine maleate and clozapine. Since clozapine related seizures and orthostatic hypotension appear to be dose related, the risk of these adverse events may be higher when fluvoxamine and clozapine are co-administered. Patients should be closely monitored when fluvoxamine maleate and clozapine are used concurrently.

Lithium: As with other serotonergic drugs, lithium may enhance the serotonergic effects of fluvoxamine and, therefore, the combination should be used with caution. Seizures have been reported with the co-administration of fluvoxamine maleate and lithium.

Lorazepam: A study of multiple doses of fluvoxamine maleate (50 mg bid) in healthy male volunteers (N=12) and a single dose of lorazepam (4 mg single dose) indicated no significant pharmacokinetic interaction. On average, both lorazepam alone and lorazepam with fluvoxamine produced substantial decrements in cognitive functioning; however, the co-administration of fluvoxamine and lorazepam did not produce larger mean decrements compared to lorazepam alone.

Methadone: Significantly increased methadone (plasma level:dose) ratios have been reported when fluvoxamine maleate was administered to patients receiving maintenance methadone treatment, with symptoms of opioid intoxication in one patient. Opioid withdrawal symptoms were reported following fluvoxamine maleate discontinuation in another patient.

Sumatriptan: There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) is clinically warranted, appropriate observation of the patient is advised.

Tacrine: In a study of 13 healthy, male volunteers, a single 40 mg dose of tacrine added to fluvoxamine 100 mg/day administered at steady-state was associated with five- and eight-fold increases in tacrine Cmax and AUC, respectively, compared to the administration of tacrine alone. Five subjects experienced nausea, vomiting, sweating, and diarrhea following co-administration, consistent with the cholinergic effects of tacrine.

Thioridazine: See **CONTRAINDICATIONS** and **WARNINGS**.

Tricyclic Antidepressants (TCAs): Significantly increased plasma TCA levels have been reported with the co-administration of fluvoxamine maleate and amitriptyline, clomipramine or imipramine. Caution is indicated with the co-administration of LUVOX® Tablets and TCAs; plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced.

Tryptophan: Tryptophan may enhance the serotonergic effects of fluvoxamine, and the combination should, therefore, be used with caution. Severe vomiting has been reported with the co-administration of fluvoxamine maleate and

tryptophan.

Other Drugs:
Theophylline: See **WARNINGS**

Warfarin: See **WARNINGS**

Digoxin: Administration of fluvoxamine maleate 100 mg daily for 18 days (N=8) did not significantly affect the pharmacokinetics of a 1.25 mg single intravenous dose of digoxin.

Diltiazem: Bradycardia has been reported with the co-administration of fluvoxamine maleate and diltiazem.

Propranolol and Other Beta-Blockers: Co-administration of fluvoxamine maleate 100 mg per day and propranolol 160 mg per day in normal volunteers resulted in a mean five-fold increase (range 2 to 17) in minimum propranolol plasma concentrations. In this study, there was a slight potentiation of the propranolol-induced reduction in heart rate and reduction in the exercise diastolic pressure.

One case of bradycardia and hypotension and a second case of orthostatic hypotension have been reported with the co-administration of fluvoxamine maleate and metoprolol.

If propranolol or metoprolol is co-administered with LUVOX® Tablets, a reduction in the initial beta-blocker dose and more cautious dose titration are recommended. No dosage adjustment is required for LUVOX® Tablets.

Co-administration of fluvoxamine maleate 100 mg per day with atenolol 100 mg per day (N=6) did not affect the plasma concentrations of atenolol. Unlike propranolol and metoprolol which undergo hepatic metabolism, atenolol is eliminated primarily by renal excretion.

Effects of Smoking on Fluvoxamine Metabolism: Smokers had a 25% increase in the metabolism of fluvoxamine compared to nonsmokers.

Electroconvulsive Therapy (ECT): There are no clinical studies establishing the benefits or risks of combined use of ECT and fluvoxamine maleate.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: There is no evidence of carcinogenicity, mutagenicity or impairment of fertility with fluvoxamine maleate.

There was no evidence of carcinogenicity in rats treated orally with fluvoxamine maleate for 30 months or hamsters treated orally with fluvoxamine maleate for 20 (females) or 26 (males) months. The daily doses in the high dose groups in these studies were increased over the course of the study from a minimum of 160 mg/kg to a maximum of 240 mg/kg in rats, and from a minimum of 135 mg/kg to a maximum of 240 mg/kg in hamsters. The maximum dose of 240 mg/kg is approximately 6 times the maximum human daily dose on a mg/m^2 basis.

Mutagenesis: No evidence of mutagenic potential was observed in a mouse micronucleus test, an *in vitro* chromosome aberration test, or the Ames microbial mutagen test with or without metabolic activation.

Impairment of Fertility: In fertility studies of male and female rats, up to 80 mg/kg/day orally of fluvoxamine maleate (approximately 2 times the maximum human daily dose on a mg/m^2 basis) had no effect on mating performance, duration of gestation, or pregnancy rate.

Pregnancy

Teratogenic Effects - Pregnancy Category C: In teratology studies in rats and rabbits, daily oral doses of fluvoxamine maleate of up to 80 and 40 mg/kg, respectively (approximately 2 times the maximum human daily dose on a mg/m^2 basis) caused no fetal malformations. However, in other reproduction studies in which pregnant rats were dosed through weaning there was (1) an increase in pup mortality at birth (seen at 80 mg/kg and above but not at 20 mg/kg), and (2) decreases in postnatal pup weights (seen at 160 but not at 80 mg/kg) and survival (seen at all doses; lowest dose tested = 5 mg/kg). (Doses of 5, 20, 80, and 160 mg/kg are approximately 0.1, 0.5, 2, and 4 times the maximum human daily dose on a mg/m^2 basis.) While the results of a cross-fostering study implied that at least some of these results likely occurred secondarily to maternal toxicity, the role of a direct drug effect on the fetuses or pups could not be ruled out. There are no adequate and well-controlled studies in pregnant women. Fluvoxamine maleate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of fluvoxamine on labor and delivery in humans is unknown.

Nursing Mothers

As for many other drugs, fluvoxamine is secreted in human breast milk. The decision of whether to discontinue nursing or to discontinue the drug should take into account the potential for serious adverse effects from exposure to fluvoxamine in the nursing infant as well as the potential benefits of LUVOX® (Fluvoxamine Maleate) Tablets therapy to the mother.

Pediatric Use

The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10-week multicenter placebo controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with fluvoxamine (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term fluvoxamine use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX® Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS, General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX® Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Table 1
ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATION OF TREATMENT IN OCD AND DEPRESSION POPULATIONS

BODY SYSTEM/ ADVERSE EVENT	PERCENTAGE OF PATIENTS FLUVOXAMINE	PLACEBO
BODY AS A WHOLE		
Headache	3%	1%
Asthenia	2%	<1%
Abdominal Pain	1%	0%
DIGESTIVE		
Nausea	9%	1%
Diarrhea	1%	<1%
Vomiting	2%	<1%
Anorexia	1%	<1%
Dyspepsia	1%	<1%
NERVOUS SYSTEM		
Insomnia	4%	1%
Somnolence	4%	<1%
Nervousness	2%	<1%
Agitation	2%	<1%
Dizziness	2%	<1%
Anxiety	1%	<1%
Dry Mouth	1%	<1%

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials:

LUVOX® Tablets have been studied in controlled trials of OCD (N=320) and depression (N=1350). In general, adverse event rates were similar in the two data sets as well as in the pediatric OCD study. The most commonly observed adverse events associated with the use of LUVOX® Tablets and likely to be drug-related (incidence of 5% or greater and at least twice that for placebo) derived from Table 2 were: *somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia, and sweating.* In a pool of two studies involving only patients with OCD, the following additional events were identified using the above rule: *dry mouth, decreased libido, urinary frequency, anorgasmia, rhinitis and taste perversion.* In a study of pediatric patients with OCD, the following additional events were identified using the above rule: *agitation, depression, dysmenorrhea, flatulence, hyperkinesia, and rash.*

Adverse Events Occurring at an Incidence of 1%: Table 2 enumerates adverse events that occurred in adults at a frequency of 1% or more, and were more frequent than in the placebo group, among patients treated with LUVOX® Tablets in two short-term placebo controlled OCD trials (10 week) and depression trials (6 week) in which patients were dosed in a range of generally 100 to 300 mg/day. This table shows the percentage of patients in each group who had at least one occurrence of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side-effect incidence rate in the population studied.

Table 2
TREATMENT-EMERGENT ADVERSE EVENT INCIDENCE RATES BY BODY SYSTEM IN ADULT OCD AND DEPRESSION POPULATIONS COMBINED[1]

	Percentage of Patients Reporting Event	
BODY SYSTEM/ ADVERSE EVENT	**FLUVOXAMINE N = 892**	**PLACEBO N = 778**
BODY AS WHOLE		
Headache	22	20
Asthenia	14	6
Flu Syndrome	3	2
Chills	2	1
CARDIOVASCULAR		
Palpitations	3	2
DIGESTIVE SYSTEM		
Nausea	40	14
Diarrhea	11	7
Constipation	10	8
Dyspepsia	10	5
Anorexia	6	2
Vomiting	5	2
Flatulence	4	3
Tooth Disorder[2]	3	1
Dysphagia	2	1
NERVOUS SYSTEM		
Somnolence	22	8
Insomnia	21	10
Dry Mouth	14	10
Nervousness	12	5
Dizziness	11	6
Tremor	5	1
Anxiety	5	3
Vasodilatation[3]	3	1
Hypertonia	2	1

BODY SYSTEM/ ADVERSE EVENT	Percentage of Patients Reporting Event FLUVOXAMINE N = 892	PLACEBO N = 778
Agitation	2	1
Decreased Libido	2	1
Depression	2	1
CNS Stimulation	2	1
RESPIRATORY SYSTEM		
Upper Respiratory Infection	9	5
Dyspnea	2	1
Yawn	2	0
SKIN		
Sweating	7	3
SPECIAL SENSES		
Taste Perversion	3	1
Amblyopia[4]	3	2
UROGENITAL		
Abnormal Ejaculation[5,6]	8	1
Urinary Frequency	3	2
Impotence[6]	2	1
Anorgasmia	2	0
Urinary Retention	1	0

1 Events for which fluvoxamine maleate incidence was equal to or less than placebo are not listed in the table above, but include the following: abdominal pain, abnormal dreams, appetite increase, back pain, chest pain, confusion, dysmenorrhea, fever, infection, leg cramps, migraine, myalgia, pain, paresthesia, pharyngitis, postural hypotension, pruritus, rash, rhinitis, thirst and tinnitus.
2 Includes "toothache," "tooth extraction and abscess," and "caries."
3 Mostly feeling warm, hot, or flushed.
4 Mostly "blurred vision."
5 Mostly "delayed ejaculation."
6 Incidence based on number of male patients.

Adverse Events in OCD Placebo Controlled Studies Which are Markedly Different (defined as at least a two-fold difference) in Rate from the Pooled Event Rates in OCD and Depression Placebo Controlled Studies: The events in OCD studies with a two-fold decrease in rate compared to event rates in OCD and depression studies were dysphagia and amblyopia (mostly blurred vision). Additionally, there was an approximate 25% decrease in nausea.

The events in OCD studies with a two-fold increase in rate compared to event rates in OCD and depression studies were: *asthenia, abnormal ejaculation (mostly delayed ejaculation), anxiety, infection, rhinitis, anorgasmia (in males), depression, libido decreased, pharyngitis, agitation, impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia and urinary retention.* These events are listed in order of decreasing rates in the OCD trials.

Other Adverse Events in OCD Pediatric Population

In pediatric patients (N=57) treated with LUVOX® Tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse events, not appearing in Table 2,

were reported in two or more of the pediatric patients and were more frequent with LUVOX® Tablets than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRI's) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Luvox in placebo controlled trials in depression and OCD.

Table 3
Percentage of Patients Reporting Sexual Adverse Events in Adult Placebo-Controlled Trials in OCD and Depression

	Luvox N=892	Placebo N=778
Abnormal Ejaculation*	8%	1%
Impotence*	2%	1%
Decreased Libido	2%	1%
Anorgasmia	2%	0%

* Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various vital signs variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various vital signs variables revealed no important differences between fluvoxamine maleate and placebo.

Laboratory Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) median change from baseline on various serum chemistry, hematology, and urinalysis variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various serum chemistry, hematology, and urinalysis variables revealed no important differences between fluvoxamine maleate and placebo.

ECG Changes
Comparisons of fluvoxamine maleate and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences between fluvoxamine maleate and placebo.

Other Events Observed During the Premarketing Evaluation of LUVOX® Tablets
During premarketing clinical trials conducted in North America and Europe, multiple doses of fluvoxamine maleate were administered for a combined total of 2737 patient exposures in patients suffering OCD or Major Depressive Disorder. Untoward events associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a limited (i.e., reduced) number of standard event categories.

In the tabulations which follow, a standard COSTART-based Dictionary terminology has been used to classify reported adverse events. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. The frequencies presented, therefore, represent the proportion of the 2737 patient exposures to multiple doses of fluvoxamine maleate who experienced an event of the type cited on at least one occasion while receiving fluvoxamine maleate. All reported events are included in the list below, with the following exceptions: 1) those events already listed in Table 2, which tabulates incidence rates of common adverse experiences in placebo-controlled OCD and depression clinical trials, are excluded; 2) those events for which a drug cause was considered remote (i.e., neoplasia, gastrointestinal carcinoma, herpes simplex, herpes zoster, application site reaction, and unintended pregnancy) are omitted; and 3) events which were reported in only one patient and judged to not be potentially serious are not included. It is important to emphasize that, although the events reported did occur during treatment with fluvoxamine maleate, a causal relationship to fluvoxamine maleate has not been established.

