CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-033

PHARMACOLOGY REVIEW(S)

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

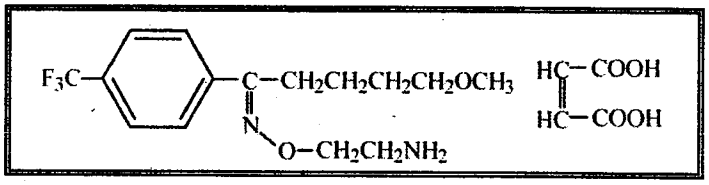
Reviewer Name: Linda H. Fossom.
Division Name: Psychiatry Products.
HFD# 130.
Review Completion Date: 12/18/07.

NDA number: 22-033.
Serial number/stamp-date/type of submission: N-000, AZ / June 22, 2007 / Response to Approvable Letter / Major amendment, multi-disciplinary.
Information to sponsor: Yes (X) No ()
Sponsor: Solvay Pharmaceuticals.

[Luvox is also under review under NDA 21-519, as an IR formulation, also sponsored by Solvay.]

Drug:

Generic Name: fluvoxamine maleate.
Trade Name: Luvox.
Molecular Formula / Molecular weight: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ / 434.41.
USAN Name: 5-methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate.
Structure:



Drug Class: Selective serotonin reuptake inhibitor (SSRI).

Indication: Treatment of Generalized Social Anxiety Disorder and Obsessive-Compulsive Disorder (OCD) in adults.

Clinical formulation: controlled-release capsules; 100- and 150-mg strengths.

Route of administration: oral.

Proposed clinical Use: For the treatment of Generalized Social Anxiety Disorder and Obsessive-Compulsive Disorder (OCD) in adults, with maximum recommended human dose (MRHD) of 300 mg per day.

Previous clinical experience: Fluvoxamine (as the maleate salt) has been marketed in the US for treatment of Obsessive-Compulsive Disorder (OCD) since ~1995. It was approved for treatment of OCD under NDA 20-243 (12/5/94) and marketed by Solvay as Luvox until 2002 (when it was put on AIP). Several (12) generic formulations of Luvox

TABLE OF CONTENTS FOR THIS REVIEW:

1 PHARMACOLOGY/TOXICOLOGY (IMPURITY/DEGRADANT) ISSUES ADDRESSED IN THIS SUBMISSION:

1.1 Action requested by the Agency in our 2/27/07 AE letter:

In our 2/27/07 AE letter, we communicated the following Pharmacology/Toxicology issues:

Pharmacology/Toxicology

- There are several impurities/degradants in the drug substance and/or CR drug product with specifications above the threshold(s) for qualification. Although you have not addressed this issue in your current NDA, you did attempt to address similar issues under your NDA 21-519 for Luvox IR tablets. Based on the toxicology studies available for review under that NDA, we have determined that only the specifications for the ——— (i.e., ——— and ——— (i.e., ——— have been set too high in the CR product and cannot be considered to be qualified by nonclinical studies that have previously been submitted. Consequently, you will need to qualify these 2 impurities/degradants, as described below, prior to approval.

- Only an additional (adequate) Ames test will be required to qualify the ——— to its higher specification in the CR drug product (——— compared with ——— for the IR product under NDA 21-519 and a threshold for qualification of ——— It should be noted that you were informed, in the AE letter for NDA 21-519 dated 11/16/06, that the Ames tests that had been submitted up to that that time (with ——— : at concentrations up to ——— would be considered adequate to qualify the specification of ——— proposed for the IR product, but not higher specifications.

- No studies that could serve to qualify ——— have been provided (under NDA 21-519 or the current NDA). Qualification of ——— will require: 1) a general toxicology study in one species of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues; 2) *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and 3) an embryofetal development study in one species.

In brief, the only Pharmacology/Toxicology concerns related to qualification of the ——— (specified at ——— and ——— specified at ——— Based on information submitted under NDA 21-519 for the IR product, we are only requiring an additional Ames test for the ——— but the full complement of studies for ———

1.2 The Sponsor's response:

The Sponsor has provided their written response to the Pharmacology/Toxicology issues communicated in our 2/27/07 AE letter (pages 0010-013, volume 1, this submission). In brief, they feel that the ——— and ——— have been qualified in the four non-clinical studies that they have submitted (draft study reports in this submission; the final reports have been subsequently submitted to NDA 21-519, for the IR formulation).

1.3 This Reviewer's comments/conclusions:

In this submission the Sponsor has provided (audited draft) reports for the following studies (see table, below), testing [The final reports for these studies were submitted to NDA 21-519 (N-000, BP, letter-dated 11/19/2007, stamp-dated 11/20/2007) and have been reviewed under that NDA (see review by this Reviewer dated 12/14/07, under NDA 21-519, N-000, AZ / stamp-dated June 21, 2007 / Response to Approvable Letter / Major amendment, multi-disciplinary).]

STUDY TYPE (STUDY #)				
(highest current specification)	spec in product)	spec in product)	in product)	in substance)
Ames test (S114.7.003)				
Mouse lymphoma assay (S114.7.004)				
14-day rat tox study (rat) (S114.7.005)				
Embryofetal (rat) (S114.7.006)				

In our AE letter (dated 2/27/07), we only had concerns about inadequate qualification of (specified at , and requiring all 4 studies for qualification) and the (Ames test if specified at).

