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RESEARCH**

*APPLICATION NUMBER:*

**21-992**

**PHARMACOLOGY REVIEW(S)**

## Memorandum

February 26, 2008

From: David Jacobson-Kram, Ph.D., DABT Office of New Drugs  
To: NDA file 21-992

Subject: Review of pharmacology/toxicology section of NDA 21-992, desvenlafaxine succinate.

I have reviewed the pharm/tox sections of the product insert and previous primary and secondary reviews of this NDA. I concur with the phase 4 agreement for a rat segment II study. I have no additional concerns or comments.

Cc

Colleen Locicero  
Robert Temple, MD  
Thomas Laughren, MD  
Barry Rosloff, Ph.D.  
Linda Fossom, Ph.D.

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/s/

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David Jacobson-Kram  
2/26/2008 01:46:42 PM  
PHARMACOLOGIST

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

Reviewer Name: Linda H. Fossom  
Division Name: Psychiatry Products  
HFD# 130  
Review Completion Date: 2/5/08.

NDA number: 21-992.

Serial number/stamp-date/type of submission: N-000, AZ / August 29, 2007 / Response to Approvable Letter / Major amendment, multi-disciplinary.

Information to sponsor: Yes (X) No ()

Sponsor: Wyeth Pharmaceuticals, Inc.

### Drug:

Trade name: (Proposed) Pristiq Extended-Release Tablets.

Generic name: desvenlafaxine succinate; *O*-desmethylvenlafaxine succinate.

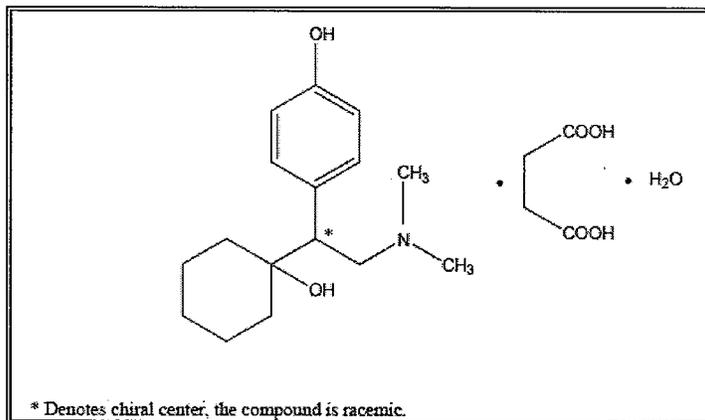
Code name: WY-45233 succinate monohydrate; WY-45233-1, ODV succinate·H<sub>2</sub>O.

Chemical name: 1-[(1*R,S*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol hydrogen butanedioate monohydrate. [Developed as an approximate 50/50 racemic mixture of R(-) and S(+)  
enantiomers.]

CAS registry number: 386750-22-7.

Molecular formula/molecular weight: C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>·H<sub>2</sub>O / 399.48 (as the succinate, monohydrate) / 263.38 (as the free base).

Structure:



**Drug class:** inhibitor of reuptake transporters for serotonin (SERT) and norepinephrine (NET); an SNRI.

**Indication:** Major Depressive Disorder (MDD) in adults.

**Clinical formulation:** 50-, 100- and 200-mg extended-release (oral) tablets.

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## 1 BACKGROUND:

Review of the original submission (received on 12/22/05) of this NDA determined that it was approvable (AE letter issued 1/22/07). There were no Pharmacology/Toxicology issues that would prevent approval at that time, except the Sponsor was asked to commit to conducting a standard embryo-fetal toxicity study in rats, because "their combined fertility and embryo-fetal toxicity study in rats did not adequately assess desvenlafaxine's potential for embryo-fetal toxicity, including teratogenicity, due to decreased number of fetuses available for analysis at the high dose of 300 mg/kg. This appeared to result from effects of desvenlafaxine on fertility and pre-implantation loss and would not be factors if dosing were only done during the period of organogenesis."

In the current submission, the Sponsor has provided a response to our request; this response was originally submitted on 4/4/07 (sequence no. 0028). [The Division responded to that submission by e-mail on 5/30/07, as follows: "We have received your submission dated 4/4/07, where you provide an argument, based on your analysis of the totality of the data in rats and rabbits, that the embryo-fetal toxicity study in rats that we requested as a postmarketing commitment would not provide useful information. We will accept this as a complete response to this issue. However, the adequacy of this argument will not be determined until it is reviewed in detail under your formal complete response to our approvable letter." ] The current review addresses the adequacy of Sponsor's response.