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

Body as a Whole: *Frequent:* accidental injury, malaise; *Infrequent*: allergic reaction, neck pain, neck rigidity, overdose, photosensitivity reaction, suicide attempt; *Rare*: cyst, pelvic pain, sudden death.

Cardiovascular System: *Frequent*: hypertension, hypotension, syncope, tachycardia; *Infrequent*: angina pectoris, bradycardia, cardiomyopathy, cardiovascular disease, cold extremities, conduction delay, heart failure, myocardial infarction, pallor, pulse irregular, ST segment changes; *Rare:* AV block, cerebrovascular accident, coronary artery disease, embolus, pericarditis, phlebitis, pulmonary infarction, supraventricular extrasystoles.

Digestive System: *Frequent*: elevated liver transaminases; *Infrequent*: colitis, eructation, esophagitis, gastritis, gastroenteritis, gastrointestinal hemorrhage, gastrointestinal ulcer, gingivitis, glossitis, hemorrhoids, melena, rectal hemorrhage, stomatitis; *Rare*: biliary pain, cholecystitis, cholelithiasis, fecal incontinence, hematemesis, intestinal obstruction, jaundice.

Endocrine System: *Infrequent:* hypothyroidism; *Rare:* goiter.

Hemic and Lymphatic Systems: *Infrequent*: anemia, ecchymosis, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare*: leukopenia, purpura.

Metabolic and Nutritional Systems: *Frequent:* edema, weight gain, weight loss; *Infrequent*: dehydration, hypercholesterolemia; *Rare:* diabetes mellitus, hyperglycemia, hyperlipidemia, hypoglycemia, hypokalemia, lactate dehydrogenase increased.

Musculoskeletal System: *Infrequent*: arthralgia, arthritis, bursitis, generalized muscle spasm, myasthenia, tendinous contracture, tenosynovitis; *Rare*: arthrosis, myopathy, pathological fracture.

Nervous System: *Frequent*: amnesia, apathy, hyperkinesia, hypokinesia, manic reaction, myoclonus, psychotic reaction; *Infrequent*: agoraphobia, akathisia, ataxia, CNS depression, convulsion, delirium, delusion, depersonalization, drug dependence, dyskinesia, dystonia, emotional lability, euphoria, extrapyramidal syndrome, gait unsteady, hallucinations, hemiplegia, hostility, hypersomnia, hypochondriasis, hypotonia, hysteria, incoordination, increased salivation, increased libido, neuralgia, paralysis, paranoid reaction, phobia, psychosis, sleep disorder, stupor, twitching, vertigo; *Rare:* akinesia, coma, fibrillations, mutism, obsessions, reflexes decreased, slurred speech, tardive dyskinesia, torticollis, trismus, withdrawal syndrome.

Respiratory System: *Frequent*: cough increased, sinusitis; *Infrequent*: asthma, bronchitis, epistaxis, hoarseness, hyperventilation; *Rare*: apnea, congestion of upper airway, hemoptysis, hiccups, laryngismus, obstructive pulmonary disease, pneumonia.

Skin: *Infrequent*: acne, alopecia, dry skin, eczema, exfoliative dermatitis, furunculosis, seborrhea, skin discoloration, urticaria.

Special Senses: *Infrequent*: accommodation abnormal, conjunctivitis, deafness, diplopia, dry eyes, ear pain, eye pain, mydriasis, otitis media, parosmia, photophobia, taste loss, visual field defect; *Rare*: corneal ulcer, retinal detachment.

Urogenital System: *Infrequent*: anuria, breast pain, cystitis, delayed menstruation[1], dysuria, female lactation[1], hematuria, menopause[1], menorrhagia[1], metrorrhagia[1], nocturia, polyuria, premenstrual syndrome[1], urinary incontinence, urinary tract infection, urinary urgency, urination impaired, vaginal hemorrhage[1], vaginitis[1]; *Rare*: kidney calculus, hematospermia[2], oliguria.

[1]Based on the number of females.
[2]Based on the number of males.

Postmarketing Reports
Voluntary reports of adverse events in patients taking LUVOX® Tablets that have been received since market

introduction and are of unknown causal relationship to LUVOX® Tablets use include: ventricular tachycardia (including torsades de pointes), porphyria, toxic epidermal necrolysis, Stevens-Johnson syndrome, Henoch-Schoenlein purpura, bullous eruption, priapism, agranulocytosis, aplastic anemia, anaphylactic reaction, angioedema, vasculitis, hyponatremia, acute renal failure, hepatitis, pancreatitis, ileus, serotonin syndrome, neuropathy, laryngismus, and severe akinesia with fever when fluvoxamine was co-administered with antipsychotic medication.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

LUVOX® Tablets are not controlled substances.

Physical and Psychological Dependence

The potential for abuse, tolerance and physical dependence with fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX® Tablets were not systematically evaluated in controlled clinical trials. LUVOX® Tablets were not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of fluvoxamine maleate misuse or abuse (i.e., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluvoxamine maleate includes over 45,000 patients treated in clinical trials and an estimated exposure of 23,000,000 patients treated during worldwide marketing experience (circa 1999). Of the 462 cases of deliberate or accidental overdose involving fluvoxamine maleate reported from this population, there were 44 deaths. Of these, six were in patients taking fluvoxamine maleate alone and the remaining 38 were in patients taking fluvoxamine maleate along with other drugs. Among non-fatal overdose cases, 373 patients had complete recovery; four patients experienced adverse sequelae of overdosage, to include persistent mydriasis, unsteady gait, kidney complications (from trauma associated with overdose), and bowel infarction requiring a hemicolectomy. In the remaining 41 patients, the outcome was unknown. The largest known ingestion of fluvoxamine maleate involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability.

Commonly (≥5%) observed adverse events associated with fluvoxamine maleate overdose include coma, hypokalemia, hypotension, nausea, respiratory difficulties, somnolence, tachycardia and vomiting. Other notable signs and symptoms seen with fluvoxamine maleate overdose (single or multiple drugs) include, bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, tremor, diarrhea, and increased reflexes.

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any antidepressant.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known.

A specific caution involves patients taking, or recently having taken, fluvoxamine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see Tricyclic Antidepressants (TCAs) under **PRECAUTIONS**).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Dosage for Adults

The recommended starting dose for LUVOX® Tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX® Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Pediatric Population (children and adolescents)

The recommended starting dose for LUVOX® Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX® Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved . It is advisable that a total daily dose of more then 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment

Although the efficacy of LUVOX® Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 25 mg: unscored, white, elliptical, film-coated (debossed "SOLVAY" and "4202" on one side)
Bottles of 100 ..... NDC 0032-4202-01
Unit dose pack of 100..... NDC 0032-4202-11

Tablets 50 mg: scored, yellow, elliptical, film-coated (debossed "SOLVAY" and "4205" on one side and scored on the other)
Bottles of 100 ..... NDC 0032-4205-01
Bottles of 1000 ..... NDC 0032-4205-10
Unit dose pack of 100..... NDC 0032-4205-11

Tablets 100 mg: scored, beige, elliptical, film-coated (debossed "SOLVAY" and "4210" on one side and scored on the other)
Bottles of 100 ..... NDC 0032-4210-01
Bottles of 1000 ..... NDC 0032-4210-10
Unit dose pack of 100..... NDC 0032-4210-11

LUVOX® Tablets should be protected from high humidity and stored at controlled room temperature, 15°-30° C (59°-86° F).

Dispense in tight containers.

Solvay
Pharmaceuticals, Inc.
Marietta, GA 30062

LUVOX NDA 20-243 S-021 PEDIATRIC LABELING APPROVAL ACTION.DOC

APPEARS THIS WAY
ON ORIGINAL

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date of Review:	December 12, 2000
NDA:	20-243
DRUG:	Luvox (fluvoxamine maleate) Tablets
Sponsor:	Solvay
Indication:	OCD
Supplements:	SE2-021 (FPL submitted 11-15-00)

Notes of interest:

- The Agency issued an AP action for this supplement in a letter dated September 28, 2000. The approval of this supplemental application cleared up all of the outstanding labeling supplements, and the Agency requested FPL identical to the attached labeling in the 9-28-00 AP letter.

NDA 20-243/SE2-021
Label Code: 1280/1285 20E
Type of Submission: FPL Post Approval
Reviewed by Medical Officer: Yes, acceptable (including one editorial change from the AP letter)

The labeling is identical to that contained in the Agency AP letter dated 9-28-00 except for a change under the **CLINICAL PHARMACOLOGY-Pediatric Subjects** section. Prior to the approval of this supplement, the Agency provided Solvay with a justification supporting the statement that steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. Solvay had initially placed this higher plasma concentration at 2-4 fold. Solvay accepted the "2-3 fold higher" figure; however, their FPL reflects the figure "2-4 fold higher" in the **CLINICAL PHARMACOLOGY-Pediatric Subjects** section but states the figure as "2-3 fold higher" in the **CLINICAL TRIALS-Pediatric OCD** section.

I discussed this discrepancy with Don Ruggirello, Regulatory Affairs at Solvay, in a telephone conversation dated January 4, 2001, and he informed me that this was a mistake on Solvay's part, and he committed to change the figure to "2-3 fold higher" under the **CLINICAL PHARMACOLOGY-Pediatric Subjects** section at the next printing of labeling.

CONCLUSIONS

1. The FPL submitted in response to the approval of the Luvox pediatric supplement, is identical to the Agency's 9-28-00 AP letter except for the one discrepancy noted above.
2. I recommend that an acknowledge and retain letter issue for this FPL with a reminder of Solvay's agreement to make the above change at the next printing of labeling.

Paul David. RPh
Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

FOOD AND DRUG ADMINISTRATION
Division of Neuropharmacological Drug Products
HFD-120, Room 4030
1451 Rockville Pike
Rockville, MD 20852

DATE: September 26, 2000

TO:		FROM:	
Name:	**Don Ruggirello, Regulatory Affairs**	Name:	**Paul David, Regulatory Project Manager**
Fax No:	770-578-5864	Fax No:	(301) 594-2859
Phone No:	770-578-5658	Phone No:	(301) 594-5530
Location:	Solvay Pharmaceuticals	Location:	FDA, Division of Neuropharmacological Drug Products

Total Pages (including cover page) = 8

Comments:

Don,
We note your agreement, in a fax dated 9/24/00, to the labeling revisions proposed in our fax dated 9/21/00. Please note that we have incorporated your corrections and minor revisions, contained in your 9/24/00 response, to the 9/21/00 labeling. These revisions are attached to this fax. Additionally, our OCPB team has responded to your questions raised to our proposed labeling. I have attached their response as well. If you have any questions regarding this labeling, please contact me ASAP since I will forward the action package to Dr. Katz by this afternoon.
Paul

/S/

NDA 20-243 / S-021 ORIG
NDA-12 / Dir File

NDA 20-243, Luvox Pediatric Supplement

Question: Please provide an explanation for the basis of 2-4 fold higher plasma concentrations in children versus adolescents. Please also explain why calculation of clearance was not appropriate.

Response: Population pharmacokinetic analysis were performed by the OCPB reviewer in consultation with the pharmacometrics scientists. Briefly, the population pharmacokinetic analysis incorporated pharmacokinetic data from pediatric and adults receiving multiple doses of fluvoxamine. The concentrations of fluvoxamine increased with dose in a non-proportional manner, suggesting non-linear pharmacokinetics. Fluvoxamine undergoes high first pass metabolism resulting in low oral bioavailability. Our population pharmacokinetic analysis of the data submitted by Solvay showed that the non-linearity in pharmacokinetics was not observed for the oral clearance (as suggested by Solvay), but for the bioavailability of fluvoxamine. Our analysis showed that fluvoxamine oral clearance is dependant on body weight and gender (for ages between 6 and 11 years). This is reflected in the ***approximately 2-3 fold higher concentrations observed in children as compared to adolescents*** and in the approximately 2-3 fold higher concentrations observed in female children compared to male children. As dose of fluvoxamine is increased, the oral bioavailability of fluvoxamine also increases, resulting in non-proportional increases in plasma fluvoxamine concentrations. The conclusions drawn from this analysis have been used to summarize pharmacokinetic results in this review as well as to provide appropriate labeling recommendations regarding dosing of fluvoxamine in children and adolescents.

elderly compared to 13.6 and 15.6 hours in the young subjects at steady state for 50 and 100 mg doses, respectively.

In elderly patients, the clearance of fluvoxamine was reduced by about 50% and, therefore, LUVOX® Tablets should be slowly titrated during initiation of therapy.