The Sponsor has retained the specification for the which was not adequately qualified in the previous Ames tests. However, the Ames test they have provided in this submission would support qualification of this impurity to based on my previous review of that study under NDA 21-519).

Based on my previous review of the studies submitted here (reviewed under NDA 21-519), the Sponsor has provided studies that would qualify to at least (based on content in the in vitro genotoxicity tests), which is adequate to qualify the current specification of in drug product. However, the general toxicity study (14-day study in rats) is not considered adequate; in our AE letter we stated that the general toxicity study for qualification of should include microscopic examination of the standard battery of tissues, but only adrenals, gross lesions, kidney, and liver were examined microscopically in the current study. Although the current study was initiated (dosing started on 2/8/07) prior to issuance of our AE letter (on 2/27/07), pathology was not completed until more than 5 months later. Furthermore, the Sponsor had received the same request for full histopathology in the general toxicity study to qualify this impurity

under NDA 21-519 in an AE letter dated 11/16/06. The Sponsor has provided no explanation for this deficiency, under either NDA.

Additionally, it should be noted that under the current specification of — patients receiving the maximum recommended human dose of 300 mg could be exposed to up to —— of —— per day, a relatively small, but not insignificant amount. For these reasons, an adequate general toxicity study, including full histopathological assessment, should be required to support qualification of this impurity/degadant. If it is not possible for the Sponsor to obtain full microscopic analysis on the remaining fixed tissues from the current study, they should conduct another study, including full histopathological assessment.

However, it is this Reviewer's opinion that this deficiency could be addressed post-marketing, rather than being required pre-approval, because: 1) there were no microscopic findings for adrenals, gross lesions, kidney, or liver (hepatocellular hypertrophy was present in males in both treated groups), and no changes in organ weights (adrenals, brain, heart, kidney, liver, mandibular, mesenteric, popliteal lymph nodes, ovaries, pituitary, prostate, spleen, testes + epididymides, thymus, thyroids + parathyroids) or in clinical chemistry or hematology parameters that would indicate changes attributable to either drug treatment (fluvoxamine alone or spiked with impurity); and 2) the results already obtained did not reveal any serious overt toxicity, such as death or ill health. [This is the same conclusion drawn in the review of NDA 21-519.]

The current rat toxicity study could provide safety margins for —— at the MRHD of 300 mg/day of fluvoxamine of 60-fold on a mg/kg basis (assumed to be relevant for gastrointestinal toxicity) and ~10-fold on a mg/m^2 basis (assumed to be relevant for systemic toxicity). [For the MRHD of 300 mg/day and the specification of — for —— patients would be exposed to —— per day; for a 60 kg adult this would be —— In the rat study, at 80 mg/kg fluvoxamine and ——, rats were exposed to — mg/kg —— or —

[It should also be noted that the Sponsor had specified —— at — in their original submission of this NDA, so it did not require qualification. This is in contrast to NDA 21-519, where this impurity was originally specified at — in the drug substance, and would have required qualification.]

2 OVERALL CONCLUSIONS:

The only Pharmacology/Toxicology issues that would prevent approval of this NDA, as communicated in our AE letter (dated 2/27/07), concerned inadequate qualification of the —— (specified at — in drug product) and —— (specified at in drug product). In the current submission, the Sponsor has adequately addressed these issues:

they have provided studies that will qualify ——— to — but see caveat below); and an Ames test that will support qualification of —— to —

It should be noted that the repeated-dose general toxicity study that was needed to support qualification of ——— was not strictly adequate, because full histopathological assessment was not conducted, as specified in our AE letter (dated 2/27/07). However, it is this Reviewer's opinion that this could be addressed in a post-marketing commitment; this conclusion is detailed above and in my review (dated 12/14/07) of NDA 21-519 (N-000, AZ / June 21, 2007 / Response to Approvable Letter / Major amendment, multi-disciplinary). If it is not possible for the Sponsor to have full microscopic analysis conducted on the remaining fixed tissues from the current study, they will need to conduct another study, including full histopathological assessment.

[During the review cycle of the current NDA (22-033), the Sponsor has agreed to address this issue as a post-marketing commitment (by having the remaining tissues from the general toxicity study in question processed and evaluated histopathologically) under their NDA 21-519, for Luvox IR.]

There are no Pharmacology/Toxicology issues that would prevent the Approval of this NDA.

3 RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, this NDA may be APPROVED.

However, the Sponsor will need to agree to a post-market commitment to provide an adequate general toxicity study to support the qualification of ——— [Requesting this commitment is necessary, but seemingly redundant, since the Sponsor has already agreed to address it as a post-marketing commitment to their NDA 21-519 for Luvox IR.]

4 INFORMATION TO BE COMMUNICATED TO THE SPONSOR:

PHARMACOLOGY/TOXICOLOGY POST-MARKETING COMMITMENTS:

You did not conduct microscopic examination of the standard battery of tissues in the general toxicity study that you submitted to support qualification of ———, as we requested in our Approvable letter (dated 2/27/2007). Consequently, you will need to address this issue by conducting complete microscopic assessment on tissues from that study or, if that is not possible, by conducting another general toxicity study to qualify ———, and including microscopic examination of the standard battery of tissues. [We recognize that a request for this same post-marketing commitment was made for

your NDA 21-519 for Luvox IR, and that under that NDA you have already committed to having the remaining tissues from the general toxicity study in question processed and evaluated histopathologically.]