## 2 PHARMACOLOGY/TOXICOLOGY ISSUE ADDRESSED IN THIS SUBMISSION:

### 2.1 Action requested by the Agency in our 1/22/07 AE letter:

In our 1/22/07 AE letter, the following PT post-marketing commitment was communicated:

#### 4. Pharmacology/Toxicology

Your combined fertility and embryo-fetal toxicity study in rats did not adequately assess desvenlafaxine's potential for embryo-fetal toxicity, including teratogenicity, due to decreased number of fetuses available for analysis at the high dose of 300 mg/kg. This appeared to result from effects of desvenlafaxine on fertility and pre-implantation loss and would not be factors if dosing were only done during the period of organogenesis. Consequently, we ask that you commit to conducting a standard embryo-fetal toxicity study in rats; this may be done after drug approval.

## 2.2 Basis for this request:

[Excerpted from the Pharmacology review of the original submission, Overall Conclusions and Recommendations, pages 116-117.]

The potential for embryo-fetal toxicity, including teratogenesis, was not adequately addressed in rats. The high dose (300 mg/kg) in the combined fertility and embryo-fetal toxicity study was arguably adequately high based on decreased food consumption and decreased body weight gain during gestation. There was no evidence of teratogenicity at this dose (or lower doses), so the NOAEL for teratogenicity is presumed to be greater than or equal to the high dose of 300 mg/kg. However, the number of fetuses evaluated at the 300 mg/kg dose was only half that for other groups, largely due to the low pregnancy rate (50%, compared with 100% for controls), but also contributed to by increased pre-implantation loss (17%, compared with 4% for controls). Since both these causes of decreased numbers of assessable fetuses have impact prior to implantation, they could be avoided by conducting a standard embryo-fetal toxicity study, where dosing starts at GD 6 [this was mistakenly noted as PND 6 in the original review], after implantation. This would allow a more reliable assessment of teratogenic potential, uncomplicated by effects on fertility.

It is especially important to have an adequate rat study, because the apparent safety margin for teratogenicity, based on the high dose in the currently available study, is relatively high (15 times the MRHD), but not reliable. Additionally, the high dose used in the rabbit study was not clearly adequate: it did not produce maternal toxicity in that study, although it resulted in decreased body weight gain and was ~1/10<sup>th</sup> the dose (675 mg/kg [this was mistakenly noted as 1000 mg/kg in the original review]) that was lethal in a dose-range finding study.

## 2.3 The Sponsor's response:

### 2.3.1 Their general response:

The Sponsor has provided a response to our request for a standard embryo-fetal development study in rats (originally provided on 4/4/07 and cited in the current submission). In their cover letter they state that there is "...a significant body of evidence from the series of reproductive studies performed to conclude that desvenlafaxine does not present a teratogenic risk at any of the dosages evaluated in rats. Based on the totality of the available data, Wyeth believes that an additional teratogenicity study with dosing limited to the period of organogenesis is unlikely to provide any differing results beyond what have already been submitted in the NDA."

### 2.3.2 Their summary of previous rat studies:

The Sponsor goes on to say that "The data from the dose-ranging and pivotal combined fertility/developmental toxicity studies in rats, the perinatal/postnatal toxicity study in rats, and the developmental toxicity data from studies in rabbits, demonstrate a consistent pattern of effects. At maternally toxic dosages, effects on the embryo/fetus were limited to fetal mortality with no evidence of anomalies in fetal development in either rats or rabbits."

They cite a GLP compliant dose-ranging fertility and development toxicity study (RPT-45574) conducted in Sprague-Dawley rats (10/sex/group), where DVS was administered by oral gavage at 0, 75, 225, and 675 mg/kg to both sexes. They present data for females only (dosed from 2 weeks prior to cohabitation through GD 20). The HD of 675 mg/kg was lowered to 450 mg/kg on day 9 of dosing, due to body weight loss (decreased 6% compared with initial weight). They cite multiple clinical signs, CNS effects such as salivation and reciprocal forepaw treading at  $\geq 75$  mg/kg and increased motor activity at 225 mg/kg, as well as red and/or yellow fur discoloration, rough hair coat, cool-to-touch, red staining of pelage, decreased feces, and alopecia. They note that at  $\geq 75$  mg/kg body weight gains were decreased (8-21%) throughout gestation compared to controls; and this was accompanied by decreased food consumption. They note that fertility rate was decreased (30%) at 675/450 mg/kg compared with controls; but that there was no effect on liver litter size at any dosage. They note that fetal weights were decreased at 225 mg/kg (decreased 7%) and at 675/450 mg/kg (decreased 12%) compared with controls. They note that there were no compound related effects in fetal external morphologic development at any dosages (up to 675/450 mg/kg).