Pediatric Subjects: The multiple-dose pharmacokinetics of fluvoxamine were determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-3 fold higher in children than in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents (see table below). As in adults, both children and adolescents exhibited nonlinear multiple-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of LUVOX® Tablets may produce therapeutic benefit (see table below). No gender differences were observed in adolescents. Steady-state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (see table below). Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between children, adolescents and adults

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)		Dose = 300 mg/day (150 mg bid)	
	Children (n=10)	Adolescent (n=17)	Adolescents (n= 13)	Adults (n=16)
AUC0-12 (ng.h/ml/kg)	155.1 (160.9)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
Cmax (ng/ml/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
Cmin (ng/ml/kg)	11.0 (11.9)	2.9 (2.0)	4.8 (3.8)	4.6 (3.2)

Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between male and female children (6-11 years)

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)	
	Male Children (n=7)	Female children (n= 3)
AUC0-12 (ng.h/ml/kg)	95.8 (83.9)	293.5 (233.0)
Cmax (ng/ml/kg)	9.1 (7.6)	28.1 (21.1)
Cmin (ng/ml/kg)	6.6 (6.1)	21.2 (17.6)

Hepatic and Renal Disease: A cross study comparison (healthy subjects vs. patients with hepatic dysfunction) suggested a 30% decrease in fluvoxamine clearance in association with hepatic dysfunction. The mean minimum plasma concentrations in renally impaired patients (creatinine clearance of 5 to 45 mL/min) after 4 and 6 weeks of treatment (50 mg bid, N=13) were comparable

to each other, suggesting no accumulation of fluvoxamine in these patients. (See **PRECAUTIONS - *Use in Patients with Concomitant Illness***)

Clinical Trials

Adult OCD Studies: The effectiveness of LUVOX® Tablets for the treatment of Obsessive Compulsive Disorder (OCD) was demonstrated in two 10-week multicenter, parallel group studies of adult outpatients. Patients in these trials were titrated to a total daily fluvoxamine maleate dose of 150 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 100-300 mg/day (on a bid schedule), on the basis of response and tolerance. Patients in these studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), total score of 23. Patients receiving fluvoxamine maleate experienced mean reductions of approximately 4 to 5 units on the Y-BOCS total score, compared to a 2 unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO ADULT OCD STUDIES		
Outcome Classification	**Fluvoxamine (N = 120)**	**Placebo (N = 134)**
Very Much Improved	13%	2%
Much Improved	30%	10%
Minimally Improved	22%	32%
No Change	31%	51%
Worse	4%	6%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

Pediatric OCD Study: The effectiveness of LUVOX® Tablets for the treatment of OCD was also demonstrated in a 10-week multicenter, parallel group study in a pediatric outpatient population (children and adolescents, ages 8-17). Patients in this study were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50-200 mg/day (on a bid schedule) on the basis of response and tolerance.

~~of~~

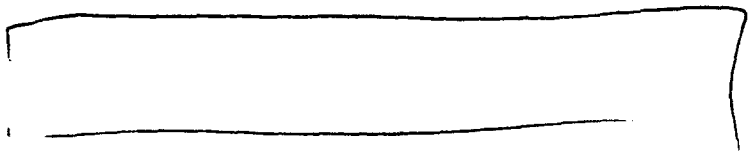
~~ebo~~

All patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score of 24. Patients

receiving fluvoxamine maleate experienced mean reductions of approximately six units on the CY-BOCS total score, compared to a three-unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impression (CGI) scale for the pediatric study.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN PEDIATRIC STUDY		
Outcome Classification	**Fluvoxamine (N= 38)**	**Placebo (N= 36)**
Very Much Improved	21%	11%
Much Improved	18%	17%
Minimally Improved	37%	22%
No Change	16%	44%
Worse	8%	6%



Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8-11 age group and essentially no effect in the 12-17 age group. While the significance of these results is not clear, the 2-3 fold higher steady state plasma fluvoxamine concentrations in children compared to adolescents (see Pharmacokinetics) is suggestive that decreased exposure in adolescents may have been a factor, and dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

INDICATIONS AND USAGE

LUVOX® Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of LUVOX® Tablets was established in three 10-week trials with obsessive compulsive outpatients with the diagnosis of Obsessive Compulsive Disorder as defined in DSM-III-R. (See **Clinical Trials** under **CLINICAL PHARMACOLOGY.**)

Obsessive Compulsive Disorder is characterized by recurrent and persistent ideas, thoughts, impulses or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Pediatric Use

The efficacy of fluvoxamine maleate for the treatment of Obsessive Compulsive Disorder was demonstrated in a 10-week multicenter placebo controlled study with 120 outpatients ages 8-17. In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 94 patient years. The adverse event profile observed in that study was generally similar to that observed in adult studies with fluvoxamine (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Decreased appetite and weight loss have been observed in association with the use of fluvoxamine as well as other SSRIs. Consequently, regular monitoring of weight and growth is recommended if treatment of a child with an SSRI is to be continued long term.

The risks, if any, that may be associated with fluvoxamine's extended use in children and adolescents with OCD have not been systematically assessed. The prescriber should be mindful that the evidence relied upon to conclude that fluvoxamine is safe for use in children and adolescents derives from relatively short term clinical studies and from extrapolation of experience gained with adult patients. In particular, there are no studies that directly evaluate the effects of long term fluvoxamine use on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding to suggest that fluvoxamine possesses a capacity to adversely affect growth, development or maturation, the absence of such findings is not compelling evidence of the absence of the potential of fluvoxamine to have adverse effects in chronic use.

Geriatric Use

Approximately 230 patients participating in controlled premarketing studies with LUVOX® Tablets were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, fluvoxamine has been associated with several cases of clinically significant hyponatremia in elderly patients (see **PRECAUTIONS, General**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX® Tablets should be slowly titrated during initiation of therapy.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Of the 1087 OCD and depressed patients treated with fluvoxamine maleate in controlled clinical trials conducted in North America, 22% discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

impotence, myoclonus/twitch, thirst, weight loss, leg cramps, myalgia and urinary retention. These events are listed in order of decreasing rates in the OCD trials.

Other Adverse Events in OCD Pediatric Population

In pediatric patients (N=57) treated with LUVOX® Tablets, the overall profile of adverse events was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse events, not appearing in Table 2, were reported in two or more of the pediatric patients and were more frequent with LUVOX® Tablets than with placebo: abnormal thinking, cough increase, dysmenorrhea, ecchymosis, emotional lability, epistaxis, hyperkinesia, infection, manic reaction, rash, sinusitis, and weight decrease.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder and with aging, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin reuptake inhibitors (SSRI's) can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Luvox in placebo controlled trials in depression and OCD.

Table 3
Percentage of Patients Reporting Sexual Adverse Events in Adult Placebo-Controlled Trials in OCD and Depression

	Luvox N=892	Placebo N=778
Abnormal Ejaculation*	8%	1%
Impotence*	2%	1%
Decreased Libido	2%	1%
Anorgasmia	2%	0%

* Based on the number of male patients.

There are no adequate and well-controlled studies examining sexual dysfunction with fluvoxamine treatment.

Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects.

DOSAGE AND ADMINISTRATION

Dosage for Adults

The recommended starting dose for LUVOX® Tablets in adult patients is 50 mg, administered as a single daily dose at bedtime. In the controlled clinical trials establishing the effectiveness of LUVOX® Tablets in OCD, patients were titrated within a dose range of 100 to 300 mg/day. Consequently, the dose should be increased in 50 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. It is advisable that a total daily dose of more than 100 mg should be given in two divided doses. If the doses are not equal, the larger dose should be given at bedtime.

Dosage for Pediatric Population (children and adolescents)

The recommended starting dose for LUVOX® Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX® Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day.

Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. It is advisable that a total daily dose of more then 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

Dosage for Elderly or Hepatically Impaired Patients

Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to modify the initial dose and the subsequent dose titration for these patient groups.

Maintenance/Continuation Extended Treatment

Although the efficacy of LUVOX® Tablets beyond 10 weeks of dosing for OCD has not been documented in controlled trials, OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

Tablets 25 mg: unscored, white, elliptical, film-coated (debossed "SOLVAY" and "4202" on one side)

Bottles of 100 ..... NDC 0032-4202-01
Unit dose pack of 100 ..... NDC 0032-4202-11

FOOD AND DRUG ADMINISTRATION
Division of Neuropharmacological Drug Products
HFD-120, Room 4030
1451 Rockville Pike
Rockville, MD 20852

DATE: September 21, 2000

TO:		FROM:	
Name:	**Don Ruggirello, Regulatory Affairs**	Name:	**Paul David, Regulatory Project Manager**
Fax No:	770-578-5864	Fax No:	(301) 594-2859
Phone No:	770-578-5658	Phone No:	(301) 594-5530
Location:	Solvay Pharmaceuticals	Location:	FDA, Division of Neuropharmacological Drug Products

Total Pages (including cover page) = 26

Comments:

Don,
Attached is the Agency's proposed labeling for the Luvox pK pediatric supplement, NDA 20-243/S-021. Note that it also includes the standard sexual dysfunction labeling which the Division has incorporated into labeling for all SSRIs. Please have your team review the labeling, and we will discuss this further on Monday morning, 9/25.
Paul

/S/ 9/21/00

... 20-243/S-021 ORIG HFD-120 / D.- FG

Electronic Mail Message

Date: 9/15/00 1:59:22 PM
From: Jacqueline O'Shaughnessy (OSHAUGHNESSY)
To: Paul David (DNPDP/ODEI) (DAVID)
Subject: Re: FWD: Luvox Pediatric Supplement; NDA 20-243/SE2-021

The following information pertains to your request for inspectional history for the clinical investigators that conducted the pediatric PK study for the Luvox supplement. Please let me know if I can provide any further assistance.

The bioequivalence branch of DSI has inspectional history for the following investigators:

Timothy Bohan (center 03)
DSI memo regarding our investigation of a complaint by the sponsor was submitted to HFD-120 on 11/11/99.

Jon Ruckle (center 10)
DSI conducted an inspection of this investigator for an ANDA in August 2000. The inspectional findings were minor and will not affect the outcome of the audited ANDA study.

The good clinical practice (GCP) branch of DSI has inspectional history for the following investigators:

James Connor (center 04)
This investigator was last inspected in 1983. The inspection was classified VAI (voluntary action indicated).

James Ferguson (center 06)
Inspections in May 1993, March 1997 and May 1998 found minor protocol deviations. All three inspections were classified VAI.

Jon Ruckle (center 10)
An August 1995 inspection found minor protocol deviations and was classified VAI.

DSI has no inspectional experience for the following investigators:

Joseph Blederman (center 01)
Graham Emslie (center 05)
Michael Labellarte (center 09)
Randy Sallee (center 11)

There is currently an inspection pending in the GCP branch for Arifulla Khan (center 07) for a Paxil supplement.

DSI memo for file.
/S/

NDA 20-243
/S/ /S/ /S/

LIST OF INVESTIGATORS

Joseph Biederman, M.D.
Massachusetts General Hospital
Boston, MA
Center Number: 01

Timothy Bohan, Ph.D., M.D.
Claghorn-Lesem Research Clinic
Bellaire, TX
Center Number: 03

James D. Connor, M.D.
University of California, San Diego
Department of Pediatrics
La Jolla, CA
Center Number: 04

Graham Emslie, M.D.
The University of Texas
Southwestern Medical Center at Dallas
Dallas, TX
Center Number: 05

James M. Ferguson, M.D.
Pharmacology Research Corporation
Salt Lake City, UT
Center Number: 06

Arifulla Khan, M.D.
Northwest Clinical Research Center
Bellevue, WA
Center Number: 07

Michael Labellarte, M.D.
John Hopkins Hospital
Division of Child and Adolescent Psychiatry
Baltimore, MD
Center Number: 09

Jon Ruckle, M.D.
Northwest Kinetics L.L.C.
Tacoma, WA
Center Number: 10

Randy Sallee, M.D., Ph.D.
Psychiatric Professional Services, Inc.
Cincinnati, OH
Center Number: 11

Bus 11/9/99
David 11/19/99
120

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 10, 1999

FROM: Jacqueline A. O'Shaughnessy, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 11/11/99
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering ~~~~~~~~~~
Luvox® (fluvoxamine maleate) Tablets
Sponsored by Solvay Pharmaceuticals, Inc.

TO: Russell G. Katz, M.D.
Director
Division of Neuropharmacological Drug Products
(HFD-120)

In response to a complaint by Solvay Pharmaceuticals alleging irregularities in the conduct of Protocol S1141102 entitled, "The Multiple-Dose Pharmacokinetics of Fluvoxamine in Children and Adolescents," the Division of Scientific Investigations initiated an inspection of clinical investigator Timothy P. Bohan, Ph.D., M.D. at the Claghorn-Lesem Research Clinic, Inc., Bellaire, Texas.

Background:

Protocol S1141102 was a Phase I multi-center study to determine the multiple dose pharmacokinetics of fluvoxamine in pediatric patients scheduled to begin fluvoxamine treatment. Dr. Bohan enrolled four patients, three of which completed the study. The sponsor's allegations of improper clinical conduct at the Claghorn-Lesem site include the following: entry criteria were not followed; source documents were illegible due to numerous corrections; and source documents were not signed until four months after the data had been collected. Solvay stated that the alleged irregularities were uncovered by the CRO monitoring the study (Quintiles CNS Therapeutics, San Diego, California).

Inspectional Findings:

Following the inspection a Form 483 was issued (attached). The objectionable items and our evaluation of these findings are as follows:

1. **Discrepancies between case report forms (CRFs) and raw data.**

   CRF entries were not always supported by the source documents. Discrepancies were found in the following examples: pharmacokinetic blood sampling times for patients 68727 (e.g., 10 minute discrepancy at 2 hours postdose) and 68726 (e.g., 60 minute discrepancy at 12 hours postdose); screening height/weight measurements for patient 68727; and date of urine collection from patient 68726 for dextromethorphan screening.