5 LABELING:

It is recommended that non-clinical sections of labeling be the same as those recommended for the IR formulation of Luvox under NDA 21-519.

6 SIGNATURES:

Linda H. Fossom, Ph.D., Reviewing Pharmacologist *{see appended electronic signature page}*
Barry Rosloff, Ph.D., Supervisory Pharmacologist *{see appended electronic signature page}*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Fossom
12/18/2007 02:54:38 PM
PHARMACOLOGIST

Barry Rosloff
12/18/2007 03:05:01 PM
PHARMACOLOGIST

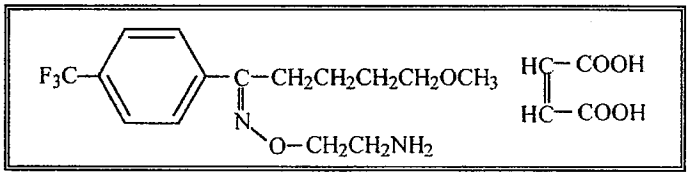
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom
Division Name: Psychiatry Products
HFD# 130.
Review Completion Date: 2/22/07.

NDA number: 22-033.
Serial number/stamp-date/type of submission: N-000 / May 1, 2006 / original submission.
Information to sponsor: Yes (X) No ()
Sponsor: Solvay Pharmaceuticals.
Manufacturer for drug substance: same.

Drug:

Code Name: not provided.
Generic Name: fluvoxamine maleate.
Trade Name: Luvox.
Molecular Formula / Molecular weight: $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ / 434.41.
USAN Name: 5-methoxy-4'-(trifluoromethyl)-valerophenone (*E*)-*O*-(2-aminoethyl)oxime, maleate.
Structure:



Relevant INDs/NDAs/DMFs:

- [redacted]
- IND 57,838 (CR capsule formulation): for treatment of Obsessive Compulsive Disorder (OCD); sponsored by Solvay;
- [redacted] under which most of the P/T information was reviewed and considered to support approval;
- [redacted];
- NDA 20-243 (IR tablets, approved for OCD (12/5/1994), supported by P/T data submitted to [redacted]; subsequently withdrawn by Commissioner (9/3/2003); sponsored by Solvay;
- [redacted]
- NDA 21-519 (IR formulation): currently pending review, for treatment of Obsessive Compulsive Disorder; sponsored by Solvay;

- DMF 5169: describing manufacture of drug substance; held by Solvay Pharmaceuticals, Inc;
- DMF [redacted] [In the current NDA (22-033), Solvay provided a letter from [redacted] to the FDA authorizing the Agency "...to reference the information provided in this DMF and its amendments in connection with any Solvay Pharmaceutical Applications (IND or NDA) or supplements thereto."]

Drug Class: Selective serotonin reuptake inhibitor (SSRI).

Indication: Treatment of Generalized Social Anxiety Disorder and Obsessive-Compulsive Disorder (OCD) in adults.

Clinical formulation: controlled-release capsules; 100- and 150-mg strengths.

Route of administration: oral.

Proposed clinical Use: For the treatment of Generalized Social Anxiety Disorder and Obsessive-Compulsive Disorder (OCD) in adults, with maximum recommended human dose (MRHD) of 300 mg per day.

Previous clinical experience: Fluvoxamine (as the maleate salt) has been marketed in the US for treatment of Obsessive-Compulsive Disorder (OCD) since ~1995. It was approved for treatment of OCD under NDA 20-243 (12/5/94) and marketed by Solvay as Luvox until 2002 (when it was put on AIP). Several (12) generic formulations of Luvox were approved in the US in 2000-2002 for this indication. A new NDA (NDA 21-519), sponsored by Solvay, is currently under review for use of Luvox as IR tablets for treatment of OCD. Clinical data has been provided with the current NDA (NDA 22-033) to support the efficacy of Luvox CR for treatment of Generalized Social Anxiety Disorder and for treatment of OCD.

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1 INTRODUCTION AND DRUG HISTORY:

1.1 Early background for Luvox:

Luvox (fluvoxamine maleate, as immediate-release tablets, under the tradename of Luvox, sponsored by Solvay) was approved for treatment of Obsessive-Compulsive Disorder (OCD) under NDA 20-243 on 12/5/94. Subsequently, that NDA was put under Application Integrity Policy (AIP) for chemistry irregularities. In an agreement with the Agency, Solvay withdrew NDA 20-243 (on 5/13/02.

The Sponsor subsequently submitted a new NDA (NDA 21-519) for the IR formulation for treatment of OCD. No non-clinical pharmacology or toxicology studies were provided in the original submission (stamp-dated 7/1/02) of NDA 21-519; the Sponsor relied upon the non-clinical studies that had been reviewed for and supported the approval of NDA 20-243 to support the current NDA. The non-clinical studies submitted under NDA 20-243 had been determined to support approval of Luvox at that time (NDA 20-243 was approved on 12/5/94) contingent upon the Sponsor's (Phase IV) commitment to conduct repeat preclinical Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) reproduction studies in the rat, because the dosing in the original studies was considered inadequate.