2. **Numerous "late entries" and other amendments to raw data, laboratory reports, and CRFs.**

   Study data were not always recorded at the time of observation. For example, progress notes regarding the discontinuation of patient 68826 were completed more than three months after the patient was dropped from the study. Further, some study data were amended without supporting documentation. For example, pharmacokinetic blood sampling times for patient 68727 were altered more than four months after the collection date without reference to the source of the change. The FDA investigator also found that in some instances, the same study record was amended on more than one occasion. Most of the "late entries" and amendments were attributable to Mary Ann Saunders, RN/NP, who resigned as study coordinator in April 1999.

3. **Incomplete CRFs.**

   Study data from the final visit of discontinued patient 68826 were not entered on the CRF.

The above observations lend credence to Solvay's allegations of poor data documentation and the failure to record/review data in a timely manner.

With regard to the allegation of failing to follow entry criteria, the FDA investigator found that patient 68826 was taking lithium at the time of enrollment. Dr. Bohan stated that

although the protocol excluded concomitant psychotropic drugs, he did not believe that lithium was prohibited. The subject was dropped from the study at the request of the sponsor.

Conclusions:

Due to discrepancies found between source data and CRFs and numerous amendments to study records, the accuracy of the clinical data is questionable. The Division of Scientific Investigations recommends that data for Protocol S1141102 from the Claghorn-Lesem Research Clinic be excluded from Agency review.

After you have reviewed this transmittal memo, please append it to the original IND submission.

/S/

Jacqueline A. O'Shaughnessy, Ph.D.

Attachment

cc:
HFA-224
HFD-45/Lepay
HFD-48/Fujiwara/O'Shaughnessy(2)/CF
HFD-120/David
HFD-860/Yuan
Draft:JAO 11/5/99
Edit:MKY MKY 11/10/99
File:

Final Classification: OAI

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	DISTRICT ADDRESS AND PHONE NUMBER 3310 Live Oak Street Dallas, Texas 75204 (214) 655-5310	
NAME OF INDIVIDUAL TO WHOM REPORT ISSUED To: Dr. Timothy P. Bohan	PERIOD OF INSPECTION 9/15-22/1999	C.F. NUMBER
TITLE OF INDIVIDUAL Prinicipal Investigator	TYPE ESTABLISHMENT INSPECTED clinical site	
FIRM NAME Claghorn-Lesem Research Clinics, Inc	NAME OF FIRM, BRANCH OR UNIT INSPECTED same	
STREET ADDRESS 6750 West Loop South, Suite 1050	STREET ADDRESS OF PREMISES INSPECTED same	
CITY AND STATE (Zip Code) Houston, Texas 77401	CITY AND STATE (Zip Code) same	

During an inspection of your firm (I) (We) observed:

1. Discrepancies between case report forms (crfs) and raw data. For example:

   a. The values recorded for height, weight, and temperature on J.A.L's 11/12/98 crf do not agree with values recorded in the progress notes for that date.

   b. Blood sample collection times in J.A.L's crf (page 15) differ from those on the lab requisition for that date

   c. C.A's records indicate dextromethorphan was given to the parent on 11/7/98. The crf indicates the dextromethorphan challenge was done 11/20/98, yet the lab requisition indicates 11/18/98.

   d. C.A's 12/12/98 crfs indicate sample times were 5 minutes off, yet the lab requisition shows the same times as the crf. Furthermore, the crf and requisition indicate the 8 hour sample was not obtained, yet progress notes for that date indicate it was.

   e. Blood sample collection times for C.A's 1/2/99 visit differ between crf and lab requisition forms.

2. Numerous "late entries" and other amendments to raw data, laboratory reports, and case report forms.

3. Incomplete case report forms. For example, A.N.P. was dropped from the study at the 12/5/98 visit, yet crfs for this visit were not completed.

SEE REVERSE OF THIS PAGE.	/s/	EI(S) NAME AND TITLE (Print or Type) Lemons, Investigator	DATE ISSUED 9/22/1999

FORM FDA 483 (6/85) PREVIOUS EDITION MAY BE USED INSPECTIONAL OBSERVATIONS PAGE 1 OF 1 PAGES

SOLVAY PHARMACEUTICALS

N20243

N20243

K1.1

K1.1

Rec. 10/26/00 8:34-pm

AY PHARMACEUTICALS, Inc., 901 Sawyer Rd., Marietta, GA 30062
Tel: (770) 578-9000 FAX: (770) 578-5864
For missing pages, Tel: (770) 578____5588___

CONFIDENTIALITY NOTICE

DATE: 9/24/00

TO: FDA DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

ATTENTION: PAUL DAVID

FAX NUMBER: (301) 594-2859 10

FROM: DON RUBITSKO **No. of pages, including cover sheet:**

MESSAGE: SUBJECT: NDA 20-243 NUVOX TABLETS

PEDIATRIC PHARMACOKINETIC LABELING

- THE PROPOSED LABELING IN YOUR TELEFAX DATED 9/21/00 IS ACCEPTABLE.
- PLEASE NOTE CORRECTIONS AND COMMENTS ON THE ATTACHED PAGES.
- PLEASE EXPLAIN THE BASIS (C_{max}, C_{ave}, etc.) FOR 2-4 FOLD HIGHER PLASMA CONCENTRATIONS AND WHY CALCULATION OF CLEARANCE IS NOT CONSIDERED APPROPRIATE. (A VOICE MESSAGE WILL BE FINE).

REVIEW AND EVALUATION OF CLINICAL DATA

NDA 20-243
SPONSOR: SOLVAY
DRUG: FLUVOXAMINE (LUVOX)
MATERIAL SUBMITTED: SUPPLEMENT FOR PEDIATRIC EXCLUSIVITY
DATE SUBMITTED: 12/2/99
DATE RECEIVED: 12/2/99

1. BACKGROUND

This Division approved a supplement for pediatric use of Luvox in the treatment of Obsessive-Compulsive Disorder (OCD) on 3/25/97. In the approval letter, the sponsor was encouraged to explore the efficacy of fluvoxamine in the adolescent population, since a subgroup analysis of the double blind efficacy trial had shown that most of the observed effect in the fluvoxamine group was contributed by the pre-adolescent subjects. In that study no pharmacokinetic samples were obtained, and while it was suspected that the adolescent subjects had been under-dosed, there was no corroboration for that explanation of the finding.

On 11/7/97, the Division requested Solvay to add a statement to labeling cautioning that there was relatively little data on the effects of Luvox on long term growth and development of children. Similar statements have been added to other psychotropic drugs approved for children.

This submission contains data intended to address these issues. Solvay has conducted a pediatric long term open label safety study and a pediatric pharmacokinetic study. These two studies were the subject of a pediatric exclusivity Written Request issued 11/30/00 by Dr. Temple. In addition, a waiver of the Application Integrity Policy (AIP) for Solvay has been granted by Dr. Woodcock to permit review of this pediatric exclusivity supplement. The agency granted Solvay six months of pediatric exclusivity for submission of this supplement.

PROPOSED LABELING (strikeout font indicates deletion of text, italics indicate new text).

Under **Clinical Pharmacology**

> *Pediatric Subjects*
> *The multiple-dose pharmacokinetics of fluvoxamine was determined in male and female children (ages 6-11) and adolescents (ages 12-17). The clearance of fluvoxamine in children was approximately half that observed in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents. As in adults, both children and adolescents exhibited nonlinear multi-dose pharmacokinetics. Female children showed significantly lower clearance values and higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of LUVOX® Tablets may produce therapeutic benefit. No gender differences were observed in adolescents. Body weight adjusted mean clearance at a dose of 300 mg/day was approximately 50% higher in adolescents compared to adults in previous studies. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.*

Under **Clinical Trials**:

> *Pediatric OCD Study:* The effectiveness of LUVOX® Tablets for the treatment of OCD was also demonstrated in a ~~10~~*ten*-week, multicenter, parallel-group, *placebo-controlled*

study in a pediatric outpatient population (children and adolescents, ages 8-17), *followed by an open-label extension of up to two years. In the double-blind phase of the study,* ~~P~~patients ~~were~~ were titrated to a total daily fluvoxamine dose of approximately 100 mg/day over the first two weeks of the trial, following which the dose was adjusted within a range of 50-200 mg/day (on a bid schedule) on the basis of response and tolerance. *All* ~~P~~patients had moderate-to-severe OCD (DSM-III-R) with mean baseline ratings on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), total score of 24. Patients receiving fluvoxamine maleate experienced mean reductions of approximately ~~6~~*six* units on the CY-BOCS total score, compared to a ~~3~~*three*-unit reduction for placebo patients.

The following table provides the outcome classification by treatment group on the Global Improvement item of the Clinical Global Impressions (CGI) scale for both studies combined.

OUTCOME CLASSIFICATION (%) ON CGI-GLOBAL IMPROVEMENT ITEM FOR COMPLETERS IN POOL OF TWO ADULT OCD STUDIES		
Outcome Classification	**Fluvoxamine (N = 120)**	**Placebo (N = 134)**
Very Much Improved	13%	2%
Much Improved	30%	10%
Minimally Improved	22%	32%
No Change	31%	51%
Worse	4%	6%

Exploratory analyses for age and gender effects on outcomes did not suggest any differential responsiveness on the basis of age or sex.

Post hoc exploratory analyses for gender effects on outcomes did not suggest any differential responsiveness on the basis of gender. Further exploratory analyses revealed a prominent treatment effect in the 8-11 age group and essentially no effect in the 12-17 age group. ~~The~~ ~~se.~~ *Follow-up data from the open extension of the study showed a further improvement as demonstrated by a decrease of an additional three to six units on the CY-BOCS in young, as well as adolescent, patients. This improvement was sustained over a one-year period in the 54 of 98 patients who completed the one-year extension and in the 12 of 22 patients who completed the two-year extension.*

Under **Indications:** The following sentence has been added.

Data from the long-term (up to two years) open-extension phase of the placebo controlled study in children supports sustained efficacy of the drug.

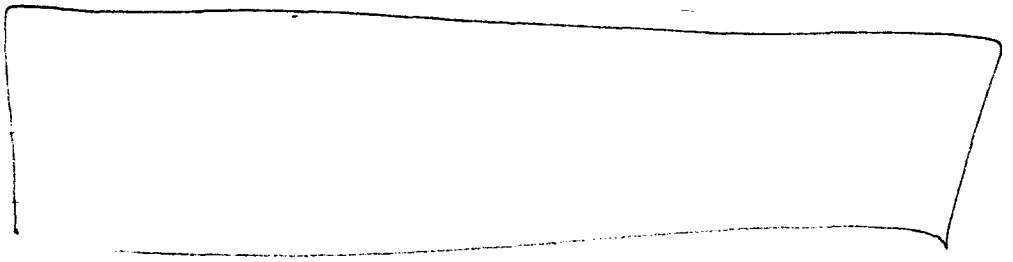
Under **Precautions, Pediatric Use**

The following statements have been added:

In addition, 99 of these outpatients continued open-label fluvoxamine maleate treatment for up to another one to three years, equivalent to 63 patient years, during which efficacy was continued and/or improved.

No detrimental effect on growth rate was apparent in the long-term, open-label study.

This statement has been removed:



Under **Dosage and Administration**

Dosage for Pediatric Population (children and adolescents)
The recommended starting dose for LUVOX® Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. In a controlled clinical trial establishing the effectiveness of LUVOX® Tablets in OCD, pediatric patients (ages 8-17) were titrated within a dose range of 50 to 200 mg/day. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved.~~, not to exceed 200 mg per day.~~ *Physicians should consider age and gender differences when dosing pediatric patients. The maximum dose in children up to age 11 should not exceed 200 mg/day. Therapeutic effect in female children may be achieved with lower doses. Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.* It is advisable that a total daily dose of more then 50 mg should be given in two divided doses. If the two divided doses are not equal, the larger dose should be given at bedtime.

CLINICAL DATA SUBMITTED

Protocol RH.114.02.01 Long term open label treatment

Investigators/Centers

Philip Chappel, MD / Mark Riddle, MD Yale Child Study Center, New Haven CT
Jessica Hellings, MD University of Kansas Department of Psychiatry, Kansas City KS
Harold Udelman, MD Bio-Medical Stress Research Foundation, Phoenix AZ
Denis Cantwell, MD UCLA-NPI, Los Angeles CA
Mark Friedlander, MD / Michael Pravetz, MD Philadelphia PA
Jose Yaryura-Tobias, MD Biobehavioral Psychiatry, Great Neck NY
John Walkup, MD Johns Hopkins Hospital, Baltimore MD
Neal Ryan, MD WPIC, Pittsburgh PA
Ronald Landbloom, M.D. St. Paul-Ramsey Medical Center, St. Paul MN
Theresa Pigott, MD Georgetown University, Washington DC

Steven Rasmussen, MD	Butler Hospital, Providence RI
Gary Gaffney, MD	University of Iowa Hospital, Iowa City IA
John Greist, MD	Dean Foundation, Madison WI
Donna Holland, MD	Boca Raton Psychiatric Group, Boca Raton FL
Brian McConville, MD	University of Cincinnati, Cincinnati OH
William Nathan, MD	Menninger Clinic, Topeka KS

Objective

This study was an extension of the double blind placebo controlled efficacy trial. The objective of the extension phase of the study was to assess the safety and efficacy of treatment with fluvoxamine for one year in pediatric patients with OCD.

Population

For the double blind acute treatment phase, subjects were between 8 and 17 years of age, diagnosed with OCD, and generally free of other significant psychiatric or medical conditions. Subjects who had successfully completed the 10 week double blind trial were eligible for the extension phase. Alternatively, subjects who had dropped out of double blind treatment after 6 weeks or longer for lack of efficacy were also eligible.

Design

Treatment was open label.

Safety and efficacy assessments for the first 6 weeks of open label fluvoxamine treatment were obtained weekly, similar to the double blind phase. Subsequently, subjects were assessed monthly for the remainder of the 12 months of treatment. At the end of double blind treatment, assessments included a physical exam, vital signs, clinical laboratories, and ECG. Clinical laboratories were repeated at week 6, month 6, month 10, and month 12. ECGs were obtained at week 6, month 6 and month 12. Vital signs (sitting only) and weight were obtained at all visits.

All subjects were titrated on the same schedule, beginning with 25 mg at bedtime, and increased in 25 mg increments to a target dose of 100 mg twice a day (200 mg/d) by the third week. Use of any concomitant medication was permitted only on a case-by-case basis. During the double blind phase, the investigator had the option of reducing the dose of study medication, but it was not clearly stated that this option applied to the extension phase as well.

Amendments to the protocol expanded the number of study sites, and permitted treatment for a second year beyond the originally planned 12 months (this continuation of treatment is referred to as the "Humanitarian Phase" by Solvay).

Results

Demographic characteristics of the sample are summarized below.

Category	N
Total	99
Aged 8-11 years	33
Aged 12-17 years	66
White	96

Non-white	3
Male	52
Female	47

Patient disposition

Twelve month extension phase: Of 120 patients who entered the double blind study, 99 participated in the 12 month open label extension; 70 subjects had completed the double blind study and 29 had withdrawn prematurely. Fifty five of the 99 subjects had initially received placebo, and 44 had initially received double blind fluvoxamine. For the 12 month phase of open label treatment, the following shows the disposition of patients.

Category	Number of patients
Total	99
Completed	54
Dropouts for Lack of efficacy	12
Dropouts for Adverse experience	9
Dropouts for Other reasons (withdrawal of consent, noncompliance)	24

Comparison of age subgroups (data not shown) revealed that more adolescents discontinued for lack of efficacy, while more preadolescents discontinued for adverse events.

Humanitarian phase:
Twenty two of the 99 subjects continued open label treatment beyond 12 months under the Humanitarian phase of the study. In the Humanitarian phase, 9 of the 22 subjects completed one year of treatment, one subject withdrew for lack of efficacy, one withdrew for adverse events, six discontinued when Luvox was marketed, and five discontinued for other reasons.

Dose and duration of treatment: The mean final dose in both the extension and humanitarian phases was approximately 150 mg/day.

In the proposed labeling, Solvay indicates that the total exposure to open label treatment was 63 patient years, although I was unable to confirm this from the study report. The following shows the number of subjects by total duration of treatment (including double blind fluvoxamine treatment in the acute treatment phase of the study):

Length of treatment (days)	No. of subjects
<365	57
365-729	32
>729	10

Efficacy measures: Solvay obtained Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS) on subjects during open label treatment. After the one year extension treatment, the mean CYBOCS for the sample decreased from 19.4 to 13.9. In the absence of a control group, of course, this observation is uninterpretable, although the sponsor has included efficacy measures in the draft labeling for this supplement (see above).

Adverse event incidence: The following adverse events occurred in at least 20% of the sample: infection, headache, insomnia, asthenia, pharyngitis, abdominal pain, nausea, rhinitis, dizziness,

hyperkinesia, flu syndrome. In the absence of a comparison group these data are difficult to interpret.

Serious adverse events: There were no deaths. There were four serious adverse events:

Patient 65811, 11 year old male, fractured wrist in a fall
Patient 65816, 11 year old female, surgery for scoliosis
Patient 65853, 14 year old male, multiple fractures after falling off a roof while evading police
Patient 66052, 15 year old female, hospitalized for suicidal ideation

In addition, there were two suicide attempts/gestures that the sponsor did not consider serious adverse events.

Adverse events associated with premature discontinuation: The following is a list of patients that had to discontinue fluvoxamine for adverse events. Note that a number of the adverse events involved agitation, hypomania, and hyperactivity. It will be recalled that the incidence of manic reaction and hyperkinesia was greater with fluvoxamine than placebo in the double blind phase of the trial (see current Luvox labeling).

Patient #	Age, sex	Adverse event
65130	11 F	Behavioral disinhibition and awakening at night
65148	16 M	Hypomania
65230	8 F	Hyperactivity, dizziness, tiredness
65231	11 M	Hyperactivity
65253	10 M	Aggression
65815	15 M	Suicidal ideation, self mutilation
65818	12 M	Agitation
65824	14 M	Insomnia
65848	10 M	Hyperactivity, oppositional behavior
65249	15 F	Panic attacks

Clinical laboratories: The sponsor established threshold values for selected laboratory parameters, to classify abnormal values as potentially clinically significant. These criteria are shown on page 102 of the study report. During the trial, the majority (n=44) of the laboratory values considered markedly abnormal by these criteria were on the general microscopic urinalysis (not further specified). The number of patients with other markedly abnormal values were as follows: chloride-1, SGOT-1, bilirubin-1, hematocrit-12, eosinophilia-6, proteinuria-4. These findings are difficult to interpret without a comparison group.

Vital signs: A similar methodology was applied to the analysis of vital sign data. The sponsor established criteria for considering vital sign readings to be markedly abnormal, as shown on page 105 of the study report. The number of patients having such abnormalities was as follows: increased pulse-1, decreased SBP-14, decreased DBP-12, increased DBP-1. Again, without a comparison group, these data are difficult to interpret.

Height and weight: Solvay presented data showing the unsurprising finding that mean height and weight increased during treatment. The increases in height and weight were somewhat more for subjects who had initially received fluvoxamine in the acute treatment trial compared to those who had initially received placebo, although there was no apparent reason for this discrepancy. Solvay concluded that there was no detrimental effect on growth.

Unfortunately, these data are very difficult to interpret. The sponsor pooled data for boys and girls into a single analysis, and pooled data for children aged 8-11 and adolescents aged 12-17. Of course, the expected gains in height and weight vary considerably by age and gender. A superior method would have been to plot each child's height and weight using a standard growth chart, and count how many subjects showed significantly altered growth velocity by predefined criteria during treatment.

ECGs: Solvay collected data on treatment emergent ECG abnormalities. Of six subjects with treatment emergent abnormalities, the most notable was one subject (65848) who had an ECG suggesting right ventricular hypertrophy; an echocardiogram was normal.

Conclusions

I do not believe this open label study supports all the labeling that the sponsor has proposed. Open label data is not easily interpreted with respect to efficacy. Also, I do not believe the sponsor has analyzed the data on weight and height in a way that would allow conclusions about the effect of fluvoxamine on growth. I believe the labeling should carry a more conservative statement to the effect that there were no unique adverse drug reactions observed with long term treatment of children in this study.

It is interesting to note the number of adverse events that could be considered evidence of behavioral activation, such as hyperkinesia, insomnia, and so forth. Again, open label data is somewhat problematic to interpret with respect to adverse events.

CLINICAL PHARMACOLOGY STUDY S1141102

I will briefly summarize the findings from the pediatric pharmacokinetic trial, which is being reviewed by HFD-860. This was a multicenter, open label, multiple dose trial. The participants were psychiatric patients who would have been appropriate for treatment with fluvoxamine on clinical grounds.

The subjects were titrated to final target doses of 200 mg/day for the children and 300 mg/day for the adolescents. Duration of treatment was 36 days for children and 43 days for adolescents. Dosing was BID.

Pharmacokinetic blood samples were obtained over 12 hours after the morning dose, from children at steady state dosing with 25 mg, 50 mg, and 100 mg BID, and from adolescents at steady state dosing with 25 mg, 50 mg, 100 mg, and 150 mg BID.

Patient sample

Subjects were 43 boys and girls aged 6-17 years; of these, 20 were aged 6-11 and 23 were aged 12-17. The sample included 20 girls and 23 boys. Five subjects withdrew prematurely, and all four subjects from site 03 (Dr. T. Bohan) were excluded from the analysis because of failures in Good Clinical Practices. This left a subgroup of 34 patients for which there was pharmacokinetic data. The subjects were phenotyped with respect to CYP 2D6 status using a dextromethorphan challenge dose, and all 34 subjects were extensive metabolizers.

Pharmacokinetic findings

At equal doses, clearance in children was roughly ½ that for adolescents, and AUC 0-12 and Cmax were correspondingly higher. Pharmacokinetics for children were non-linear, with disproportionate increases in Cmax and AUC with increasing dose. The nonlinearity was present to a lesser degree in the adolescent pharmacokinetic data. With respect to gender differences, in the children, girls had about a two-fold lower clearance than boys, not accounted for by differences in weight. There were no obvious gender differences in the data from the adolescent subjects, however.

Solvay compared the adolescent pharmacokinetic data at 150 mg BID to pharmacokinetic data from adults also adminstered 150 mg BID in a previous trial (CR100.0059). Mean plasma concentrations over 12 hours were very similar between the two populations

Safety findings

The sample for safety analyses was the larger group of 43 patients. Adverse events reported in at least 20% of patients included headache, asthenia, and infection. For some of the more frequent adverse events (asthenia, headache, insomnia, nausea, somnolence, and vomiting), the sponsor attempted to determine if there was a relationship between Cmax or AUC and the occurrence of these adverse events. No such correlation was found.

Four subjects had serious adverse events, and four withdrew for adverse events, as summarized below.

Patient	Adverse Event
Serious Adverse Events	
68720, 11 y.o. M	Psychiatric hospitalization for post-traumatic stress disorder
68727, 9 y.o. M	Oculogyric crisis; was receiving concomitant pimozide
68736, 11 y.o. F	Depression, self mutilation
68819, 16 y.o. F	Pregnancy (spontaneous abortion 3 wks. after fluovoxamine stopped)
Premature discontinuations due to adverse events	
68721, 6 y.o. M	Mania, resolved after fluvoxamine discontinued
68722, 10 y.o. F	Insomnia
68723, 8 y.o. F	Insomnia
68747, 11 y.o. F	Dizziness, asthenia, nausea

There were no findings of significance with respect to clinical laboratories, vital signs, or ECGs, although the sponsor conducted only a limited analysis of these safety parameters. There was a slight decrease in pulse with treatment, by about 5 bpm on average.

Conclusions about pharmacokinetic study

On balance, the data in the sponsor's pediatric pharmacokinetic study support the proposed labeling. This study will also be reviewed by HFD-860, of course.

Conclusions and recommendations

From a clinical standpoint this supplement is approvable. Some of the proposed labeling overinterprets the open label study data with respect to safety and efficacy, in my opinion, and should be revised

/S/ — 8/8/00

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 20-243
Div file
HFD-120 Laughren, David, Dubitsky, Mosholder

9-13-00

I agree that this supplement is approvable. See memo & file for more detailed response

/S/

TL, PDP

APPEARS THIS WAY
ON ORIGINAL

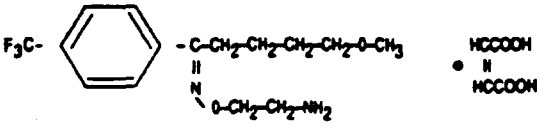
CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Luvox® (Fluvoxamine)
NDA: 20243 SLR
FORMULATION: Tablets
APPLICANT: Solvay Pharmaceuticals

PRIMARY REVIEWERS: Vanitha J. Sekar, PhD
TYPE: Efficacy supplement
STRENGTH: 25 mg, 50 mg and 100 mg

Background: Fluvoxamine maleate is a selective serotonin (5-HT) reuptake inhibitor (SSRI). It is chemically unrelated to other SSRIs and clomipramine. Its molecular weight is 434.4. The structural formula is:

Figure 1



LUVOX® (Fluvoxamine Maleate) tablets are available in 25 mg, 50 mg and 100 mg strengths for oral administration. LUVOX® Tablets are indicated for the treatment of obsessions and compulsions in patients with Obsessive Compulsive Disorder (OCD), as defined in the DSM-III-R. The mechanism of action of fluvoxamine maleate in Obsessive Compulsive Disorder is presumed to be linked to its specific serotonin reuptake inhibition in brain neurons.

The absolute bioavailability of fluvoxamine maleate is 53%. Oral bioavailability is not significantly affected by food. 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. Fluvoxamine had nonlinear pharmacokinetics over this dose range, i.e., higher doses of fluvoxamine maleate produced disproportionately higher concentrations than predicted from the lower dose. The mean apparent volume of distribution for fluvoxamine is approximately 25 L/kg, suggesting extensive tissue distribution. Approximately 80% of fluvoxamine is bound to plasma protein, mostly albumin, over a concentration range of 20 to 2000 ng/mL. Fluvoxamine maleate is extensively metabolized by the liver; the main metabolic routes are oxidative demethylation and deamination. Nine metabolites were identified following a 5 mg radiolabelled dose of fluvoxamine maleate, constituting approximately 85% of the urinary excretion products of fluvoxamine. The main human metabolite was fluvoxamine acid which, together with its N-acetylated analog, accounted for about 60% of the urinary excretion products. A third metabolite, fluvoxethanol, formed by oxidative deamination, accounted for about 10%. Fluvoxamine acid and fluvoxethanol were tested in an *in vitro* assay of serotonin and norepinephrine reuptake inhibition in rats; they were inactive except for a weak effect of the former metabolite on inhibition of serotonin uptake (1-2 orders of magnitude less potent than the parent compound). Approximately 2% of fluvoxamine was excreted in urine unchanged. The mean plasma half-life of fluvoxamine at steady state after multiple oral doses of 100 mg/day in healthy, young volunteers was 15.6 hours.