The initial submission of NDA 21-519 (stamp-dated 7/1/02) was determined to be fileable. However, the Agency issued a letter (dated 9/5/02) reminding the Sponsor that the review of their submission would not continue until they were notified by the Director, Center for Drug Evaluation and Research, that the AIP had been revoked (or we had determined that the AIP no longer applied or that the product was medically necessary). In that letter, the Division also communicated several requests, including the following two which were relevant to Pharmacology/Toxicology: 1) to provide a rationale and justification for the selection of the proposed specifications for impurities/degradants in Luvox drug product that exceeded the 0.2% threshold for qualification of degradation products as described in the "Guidance for Industry-Q3B Impurities in New Drug Products." [This guidance was published in the *Federal Register* on May 19, 1997 (62 FR 27454), well after the approval of NDA 20-243 in 1994.]; and 2) a reminder of their Phase IV commitment to either repeat the Segment I and II reproduction studies in the rat or provide adequate justification for the doses which were used in the original studies.

The Sponsor addressed the issues regarding impurities/degradants raised by the Agency's 9/5/02 letter in an amendment to NDA 21-519 (letter-dated 5/7/03), referring to (and resubmitting) an earlier submission (letter-dated 10/22/98) to NDA 20-243. In that same amendment to NDA 21-519, the Sponsor submitted study reports for Segment I and Segment II reproductive toxicology studies in support of their Phase IV commitment. [Those reproductive toxicology studies were reviewed and the results included in revised labeling provided to the Sponsor in our AE letter (dated 2/9/04).]

During the course of reviewing that submission, it was determined that specifications for several (other) impurities in drug substance had also been set above the threshold for qualification (as described in the "Guidance for Industry-Q3A Impurities in New Drug Substances;" 1996, revised in 2003). It was concluded that the impurity/degradant issues had not been adequately addressed.

On 2/9/04, the Agency issued an Approvable Letter for NDA 21-519 that included the following description of the Pharmacology/Toxicology issues that would need to be addressed before the NDA could be approved:

Pharmacology/Toxicology

The specifications set for a number of impurities are above the threshold for qualification in drug substance (i.e., above 0.15%) and/or drug product (i.e., above 0.2%). We recommend that you lower the specifications for these impurities to below the qualification threshold. If this is not possible, you need to qualify these impurities in the following studies (note exceptions below):

- **a general toxicology study in one species, of 14-90 days duration;**
- ***in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]);**
- **an embryofetal development study in one species;**
- **a juvenile study in one species.**

For the general toxicology, embryofetal development, and juvenile studies, justification should be provided for the species selected for each study.

Based on the information provided, we consider the [redacted] qualified for general toxicity in a 13-week study in rats and all but the [redacted] qualified in the embryofetal development study in rat (Study No. TX.114.07.05P). You indicated that there has been considerable human exposure to older formulations of fluvoxamine (possibly containing higher levels of one or more impurities) marketed (since late 1993) in several foreign countries. To the extent that you can provide documentation (i.e., actual levels of impurities rather than specifications) that the impurities have been qualified by this clinical use, no further testing of general toxicity would be needed.

With the exceptions noted, all the impurities with specifications set above the qualification threshold need to be qualified in the studies as listed above. These studies, except for the juvenile study, will be required prior to approval if the specifications cannot be lowered to below the qualification threshold.

In response to our 2/9/04 AE letter (for NDA 21-519), the Sponsor addressed our issues related to the qualification of impurities/degradants (N-000, AZ, stamp-dated 5/17/06). Upon review of that submission, it was determined that some but not all of the Pharmacology/Toxicology concerns for qualification of impurities/degradants had been adequately addressed. Another AE letter (for NDA 21-519) issued on 11/16/06, containing the unresolved Pharmacology/Toxicology issues (see next section of this review).

1.2 Most recent AE letter for Luvox IR tablets (NDA 21-519), which issued 11/16/06:

The Pharmacology/Toxicology issue that prevented approval of NDA 21-519 for Luvox IR tablets was inadequate qualification of 2 impurities/degradants: [redacted], in drug product and [redacted], in the drug substance (see excerpt from AE letter below).

> **Pharmacology/Toxicology Review**
> The specification for [redacted] in the drug product is set at [redacted] which is above the threshold for qualification (i.e., above 0.2%). Based on the most recent stability data, it appears that you are unable to lower this specification. Consequently, you will need to qualify this impurity/degradant in the following studies prior to approval:
>
> - a general toxicology study in one species, of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues;
> - *in vitro* genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and
> - an embryofetal development study in one species.
>
> The specification for [redacted] in the drug substance is set at [redacted] which is above the threshold for qualification (i.e., above 0.15%). You have indicated that you intend to lower this specification, but have not provided us with documentation of your revised specification. Such documentation or qualification of this impurity in the studies listed above will be needed prior to approval. If qualification is required, this impurity is currently considered to be qualified for embryo-fetal toxicity, but not for genotoxicity or general toxicity, as communicated in our previous AE letter (dated 2/9/04).
>
> Although the [redacted] is considered to be adequately qualified for the current [redacted] specification in drug substance and product, the [redacted] level of this impurity in the Ames test will not be adequate to qualify specifications higher than [redacted]

Additionally, the Sponsor was told that if the specification for a 3rd impurity, the [redacted] was set higher than the then-proposed level of [redacted], qualification would not be considered to be adequate, based on the Ames tests that had been submitted to that time. This information would not have been normally communicated to the Sponsor, since the qualification was considered adequate for that NDA. However, the Reviewer was aware of the apparently higher specification for that impurity in the CR formulation that was being reviewed under the current NDA (NDA 22-033) at the same time.