This submission contains results from 2 studies that have been submitted as a response to a pediatric written request from the Agency. One of these 2 studies is a long term safety and efficacy trial in pediatric patients with OCD. The second study is a pharmacokinetic study of fluvoxamine in the pediatric population; the results from this study are reviewed as part of this clinical pharmacology/biopharmaceutics review.

Title of Study: The Multiple-Dose Pharmacokinetics of Fluvoxamine in Children and Adolescents.

Objectives: The primary objective of this study was to determine the multiple-dose pharmacokinetics of fluvoxamine in male and female child and adolescent patients scheduled to begin treatment with fluvoxamine maleate. The secondary objective of this study was to compare the pharmacokinetics of fluvoxamine in the adolescent pediatric population with multiple-dose pharmacokinetic data previously obtained in adults.

Study Design: Multicenter, multiple-dose, open-label, parallel group study in male and female patients ages 6 to 17 years. Patients were scheduled to begin treatment with fluvoxamine maleate for the treatment of obsessive compulsive disorder or other psychiatric illnesses for which the investigator believes that the patient will benefit from the treatment of fluvoxamine maleate. Thirty-two patients (16 patients aged 6 to 11, and 16 patients aged 12 to 17) planned; 34 patients (16 patients aged 6 to 11, and 18 patients aged 12 to 17) analyzed in the pharmacokinetic patient sample. Determination of cytochrome P450 2D6 (CYP450 2D6) phenotype status after administration of dextromethorphan was done for all patients.

Formulation characteristics: Fluvoxamine maleate 25 (Lot # 88494), 50 (Lot # 89393), and 100 mg (Lot # 89425) tablets were administered orally.

Study treatments: The total daily dose was titrated from 50 to 200 mg per day in child patients and titrated from 50 to 300 mg per day in adolescent patients. Child and adolescent patients were administered the study medication twice daily as a morning and bedtime dose. The duration of treatment was approximately 36 days in pediatric patients ages 6 to 11, and approximately 43 days for pediatric patients ages 12 to 17.

Table 1

Study Medication Titration Schedule for Child and Adolescent Patients

		Patients aged 6-11 years		Patients aged 12-17 years	
		a.m.	p.m.	a.m.	p.m.
Visit 1	Day 1	N/A	25	N/A	25
	Days 2-7	25	25	25	25
Visit 2	Day 8	25	50	25	50
	Days 9-14	25	50	50	50
Visit 3	Day 15	25	50	50	75
	Days 16-21	50	50	75	75
Visit 4	Day 22	50	75	75	100
	Days 23-28	75	75	100	100
Visit 5	Day 29	75	100	100	125
	Days 30-35	100	100	125	125
Visit 6	Day 36	100	N/A	125	150
	Days 37-42	N/A	N/A	150	150
Visit 7	Day 43	N/A	N/A	150	N/A

N/A = not applicable

Pharmacokinetics:

Pharmacokinetic Sample Collection: Urine samples were collected for determination of cytochrome P450 2D6 (CYP450 2D6) phenotype status after administration of dextromethorphan. Each patient between the ages of 6 -11 was scheduled to have 5 ml whole blood samples collected for the measurement of fluvoxamine at the following times:

- Day 8 (Visit 2) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 25-mg dose of fluvoxamine maleate.
- Day 22 (Visit 4) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 50-mg dose of fluvoxamine maleate.
- Day 36 (Visit 6) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning

100-mg dose of fluvoxamine maleate.
Each patient between the ages of 12-17 was scheduled to have 5 ml whole blood samples collected for the measurement of fluvoxamine at the following times:
· Day 8 (Visit 2) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 25-mg dose of fluvoxamine maleate.
· Day 15 (Visit 3) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 50-mg dose of fluvoxamine maleate.
· Day 29 (Visit 5) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 100-mg dose of fluvoxamine maleate.
Day 43 (Visit 7) prior to (0), and at 2, 4, 6, 8, 10, and 12 hours after the morning 150-mg dose of fluvoxamine maleate.

Pharmacokinetic Patient Sample: All patients who completed at least one 12-hour pharmacokinetic sampling period were included in the pharmacokinetic patient sample with the exception of Patient 68719 (this patient was administered prescription fluvoxamine maleate rather than study supplied fluvoxamine maleate during the first week of enrollment). The pharmacokinetic patient sample included a total of 34 patients (16 children and 18 adolescents). A total of nine patients, four children and five adolescents, were not included in the pharmacokinetic patient sample. Patient 68712 withdrew consent prior to completing a 12-hour pharmacokinetic sampling period. Patient 68819 discontinued the study due to an adverse event prior to completing a 12-hour pharmacokinetic sampling period. Patient 68803 had two consecutive failed attempts to take fluvoxamine maleate at a fixed dosage level for 12 consecutive doses prior to completing a12-hour pharmacokinetic sampling period. Patient 68719 was administered fluvoxamine maleate by prescription during the first week following enrollment. Patient 68832 discontinued the study due to high Baseline visit TSH levels and increased baseline ALT and AST levels. Lastly, all patient data at study center 03 (Patients 68726, 68727, 68826, and 68827) were not included in the pharmacokinetic sample due to significant study protocol deviations and a failure to conduct the study in accordance with GCP.

Bioanalytical Analysis:
Urine Dextromethorphan: Dextromethorphan and dextrorphan concentrations in human urine were determined using a validated liquid chromatography fluorescence method. The correlation coefficients for linear regression analysis of the calibration standards were 0.9983 and 0.9974 for dextromethorphan and dextrorphan, respectively. The accuracy (determined as percent of nominal) for each calibration standard level ranged from 96.7 – 105% and 96.0 – 106% for dextromethorphan and dextrorphan, respectively. For dextromethorphan, accuracies of QC's (determined as percent of nominal) were 94.7, 87.1, and 94.7% for the 150, 800, and 4000 ng/mL levels, respectively. For dextrorphan, accuracies of QC's were 92.5, 90.3, and 96.5% for the 1500, 8000, and 40000 ng/mL levels, respectively.

Patients with a dextromethorphan to dextrorphan metabolic ratio of <0.3 were classified as extensive metabolizers (EM) and those with a ratio of ≥ 0.3 were considered poor metabolizers (PM) for the CYP450 2D6 isoenzyme. All patients included in the pharmacokinetic analysis were phenotyped as extensive metabolizers.

Plasma Fluvoxamine: Fluvoxamine concentrations in human plasma were determined using a validated liquid chromatography/mass spectrometry/mass spectrometry method (LC/MS/MS). Correlation coefficients for linear regression analysis of the calibration standards ranged from 0.9936 to 0.9979. The accuracy for each calibration standard level ranged from 89.7 to 106% during the analysis with the original extraction method and 91.5 to 108% with the modified extraction method. The precision (%RSD) of the standards ranged from 2.41 to 8.20% during the analysis with the original extraction method and 2.73 to 6.21% with the modified extraction method. For QC's included during analysis with the original extraction method, accuracies (determined as percent of nominal) were 95.2, 104, and 98.6% and precisions (%RSD) were 8.68, 14.6, and 5.05% respectively for the 0.750, 25.0, and 850 ng/mL levels. For QC's included

during analysis with the modified extraction method, accuracies were 95.3, 103, and 92.0% and precisions were 17.3, 5.23, and 6.34% respectively for the 0.750, 25.0, and 850 ng/mL levels.

Subjects' demographics:

Table 2

Demographic and Other Baseline Characteristics, Pharmacokinetic Patient Sample

Characteristics	Total (N=34)	Children (N=16)	Adolescents (N=18)
Age (years): Mean (SD)	11.9 (2.9)	9.4 (1.7)	14.1 (1.7)
Range	8.0 – 17.0	8.0 – 11.0	12.0 – 17.0
Ethnicity N(%):			
Caucasian	29 (85%)	13 (81%)	16 (89%)
Hispanic	1 (3%)	1 (6%)	0
Black	2 (6%)	1 (6%)	1 (6%)
Asian	2 (6%)	1 (6%)	1 (6%)
Gender N(%):			
Female	16 (47%)	7 (44%)	9 (50%)
Male	18 (53%)	9 (56%)	9 (50%)
Metabolic Phenotype* N(%):			
Extensive Metabolizer	30 (88%)	13 (81%)	17 (94%)
Poor Metabolizer	0	0	0
Tanner Stage** N(%):			
Stage 1	12 (35%)	11 (69%)	1 (6%)
Stage 2	7 (21%)	4 (25%)	3 (17%)
Stage 3	4 (12%)	0	4 (22%)
Stage 4	6 (18%)	0	6 (33%)
Stage 5	3 (9%)	0	3 (17%)
Weight (lbs.): Mean (SD)	114.6 (42.3)	94.4 (47.1)	132.6 (28.1)
Range	50.2 – 224.3	50.2 – 224.3	96.0 – 212.6
Height (in.): Mean (SD)	60.1 (6.5)	54.9 (5.1)	64.8 (3.2)
Range	47.8 – 70.5	47.8 – 66.5	58.0 – 70.5

* Metabolic phenotype data were not available for Patients 68701, 68711, 68713, and 68811.
** Patients 68706 and 68809 refused to have Tanner stage assessment.

Pharmacokinetic data analysis:

- The study design used by the applicant for performing pharmacokinetic analysis does not allow for obtaining accurate estimates of fluvoxamine clearance and half-life
- The pharmacokinetic sampling for this study is limited to 12 hours post-dose. Since the half-life for fluvoxamine is approximately 15-20 hours, pharmacokinetic sampling for at least 3-4 half-lives following the last dose should have been performed; This would have allowed for more accurate estimates of fluvoxamine clearance.
- The applicant has performed pharmacokinetic data analysis using non-compartmental methods. No modeling approaches were employed.
- The applicant's pharmacokinetic analysis is based on the assumption of dose-proportional or linear pharmacokinetics. Since fluvoxamine follows nonlinear pharmacokinetics, a population pharmacokinetic modeling approach utilizing the plasma concentration-time data for all doses in both the pediatric as well as adult population (along with pharmacokinetic data following a more extensive sampling schedule) would be a more appropriate approach to analyze this data.
- Population pharmacokinetic analysis were performed by the reviewer in consultation with the pharmacometrics scientists.
  - Briefly, the population pharmacokinetic analysis incorporated pharmacokinetic data from pediatric and adults receiving multiple doses of fluvoxamine.
  - The concentrations of fluvoxamine increased with dose in a non-proportional manner, suggesting non-linear pharmacokinetics.
  - Fluvoxamine undergoes high first pass metabolism resulting in low oral bioavalilability.
  - Our population pharmacokinetic analysis of the data submitted by the applicant showed that the non-linearity in pharmacokinetics was not observed for the oral clearance (as suggested by the applicant), but for the bioavailability of fluvoxamine.
  - As dose of fluvoxamine is increased, the oral bioavailability of fluvoxamine also increases, resulting in non-proportional increases in plasma fluvoxamine concentrations

- Our analysis showed that fluvoxamine oral clearance is dependant on body weight and gender (for ages between 6 and 11 years). This is reflected in the 3-4 fold higher concentrations observed in children as compared to adolescents and in the 2-3 fold higher concentrations observed in female children compared to male children.
- The conclusions drawn from this analysis have been used to summarize pharmacokinetic results in this review as well as to provide appropriate labeling recommendations regarding dosing of fluvoxamine in children and adolescents.

Statistical Methods: Descriptive statistics were performed for the pharmacokinetic parameters. The primary objective was addressed by an analysis of covariance (ANCOVA) on both original and dose normalized pharmacokinetics parameters. The ANCOVA model included dose, gender, Tanner stage and age-group as fixed effects and body weight as a covariate. The secondary objective was addressed by comparing the pharmacokinetics (at the administered dose of 150 mg) in adolescents from this study to those in adults from study CR100.0059. Ratios and 90% confidence intervals for comparison of pharmacokinetic parameters between adolescents and adults were computed and presented with the arithmetic and least-squares means and standard deviations of the adolescent and adult populations.

Pharmacokinetic Results:

Age Differences in Pharmacokinetics – Children versus Adolescents:

- at each dose level, mean plasma concentrations were markedly higher in children (n=16) as compared to adolescents (n=18) (see figures 1, 2 and 3)
- mean Cmax, Cmin, and AUC(0-12) values were consistently higher in children compared to adolescents at all dose levels. (see tables 3 and 4)
- there was a large variability in the pharmacokinetic parameters (approx. 100%) in children and adolescents (see tables 3 and 4)
- Statistically significant differences (p-values < 0.05) between children and adolescents were seen at the 50 mg dose level for the PK parameters (see tables 3 and 4).

Figure 1

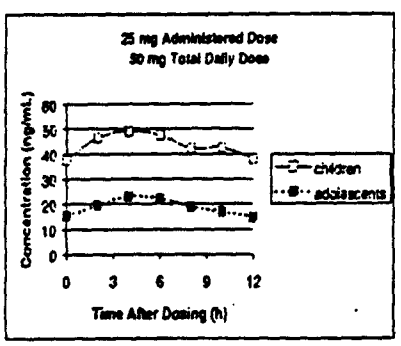


Figure 2

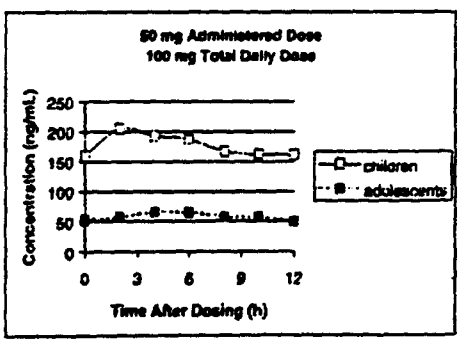
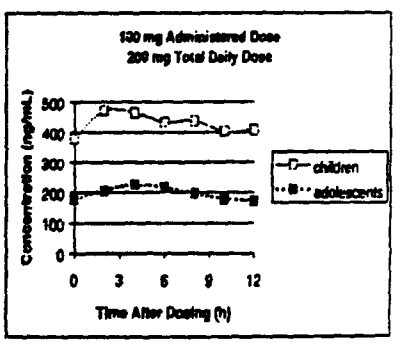


Figure 3



Fluvoxamine PK parameters in children and adolescents (not normalized for body weight)

Table 3

Parameter	Dose	Group** (N)	Mean	SD	Adjusted Mean	Pair	Pairwise Comparisons Ratio (%)	90% CI on Ratio
CL/F (L/h)	25	C (16)	60.91	32.56	44.66			
		A (18)	122.53	104.62	77.90	25 C/A	87.88	32.2, 102.8
	50	C (15)	30.39	29.73	20.94			
		A (17)	104.60	134.27	56.59	50 C/A	36.61†	18.0, 74.6
	100	C (10)	21.20	14.56	19.36			
		A (17)	87.25	64.13	33.21	100 C/A	58.39	28.9, 117.8
Tmax (h)	25	C (16)	4.391	2.447	4.553			
		A (18)	4.646	1.937	3.959	25 C/A	117.64	71.1, 194.4
	50	C (15)	3.235	1.482	4.662			
		A (17)	4.588	1.536	3.942	50 C/A	118.77	78.8, 178.9
	100	C (10)	4.587	3.452	4.220			
		A (17)	4.476	1.621	4.412	100 C/A	95.65	55.3, 165.6
Cmax (ng/mL)	25	C (16)	99.19	32.89	41.27			
		A (18)	24.67	13.66	28.37	25 C/A	186.82	93.6, 281.9
	50	C (15)	227.93	170.88	182.45			
		A (17)	70.39	47.22	67.30	50 C/A	270.29†	137.9, 529.9
	100	C (10)	501.40	318.58	371.47			
		A (17)	233.12	153.84	217.89	100 C/A	170.48	86.3, 325.6
Cmin (ng/mL)	25	C (16)	34.41	25.39	26.26			
		A (18)	12.61	9.20	12.46	25 C/A	210.44	112.3, 394.4
	50	C (15)	147.61	112.93	114.05			
		A (17)	42.83	31.89	40.06	50 C/A	284.68†	134.4, 603.0
	100	C (10)	385.10	251.85	268.64			
		A (17)	160.64	102.28	148.12	100 C/A	183.66	97.2, 387.6
AUC(0-12) (ng/mL•h)	25	C (16)	549.3	360.0	410.1			
		A (18)	229.9	137.2	236.1	25 C/A	173.67	87.3, 310.2
	50	C (15)	2236.4	1677.0	1801.6			
		A (17)	699.4	479.2	659.4	50 C/A	273.20†	134.2, 556.3
	100	C (10)	5211.3	3417.6	3785.9			
		A (17)	2401.8	1436.9	2207.0	100 C/A	171.54	85.0, 346.1

* Adjusted means and pairwise comparisons were calculated within dose using the model: ln(value) = gender age Tanner stage bodyweight.
** C=Children; A=Adolescents
† $p \leq 0.05$

Table 4

Fluvoxamine PK parameters in children and adolescents (normalized for body weight)

Parameter	Dose	Group** (N)	Mean	SD	Adjusted Mean	Pair	Pairwise Comparisons Ratio (%)	90% CI on Ratio
CL/F (L/h/kg)	25	C (16)	1.268	0.780	0.969			
		A (18)	1.931	1.169	1.502	25 C/A	64.56	35.9, 116.0
	50	C (15)	0.690	0.481	0.432			
		A (17)	1.567	1.375	1.074	50 C/A	40.25†	19.5, 82.9
	100	C (10)	0.449	0.261	0.385			
		A (17)	0.884	0.737	0.613	100 C/A	62.78	31.0, 127.2
Cmax (ng/mL/kg)	25	C (16)	1.725	1.447	0.895			
		A (18)	0.444	0.264	0.510	25 C/A	175.47	103.5, 297.6
	50	C (15)	7.006	6.650	3.877			
		A (17)	1.264	0.910	1.304	50 C/A	297.22†	151.4, 583.4
	100	C (10)	14.792	14.856	7.379			
		A (17)	4.249	2.585	4.019	100 C/A	183.61	94.9, 355.3
Cmin (ng/mL/kg)	25	C (16)	1.060	1.109	0.570			
		A (18)	0.226	0.166	0.241	25 C/A	235.92†	125.8, 442.3
	50	C (15)	4.564	4.498	2.615			
		A (17)	0.769	0.619	0.839	50 C/A	311.51†	143.4, 676.7
	100	C (10)	10.972	11.946	5.336			
		A (17)	2.934	1.952	2.695	100 C/A	198.01	92.8, 422.6
AUC(0-12) (h*ng/mL/kg)	25	C (16)	17.07	15.85	8.90			
		A (18)	4.11	2.63	4.57	25 C/A	194.70	107.8, 351.6
	50	C (15)	89.18	67.16	38.26			
		A (17)	12.71	9.05	12.74	50 C/A	300.42†	147.5, 611.8
	100	C (10)	155.09	160.88	76.20			
		A (17)	43.99	27.87	40.71	100 C/A	184.74	90.6, 376.8

* Adjusted means and pairwise comparisons were calculated within dose using the model: ln(value) = gender age Tanner stage bodyweight.
** C = Children; A = Adolescents
† $p \leq 0.05$

Dose Proportionality:

- Non-dose-proportional increases in mean Cmax, Cmin, and AUC(0-12) were observed in children and adolescents; however, the data were highly variable (see tables 5 and 6)
- No changes in Tmax were seen with an increase in dose in children or adolescents
- The non-linearity in fluvoxamine pharmacokinetics in children and adolescents is consistent with results from other pharmacokinetic studies with fluvoxamine in adults.

Table 5
Assessment of dose proportionality (in children)

					Pairwise Comparisons		
Parameter	Dose (n)	Mean	SD	Adjusted Mean	Pair	Ratio (%)	90% CI on Ratio
CL/F (L/h/kg)	25 (16)	1.268	0.780	0.931			
	50 (15)	0.690	0.481	0.519	50/25	56.70 †	41.3, 75.1
	100 (10)	0.449	0.281	0.346	100/25	37.19 †	26.5, 52.3
					100/50	66.78	47.2, 94.3
nCmax** (ng/mL)	25 (16)	56.19	32.65	51.50			
	50 (15)	113.87	85.29	89.21	50/25	173.21 †	131.6, 228.0
	100 (10)	125.35	78.64	123.91	100/25	240.60 †	175.8, 329.3
					100/50	138.91	101.0, 191.0
nAUC(0-12)** (ng/mL•h)	25 (16)	649.3	368.8	487.1			
	50 (15)	1118.2	838.5	862.9	50/25	177.15 †	131.1, 239.4
	100 (10)	1302.8	854.4	1285.9	100/25	263.97 †	187.2, 372.2
					100/50	149.01	105.1, 211.2

* Adjusted means and pairwise comparisons were calculated within age group using the model: ln(value) = dose gender Tanner stage bodyweight.
** Cmax and AUC(0-12) values were normalized for dose (divided by factors of 1, 2, or 4 for the 25, 50, and 100 mg administered doses, respectively) prior to statistical analyses and are shown as nCmax and nAUC(0-12).
† $p \leq 0.05$

Table 6
Assessment of dose proportionality (in adolescents)

					Pairwise Comparisons		
Parameter	Dose (n)	Mean	SD	Adjusted Mean	Pair	Ratio (%)	90% CI on Ratio
CL/F (L/h/kg)	25 (16)	1.931	1.169	1.599			
	50 (17)	1.567	1.375	1.145	50/25	71.59	52.7, 97.3
	100 (17)	0.894	0.737	0.662	100/25	40.78 †	30.0, 55.4
					100/50	56.93 †	41.7, 77.7
	150 (13)	0.999	0.784	0.639	150/25	38.83 †	28.6, 52.8
					150/50	55.78 †	39.8, 78.3
					150/100	97.97	69.8, 137.5
nCmax** (ng/mL)	25 (16)	24.87	13.68	22.14			
	50 (17)	35.19	23.61	28.46	50/25	128.65	88.6, 171.4
	100 (17)	58.28	33.46	48.86	100/25	220.73 †	165.7, 294.0
					100/50	171.66 †	126.3, 229.5
	150 (13)	60.29	36.99	50.38	150/25	227.60 †	166.9, 310.9
					150/50	176.91 †	128.9, 242.8
					150/100	103.11	78.1, 141.9
nAUC(0-12)** (ng/mL•h)	25 (16)	229.9	137.2	196.0			
	50 (17)	349.7	239.5	276.7	50/25	141.16	103.6, 191.8
	100 (17)	609.4	359.2	488.2	100/25	249.08 †	183.3, 338.4
					100/50	176.46 †	129.3, 240.8
	150 (13)	691.2	404.9	605.8	150/25	257.66 †	184.8, 359.9
					150/50	182.66 †	130.3, 256.2
					150/100	103.53	73.8, 145.2

* Adjusted means and pairwise comparisons were calculated within age group using the model: ln(value) = dose gender Tanner stage bodyweight.
** Cmax and AUC(0-12) values were normalized for dose (divided by factors of 1, 2, 4, or 6 for the 25, 50, 100, and 150 mg doses, respectively) prior to statistical analyses and are shown as nCmax and nAUC(0-12).
† $p \leq 0.05$

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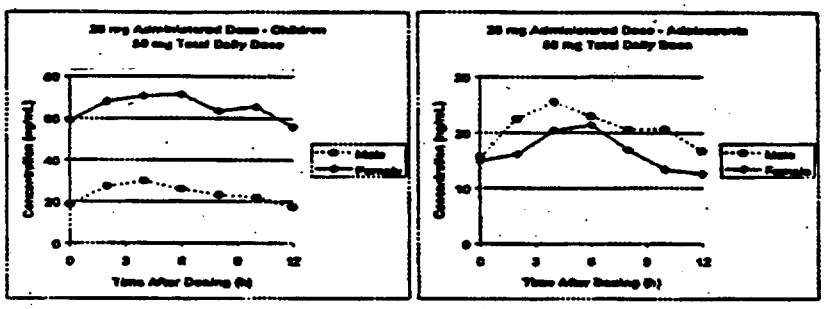
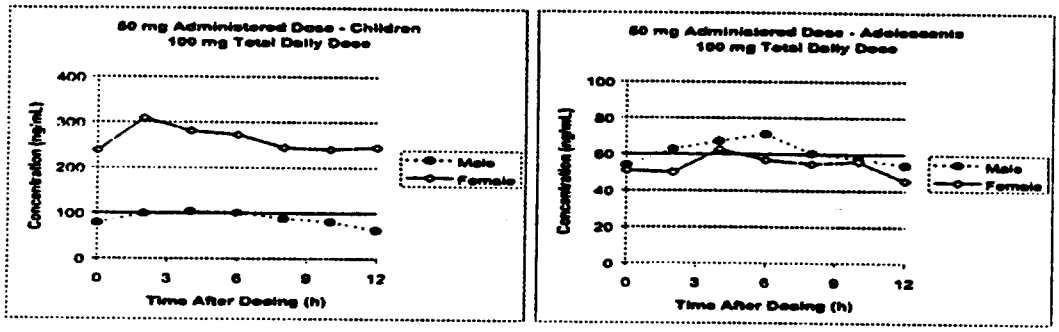
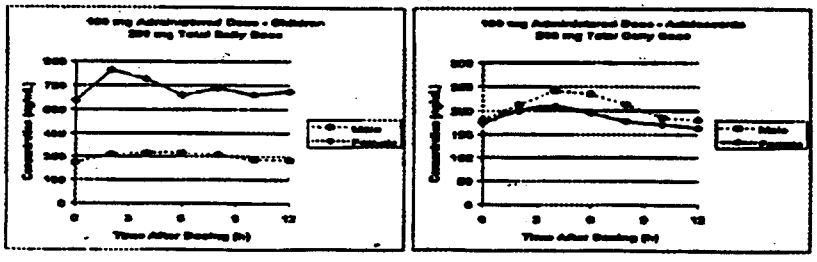
Gender Differences in Pharmacokinetics:

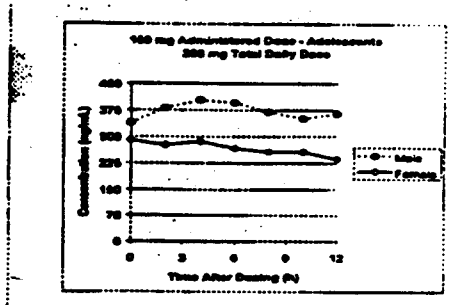
- In children (ages 6-11 years), females consistently had higher plasma concentrations of fluvoxamine than males at all dose levels (see figures 4, 5, 6 and 7)
- Mean Cmax, Cmin, and AUC(0-12) values consistently higher, in female children as compared to male children. No differences between genders were seen for Tmax values.
- For adolescents, no gender differences in pharmacokinetic parameters were apparent.
- Normalization of the PK parameters for body weight had no impact on these results.
- In another study in adults were given 50 mg fluvoxamine twice a day for 2 weeks and 100 mg twice a day thereafter (Hartter S, et al, *Ther Drug Monit* 1998 Aug;20(4):446-9), gender difference in fluvoxamine PK were observed. Steady-state fluvoxamine serum concentrations were highly variable between patients. After the dose was doubled, the serum concentrations of fluvoxamine increased disproportionately (mean, 3.4-fold), and there was a significantly ($p < 0.05$) more pronounced increase in men (4.6-fold) than in women (2.4-fold). These results support the gender effect in fluvoxamine pharmacokinetics in children
- However the pharmacokinetic data from the adult study submitted to this submission (CR100.0059) do not show a gender difference in fluvoxamine pharmacokinetics as supported by our population pharmacokinetic analysis.
- It is not clear as to why the gender effect was not observed in adolescents and adults.