1.3 The current submission:

The current NDA (22-0033) is for a controlled-release (CR) formulation of fluvoxamine maleate. In this submission, the Sponsor has provided the report for a "2-week oral toxicity study in dogs designed to evaluate the potential of the controlled-release fluvoxamine formulation (fluvoxamine CR) to cause gastrointestinal irritation..." According to the original submission (Nonclinical Pharmacology and Toxicology Summary, section 3.5; stamp-dated 5/1/06), no other non-clinical information was provided in this submission. [A recent amendment to this NDA (letter-dated 2/13/07, stamp-dated 2/15/07) contained information that had been requested by our CMC team, including the specifications for impurities/degradants in the drug product, which had not

previously been provided to the NDA (but were known to the Agency through DMF — , held by ————————

2 IMPURITY AND DEGRADANT ISSUES:

The Sponsor provided specifications for impurities/degradants in drug substance in the original submission of this NDA through their DMF for the drug substance (DMF 5169); these specifications are provided in the table, below. Although the Sponsor did not provide specifications for impurities/degradants in the drug product in their original NDA submission, they did provide this information during the review cycle in response to requests from both CMC and P/T; these specifications are also provided in the table, below. [The DMF (——) for the drug product (held by ———————— ———————— also contains these same specifications.]

Specifications for the 4 impurities in the drug substance which are set above the threshold for qualification (i.e., >0.15%) are considered to be adequately supported by non-clinical studies; and the specification for ———————— as been lowered from —— to —— % and does not require qualification (see table, below).

The specifications for 3 impurities/degradants in the drug product have been set at values above the threshold for qualification (i.e., >0.2%): the —— specified at ———— —— specified at——, and the ———— specified at —— Based on the studies that had been previously submitted by the sponsor of the current NDA (under various INDs or NDAs for fluvoxamine maleate) (see table, below):

- the ———— has been **adequately qualified** for the —— specification;
- the —— has been **adequately qualified** for the —— specification, **except for the Ames test**; and
- ———— **has not been qualified at all** (and is specified at ——).

Table 1. Summary of the studies that would serve to qualify the specifications for impurities/degradants that are above qualification thresholds in drug substance (DS) and/or drug product (DP). [Modified from a table (Table 2) that was compiled for a (previous) review of the IR formulation under NDA 21-519, N-000, AZ, stamp-dated 5-17-06.]

IMPURITY/DEGRADANT	DS SPEC	DP SPEC	AMES TEST	CHROM AB	GENERAL TOX	SEG II
						√[5]
						√[5]
						√[5]
						√[3]
						√[3]

[1]: based on the Ames test provided in NDA 21-519, N-000, AZ (stamp-dated 5/17/06).
[2]: based on an Ames test conducted in Japan in 1993 and provided to in 1997 in submission where it has been reviewed.

[3]: based on MLA provided in NDA 21-519, N-000, AZ (stamp-dated 5/17/06).
[4]: based on 14-day study provided in NDA 21-519, N-000, AZ (stamp-dated 5/17/06).
[5]: based on previous review of Segment II study (submitted to NDA 21-519, amendment dated 5/7/03).
[6]: based on previous review of 13-month rat study (submitted under [redacted] and used in support of NDA 20-243).

3 LOCAL TOXICITY / LOWER GI STUDY IN DOGS:

Summary: When fluvoxamine CR formulation was given to Beagle dogs at doses of 150 or 450 mg/day for 14 days, there was no indication of gastrointestinal irritation and/or toxicity at either dose. However, there was indication of systemic exposure, based on plasma level measurements, clinical signs (emesis, diarrhea/bloody diarrhea, and behavioral changes, such as side-to-side head movements and hunched posture), decreased food consumption and decreased body weights at HD during the first week of dosing, changes in clinical chemistry (increased BUN, creatinine, and fibrinogen concentrations), and histopathologic changes in kidneys, spleen, and mesenteric and mandibular lymph nodes.

Compared with the MRHD of 300 mg/day (which would be 5 mg/kg for a 60-kg adult), these doses in dogs give 4- and 11-fold coverage for the MRHD on a mg/kg basis, which is more appropriate for local, GI toxicity than mg/m^2 comparisons.