Figures 4, 5, 6 and 7









Comparison of mean fluvoxamine PK parameters between male and female children

Table 7

Parameter	Dose	Group** (n)	Mean	SD	Adjusted Mean	Pairwise Comparisons: Pair	Ratio (%)	90% CI on Ratio
CL/F (L/h/kg)	25	F (7)	0.732	0.333	0.594			
		M (9)	1.685	0.782	1.579	25 F/M	37.64 †	23.8, 59.6
	50	F (7)	0.476	0.478	0.336			
		M (8)	0.878	0.424	0.789	50 F/M	42.55	19.7, 92.1
	100	F (3)	0.243	0.022	0.226			
		M (7)	0.537	0.268	0.490	100 F/M	46.19	24.2, 88.2
Cmax (ng/mL/kg)	25	F (7)	2.859	1.464	2.023			
		M (9)	0.842	0.562	0.829	25 F/M	244.06 †	154.7, 385.0
	50	F (7)	11.810	6.847	6.974			
		M (8)	2.807	2.241	2.959	50 F/M	235.68	113.8, 487.9
	100	F (3)	28.080	21.054	16.414			
		M (7)	9.097	7.561	7.204	100 F/M	227.84	106.9, 476.7
Cmin (ng/mL/kg)	25	F (7)	1.673	1.265	1.226			
		M (9)	0.463	0.359	0.468	25 F/M	262.61 †	147.2, 468.4
	50	F (7)	7.809	4.649	4.655			
		M (8)	1.726	1.483	1.621	50 F/M	287.12 †	127.2, 647.9
	100	F (3)	21.160	17.586	11.893			
		M (7)	6.606	6.067	5.012	100 F/M	237.31	98.3, 573.2
AUC(0-12) (h*ng/mL/kg)	25	F (7)	29.35	16.65	20.40			
		M (9)	7.52	5.33	7.88	25 F/M	265.61 †	156.6, 449.8
	50	F (7)	117.39	69.12	69.78			
		M (8)	27.00	23.83	26.85	50 F/M	259.88	119.1, 567.2
	100	F (3)	293.49	232.98	167.62			
		M (7)	95.78	83.89	73.13	100 F/M	229.20	102.6, 512.1

* Adjusted means and pairwise comparisons were calculated within dose and age group using the model: ln(value) = gender Tanner stage bodyweight. Adjusted means are the antilog (base e) transformation of the least-square means from the ANCOVA.
** M = Male; F = Female
† $p \leq 0.05$

Comparison of mean fluvoxamine PK parameters between male and female adolescents
Table 8

Parameter	Dose	Group**	n	SD	Adjusted Mean	Pairwise Comparisons: Pair	Ratio (%)	90% CI on Ratio
CL/F (L/h/kg)	25	F (9)		1.213	1.358			
		M (9)		1.189	1.561	25 F/M	87.05	51.6, 146.4
	50	F (8)		1.723	1.009			
		M (9)		1.076	1.312	50 F/M	76.94	39.6, 149.4
	100	F (8)		0.752	0.522			
		M (9)		0.769	0.703	100 F/M	74.24	36.7, 150.2
	150	F (7)		0.984	0.749			
		M (6)		0.471	0.769	150 F/M	97.39	34.5, 274.7
Cmax (ng/mL/kg)	25	F (9)		0.231	0.431			
		M (9)		0.261	0.398	25 F/M	108.23	66.5, 176.1
	50	F (8)		0.701	1.103			
		M (9)		1.060	0.893	50 F/M	123.44	64.6, 235.8
	100	F (8)		2.586	4.005			
		M (9)		2.593	3.262	100 F/M	122.78	63.3, 238.1
	150	F (7)		4.174	4.303			
		M (6)		3.784	4.704	150 F/M	91.48	38.2, 219.0
Cmin (ng/mL/kg)	25	F (9)		0.139	0.192			
		M (9)		0.184	0.183	25 F/M	104.84	57.5, 191.1
	50	F (8)		0.436	0.776			
		M (9)		0.731	0.573	50 F/M	135.39	59.8, 306.7
	100	F (8)		2.101	2.976			
		M (9)		1.903	2.020	100 F/M	147.33	70.2, 309.2
	150	F (7)		3.764	2.251			
		M (6)		3.957	4.148	150 F/M	54.25	18.0, 163.5
AUC(0-12) (h*ng/mL/kg)	25	F (9)		2.089	3.895			
		M (9)		2.925	3.526	25 F/M	110.47	65.7, 185.6
	50	F (8)		7.301	10.731			
		M (9)		10.407	8.906	50 F/M	124.67	64.7, 240.2
	100	F (8)		28.095	42.012			
		M (9)		27.984	32.031	100 F/M	131.16	64.9, 265.3
	150	F (7)		47.633	43.052			
		M (6)		43.336	45.047	150 F/M	95.57	35.6, 256.7

* Adjusted means and pairwise comparisons were calculated within dose and age group using the model: ln(value) = gender Tanner stage bodyweight. Adjusted means are the antilog (base e) transformation of the least-square means from the ANCOVA.
** M = Male; F = Female

Comparison of fluvoxamine pharmacokinetics between adolescents and adults:

- PK data from the adolescent population in this study was compared to adult data from a previous study (CR100.0059). Both populations received a 300 mg total daily dose of fluvoxamine preceding pharmacokinetic evaluation.
- Comparison of the mean plasma concentration-time profiles from the two populations suggests no significant differences in the pharmacokinetics of fluvoxamine in adolescents and adults (see Figure 8 below).
- No significant difference were noted for mean AUC, Cmax or Cmin between adults and adolescents (see table 9)

Comparison of fluvoxamine PK parameters in adolescents and adults (dose=300 mg/day)

Figure 8

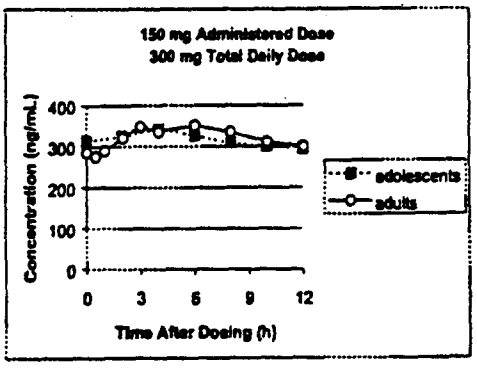


Table 9

					Pairwise Comparisons		
Parameter	*Age Group (n)*	*Ra*	*SD*	*Adjusted Mean*	*Pair*	*Ratio (%)*	*90% CI on Ratio*
CL/F	Adolescent (13)		63.53	44.27			
(L/h)	Adult (16)		27.2	29.54	Adol./Adult	149.8	98.3, 233.1
Cmax	Adolescent (13)		215.91	248.86			
(ng/mL)	Adult (16)		228.45	356.48	Adol./Adult	69.8	46.3, 105.3
Cmin	Adolescent (13)		202.40	197.41			
(ng/mL)	Adult (16)		192.75	251.64	Adol./Adult	78.4	38.9, 156.0
AUC(0-12)	Adolescent (13)		2429.15	2483.52			
(ng/mL•h)	Adult (16)		2404.75	3721.70	Adol./Adult	66.7	42.9, 103.8
Tmax	Adolescent (13)		2.53	3.71			
(h)	Adult (16)		3.30	5.04	Adol./Adult	73.8	51.1, 106.4
			Normalized for Body Weight				
CL/F	Adolescent (13)		0.78	0.71			
(L/h/kg)	Adult (16)		0.35	0.46	Adol./Adult	154.6	98.8, 241.7
Cmax	Adolescent (13)		4.18	4.01			
(ng/mL/kg)	Adult (16)		3.94	5.57	Adol./Adult	72.0	47.9, 108.1
Cmin	Adolescent (13)		3.83	3.19			
(ng/mL/kg)	Adult (16)		3.20	4.05	Adol./Adult	78.8	39.2, 158.4
AUC(0-12)	Adolescent (13)		46.63	40.02			
(h•ng/mL/kg)	Adult (16)		40.92	56.14	Adol./Adult	68.8	44.5, 106.6

* Adjusted means and pairwise comparisons were calculated using the model: ln(value) = gender bodyweight age group.

Proposed Dosing Regimen for Pediatric Population (children and adolescents): The applicant's recommended starting dose for LUVOX® Tablets in pediatric populations (ages 8-17 years) is 25 mg, administered as a single daily dose at bedtime. The dose should be increased in 25 mg increments every 4 to 7 days, as tolerated, until maximum therapeutic benefit is achieved. The maximum dose in children up to age 11 should not exceed 200 mg/day.

The applicant recommends in the label that physicians should consider age and gender differences when dosing pediatric patients. Based on this, the label recommends that:

- therapeutic effect in female children may be achieved with lower doses, since steady-state concentrations of fluvoxamine are higher in female children (6-11 years) than in male children
- dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit, since steady-state fluvoxamine concentrations in adolescents (12-17 years) are similar to those in adults.
- The applicant's proposal is acceptable

Conclusions:

- Higher fluvoxamine exposure in children relative to adolescents was observed at every dose level tested. In children, Cmax and AUC(0-12) were 1.5- to 2.7-fold higher than those observed in adolescents. These differences were statistically significant at the 50 mg administered dose level.
- Comparison of adolescent pharmacokinetic data from this study to pharmacokinetic data in adults from a previous study indicated that there were no statistical differences between the pharmacokinetic parameters of adolescents and adults. Since steady-state plasma fluvoxamine concentrations are similar in adolescents and adults, doses up to 300 mg per day, as permitted in adults, may be useful in the treatment of adolescent patients.
- As has been shown in previous studies with fluvoxamine in adults, both children and adolescents showed evidence of nonlinear pharmacokinetics defined as disproportionate increases in AUC(0-12) and Cmax, as a function of increasing dose. Statistical analysis generally supported this concept although data were highly variable.
- Female children (ages 6-11 years) showed significantly higher AUC(0-12) and Cmax values as compared to males. For adolescents (12-17 years), no gender differences were detected.
- The applicant's proposed dosing regimen in children and adolescents is acceptable.

Recommendation: The pharmacokinetic studies provided in this pediatric supplement for NDA 20243 submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of fluvoxamine in pediatric patients between the ages of 6 and 17 years, inclusive. The information on the pharmacokinetics of fluvoxamine(Luvox®) provided in the pediatric population is adequate to support approval.

Labeling comments:

1. The applicant's proposed labeling is not acceptable. Please see below for OCPB labeling recommendations.

Pediatric Subjects

The multiple-dose pharmacokinetics of fluvoxamine was determined in male and female children (ages 6-11) and adolescents (ages 12-17). Steady-state plasma fluvoxamine concentrations were 2-4 fold higher in children than in adolescents. AUC and Cmax in children were 1.5- to 2.7-fold higher than that in adolescents (see table below). As in adults, both children and adolescents exhibited nonlinear multi-dose pharmacokinetics. Female children showed significantly higher AUC (0-12) and Cmax compared to male children and, therefore, lower doses of LUVOX® Tablets may produce therapeutic benefit (see table below). No gender differences were observed in adolescents. Steady state plasma fluvoxamine concentrations were similar in adults and adolescents at a dose of 300 mg/day, indicating that fluvoxamine exposure was similar in these two populations (see table below)

Dose adjustment in adolescents (up to the adult maximum dose of 300 mg) may be indicated to achieve therapeutic benefit.

We recommend that you include the following table:

Table Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between children, adolescents and adults

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)		Dose = 300 mg/day (150 mg bid)	
	Children (n=10)	Adolescent (n=17)	Adolescents (n= 13)	Adults (n=16)
AUC0-12 (ng.h/ml/kg)	155.0 (160.8)	43.9 (27.9)	69.6 (46.6)	59.4 (40.9)
Cmax (ng/ml/kg)	14.8 (14.9)	4.2 (2.6)	6.7 (4.2)	5.7 (3.9)
Cmin (ng/ml/kg)	10.9 (11.9)	2.9 (1.9)	4.8 (3.8)	4.6 (3.2)

Table Comparison of Mean (SD) fluvoxamine pharmacokinetic parameters between male and female children (6-11 years)

Pharmacokinetic Parameter (body weight corrected)	Dose = 200 mg/day (100 mg bid)	
	Male Children (n=7)	Female children (n= 3)
AUC0-12 (ng.h/ml/kg)	95.8 (83.9)	293.4 (232.9)
Cmax (ng/ml/kg)	9.1 (7.6)	28.1 (21.1)
Cmin (ng/ml/kg)	6.6 (6.1)	21.2 (17.6)

U 9/7/00

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

9/7/2000

Concurrence: Emmanuel Fadiran, Ph.D.
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