Methods: [redacted] study no. 9312.3 (GLP/QA); conducted by/at [redacted]; dosing started on 2/24-25/00; drug product: fluvoxamine maleate CR 150-mg capsules (lot no. DE6890, CoA dated 4/29/99; analysis of impurities: [redacted]); Beagle dogs (4/sex/dose; 7-8 months old at start of dosing, from [redacted] at doses of 0 (3 placebo capsules), 150 (1 CR capsule) or 450 (3 CR capsules) mg/day for 14 days; clinical observations once daily after dosing; mortality/moribundity assessed twice daily; body weights prior to study, and prior to dosing on days 1 and 8 and on day 15; food consumption qualitatively measured daily (days 1-14); hematology (WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, MPV, RETIC, differential), clinical chemistry (AST, ALT, BUN, GLUC, TBIL, TPROT, ALB, GLOB, CREA, CK, LDH, Ca, PHOS, Na, K, Cl), coagulation (PT, APTT, FBGN) on blood drawn pre-study, and on days 8 and 15; PK on dosed dogs (not those receiving placebo) on days 1 and 14 (prior to dosing on day 1 and 1, 3, 5, 10, and 24 hr after dosing on both days); full gross examination on all dogs; histopathological examination on all dogs for the following tissues/organs: esophagus, stomach, small intestine (duodenum, jejunum, ileum), large intestine (cecum, colon, rectum), liver, kidney, spleen, lymph nodes (mesenteric and mandibular), and gross lesions.

Results: Mortality: all dogs survived the 14-day study. Clinical observations: treatment-related findings essentially limited to increased incidence of hunched posture at HD in during week 2 of dosing (almost daily during the second week in 2/4 HDMs and 3/4

HDFs); side-to-side movements were noted in 1HDM during week 1 (days 2-5) who also displayed hunched posture during week 2 and in 2 HDFs coincident with some of the observations of hunched posture during week 2; incidence of diarrhea was slightly increased at HD, but was still infrequent (7 times total in 4/4 HDMs between days 4-15, compared with once in 1 LDM at day 14, and in no control males; 3 times total in 2/4 HDFs between days 3-8, compared with once in 1 LDF and once in 1 control female, both at day 13); bloody diarrhea (day 13) and blood in feces (day 9) was seen in 1 HDM and no other male dogs; bloody diarrhea was seen in twice (days 9 and 12) in a single LDF, but in no HDF or control females. Body weights and (qualitative) food consumption (1-2 hr ad lib access to dry food [redacted] per day, at least 6 hr after dosing): body weights were decreased 12-15% during the first week in 1/4 MDF, 2/4 HDM and 4/4 HDF (compared with decreases of ≤5% or slight increases in controls and other LD and HD dogs); this was accompanied by decreased food consumption; from day 5/6, HD dogs were supplemented with wet/canned food, which attenuated the decreased food consumption and body weight loss. Hematology and Clinical Chemistry: changes were essentially limited to HD: in HDF, there were increases in BUN and creatinine, consistent with renal damage, and increased fibrinogen, which the report noted is also consistent with the subacute renal inflammation noted at necropsy; in HDM, only creatinine was increased (BUN was elevated in all groups of males, compared with pre-dosing values). Gross and microscopic examination at necropsy: findings were confined to the HD group: treatment-related gross lesions limited to *small thymus, confirmed microscopically as lymphoid depletion*, in 2 HDM and 1 HDF (considered to be secondary to stress in the report); *kidney*: (minimal) necrosis and (mild or moderate) renal tubular regeneration, dilatation, and protein casts in 2/4 HDM and 4/4 HDF (the report suggests that these changes may reflect "reparative or residual changes that followed an earlier or more overt tubular necrosis" and cites the increases in BUN and/or creatinine); *cytoplasmic vacuolation*: in spleen, mesenteric and mandibular lymph nodes, and Peyer's patches (mucosal and submucosal lymphoid tissue) of the intestinal tract; *gastro-intestinal tract*: quoting from the report, "no ulcerative, erosive, or inflammatory changes involving the mucosa of the alimentary tract were observed in any dogs in the study." Systemic Exposures: analysis indicated that dosed dogs were exposed to fluvoxamine; in spite of considerable inter-animal variability, it appeared that Cmax and AUC were dose-related and higher on day 14 than of day 1 at HD but not LD.

Comparison to previous toxicity studies in dogs: It should be noted that toxicities found in the current study are similar to those found in the 7-month and 12-month oral (capsule) toxicity studies in dogs that were reviewed under [redacted] (review by Barry Rosloff, Ph.D., dated 11/30/1984). Based on that review, fluvoxamine was considered to be "not well tolerated at 60 mg/kg and above; toxic signs at these doses included anorexia, emesis, poor general condition, diarrhea, ataxia, whimpering, and coughing;" decreased body weight and/or weight gain and decreased food consumption was seen at ≥60 mg/kg; and the primary histopathologic findings were: kidney pathology, including chronic interstitial nephritis; and the presence of foam cells or foamy macrophages "in several organs, including spleen, GI tract (Peyer's patches), and lymph nodes."

Comparison of doses in dogs and humans: Groups of Beagle dogs (4/sex) weighing approximately 8 kg were given 150 and 450 mg Luvox CR daily for 14 days. These doses would be equivalent to 18.75 and 56.25 mg/kg, respectively, which are 4 and 11 times the MRHD of 300 mg/day (i.e., 5 mg/kg/day for a 60-kg human) on a mg/kg basis. These doses in dogs would be 2 and 6 times the MRHD on a mg/m^2 basis. For local, gastro-intestinal toxicity, dose comparisons based on mg/kg are usually more appropriate; for systemic toxicity, dose comparisons based on mg/m^2 are usually more appropriate.

4 OVERALL CONCLUSIONS:

This is a new, controlled-release formulation of a drug (fluvoxamine maleate) that has previously been approved as an IR formulation and is currently marketed in the US as generic IR tablets for treatment of Obsessive-Compulsive Disorder (OCD).

The innovator (i.e., this sponsor) does not currently have an approved NDA for the IR (or any other) formulation; their current NDA 21-519 for the IR formulation is considered approvable, based in part on qualification issues for impurities/degradants. Other than the impurity/degradant issues, there were no other Pharmacology/Toxicology issues that would prevent the approval of NDA 21-519 for the IR tablet formulation of fluvoxamine maleate for treatment of OCD.

The non-clinical studies that would support the approval of the IR formulation for a chronic indication like OCD, with a maximum recommended human daily dose (MRHD) of 300 mg for adults and adolescents (but only 200 mg for children up to age 11 years), would also support the approval of the CR formulation for OCD and generalized social anxiety disorder in adults, up to the MRHD of 300 mg. Additionally, in the current submission, the Sponsor provided a local toxicity study of the CR formulation in dogs: doses of Luvox CR up to 450 mg/day (i.e., up to 11 times that MRHD of 300 mg/day on a mg/kg basis) did not result in gastrointestinal toxicity.

Qualification of impurities in the drug substance/product was an issue for the IR formulation (under NDA 21-519) and continues to be an issue for the CR formulation under the current NDA. Specifications for both the —— and —— have been set too high to be considered qualified by the studies that were used to support qualification of these impurities/degradants in the IR formulation (under NDA 21-519). Based on previously submitted studies, only an additional (adequate) Ames test would be required to qualify the —— to this higher specification (——, compared with —— under NDA 21-519). [It should be noted that the Sponsor was warned, in the AE letter for NDA 21-519 dated 11/16/06, that the Ames tests that had been submitted up to that that time (at concentrations up to —— would be considered adequate to qualify the specification of —— but not higher specifications.] No studies that would serve to qualify —— have been provided/referenced (under NDA 21-519 or under the current NDA). [It should also be noted that the Sponsor did not address any impurity/degradant issues under the current NDA (22-033).]

Finally, it appears that the specification for ——————— in the drug substance has been lowered from — to —, as the Sponsor had promised repeatedly to do under NDA 21-519; consequently, this impurity will not require qualification.

5 RECOMMENDATIONS:

From a Pharmacology/Toxicology perspective, this NDA (22-033) is APROVABLE, but cannot be approved until 2 impurities/degradants with specifications above the threshold for qualification in the drug product have been adequately qualified. The full compliment of qualification studies will be required for ———, which has a specification of — in the CR drug product under the current NDA (compared with a specification of — for the IR product under NDA 21-519 and a threshold for qualification of 0.2%), because no studies that could serve to qualify this impurity/degradant were submitted under either the current NDA or under NDA 21-519 for the IR formulation. Only an additional (adequate) Ames test would be required to qualify the —— to its higher specification in the CR drug product (—, compared with — for the IR product under NDA 21-519 and a threshold for qualification of 0.2%).

6 INFORMATION TO BE COMMUNICATED TO THE SPONSOR:

There are several impurities/degradants in the drug substance and/or CR drug product with specifications above the threshold(s) for qualification. Although you have not addressed this issue in your current NDA, similar issues were addressed under your NDA 21-519 for Luvox IR tablets. Based on the toxicology studies available for review under that NDA, we have determined that only the specifications for the —— (i.e., ——) and ——— (i.e., —) have been set too high in the CR product and cannot be considered to be qualified by nonclinical studies that have previously been submitted. Consequently, you will need to qualify these 2 impurities/degradants, as described below, prior to approval.

Only an additional (adequate) Ames test will be required to qualify the ——— to its higher specification in the CR drug product (—), compared with — for the IR product under NDA 21-519 and a threshold for qualification of 0.2%). It should be noted that you were informed, in the AE letter for NDA 21-519 dated 11/16/06, that the Ames tests that had been submitted up to that that time (with ——— at concentrations up to — would be considered adequate to qualify the specification of — proposed for the IR product, but not higher specifications.

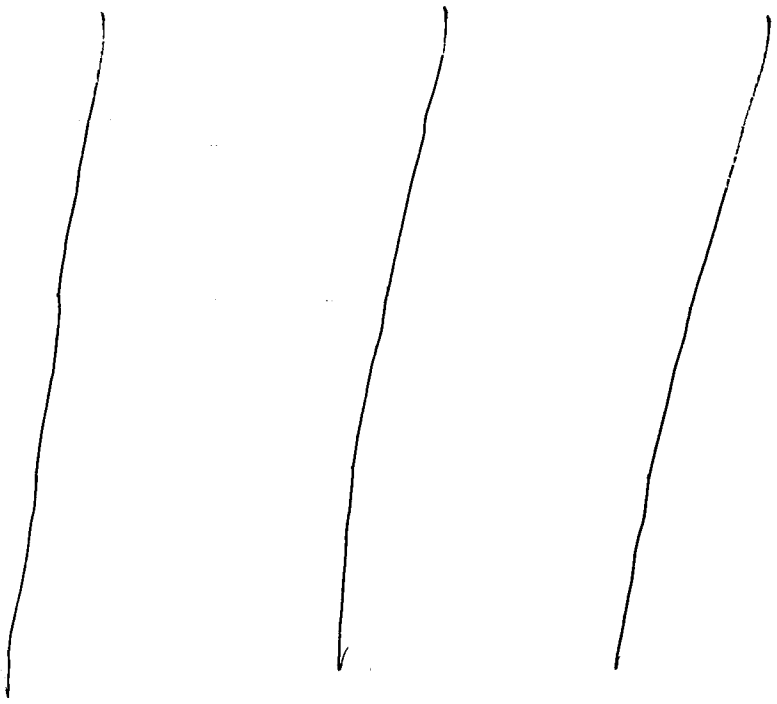
Apparently, no studies that could serve to qualify ——— have been provided (under NDA 21-519 or the current NDA). Qualification of ——— will require: 1) a general toxicology study in one species of 14-90 days duration, which should include microscopic, as well as macroscopic, evaluation of the standard battery of tissues; 2) *in*

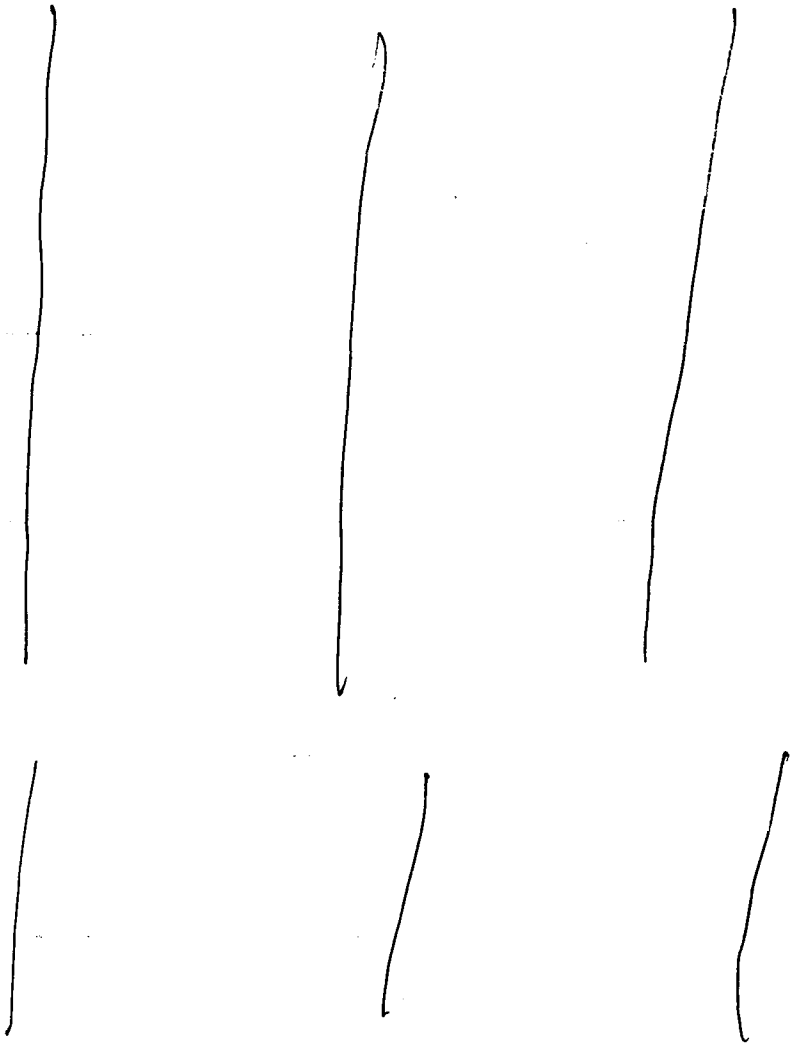
vitro genotoxicity studies (*in vitro* gene mutation in bacteria and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay [with colony sizing]); and 3) an embryofetal development study in one species.

7 LABELING:

[It should be noted that the Sponsor has used our suggested labeling for Impairment of Fertility and Pregnancy sections, as communicated in the AE letter for NDA 21-519 dated 2/9/04. This revised labeling includes the results from the Segment I (fertility and early embryonic development) and Segment II (embryo-fetal development) studies that were conducted as a Phase IV commitment to NDA 20-243, which was approved on 12/5/94, but subsequently withdrawn by Commissioner (9/3/2003).]

Revised labeling for Pharmacology/Toxicology sections (provided below) will be essentially the same as that provided to the Sponsor for the IR formulation under NDA 21-519 in our AE letter dated 2/9/04, but incorporating the comments that were communicated to the Sponsor for the IR formulation under NDA 21-519 in our AE letter dated 11/16/06.





8 SIGNATURES:

Linda H. Fossom, Ph.D., Pharmacologist *{see appended electronic signature page}*
Barry Rosloff, Ph.D., Supervisor *{see appended electronic signature page}*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Linda Fossom
2/22/2007 09:34:17 AM
PHARMACOLOGIST

Barry Rosloff
2/22/2007 03:27:36 PM
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