They also cite their GLP-compliant pivotal combined fertility/developmental toxicity study (RPT-46325) conducted in Sprague-Dawley rats (25/sex/group), where DVS was administered by oral gavage at 0, 30, 100, and 300 mg/kg to both sexes. They present data for females only (dosed from 2 weeks prior to cohabitation through GD 20). They cite clinical observations: salivation at  $\geq 30$  mg/kg; red pigment around the nose/mouth and reciprocal forepaw treading at  $\geq 100$  mg/kg; and yellow discoloration of the perineal pelage at 300 mg/kg. They cite decreased food consumption at 100 and 300 mg/kg during the first week of dosing, but no effects on body weight during the 2 weeks prior to cohabitation. They cite decreased absolute body weight gains (81% vs controls) during gestation (GD 0-20), as well as decreased gravid uterine weights (86% of controls), at 300 mg/kg; and decreased adjusted (for gravid uterine weight) body weight gains at 100 and 300 mg/kg (81% and 73% of controls, respectively). They also cite dose-related decreases (81-94% of controls) in food consumption at  $\geq 30$  mg/kg during preimplantation period (GD 0-5), with significantly decreased food consumption (88% of controls) throughout gestation at 300 mg/kg. They also note: disrupted estrous cycle irregularities at  $\geq 30$  mg/kg; increased time-to-mating at all doses; and decreased fertility rates at 100 and 300 mg/kg (83% and 50%, respectively). They state that at doses of 0, 30, 100, and 300 mg/kg, 22, 22, 19, and 11 litters were evaluated, respectively. They note increased preimplantation embryonic loss, decreased mean number of implantations per litter, and decreased live fetuses per litter at 300 mg/kg. They state that there were no

effects on fetal external, visceral, or skeletal development at any dosage, including the 138 fetuses from the 11 litters at 300 mg/kg.

They also cite their GLP-compliant pivotal perinatal/postnatal toxicity study (RPT-56483) conducted in mated Sprague-Dawley rats (25/ group), where DVS was administered by oral gavage at 0, 30, 100, and 300 mg/kg from GD 6 through PND 21. They note maternal toxicity at 300 mg/kg: salivation; transient weight loss from GD6-7 (but gain thereafter), with decreased food consumption ( $\downarrow$ 24%) from GD 6-9, and decreased overall body weight gain ( $\downarrow$ 18%). They note no effects on pregnancy rate, gestation index, pup sex ratio, number of live pups; but decreased pup weights ( $\downarrow$ 10-12.5%) at birth at 300 mg/kg. They note that in spite of the decreased birth weights (and decreased viability at PND4) at 300 mg/kg, there was no overt teratogenicity [based on gross examination only] evident in any of the 313 pups (from 24 litters) that were delivered at that dose. Additionally, they note that no obvious postmortem basis could be identified for the premature (by PND 4) deaths at this dose.

### 2.3.3 Their newly-performed power calculations:

They have performed power calculations as a measure of statistical sensitivity for detecting a difference among dosage groups, comparing the actual number of litters/dosage group in the pivotal combined fertility /developmental toxicity study in rats with a theoretical study with 16 litters/dosage group.

They have compared the actual sample sizes (22, 22, 19, and 11 litters for control, LD, MD, and HD groups, respectively) to a theoretical study (16 litters/group); they say 16 is the minimum number suggested in the ICH Harmonized Tripartite Guideline S5 (R2): Detection of toxicity to reproduction for medicinal products and toxicity to male fertility (Parent guideline dated 14 June 1993; Addendum dated 09 November 2000, incorporated in November 2005). [This is a misinterpretation of the guideline; see this Reviewer's comments, below.]

They conclude that "...the ability to detect a statistically significant increase in the incidence of a malformation is minimally different when the litter size/dosage group is set at 16 compared with the actual litter size/dosage in the pivotal combined fertility/developmental toxicity study in rats."

### 2.3.4 Their summary of previous rabbit studies:

They cite a GLP compliant dose-ranging fertility and development toxicity study (RPT-45134) conducted in mated rabbits (6/group), where DVS was administered by oral gavage at 0, 75, 225, and 675 mg/kg to both sexes; the HD group was terminated on GD 12/13 due to clinical signs, decreased body-weight gain, and minimal food consumption. The MD of 225 mg/kg was considered a maternally toxic dose, based on clinical signs

and decreased body weight gain and decreased food consumption; at this dose there was increased embryo/fetal loss, but no effect on fetal weights or external morphologic development [more detailed evaluation was not conducted].

They also cite their GLP compliant pivotal developmental toxicity study (RPT-46439) conducted in mated rabbits (20/sex/group), where DVS was administered by oral gavage at 0, 7.5, 25, and 75 mg/kg from GD 6-18. In contrast to the dose range finding study, they note lack of maternal toxicity (no effects on clinical observations, postmortem observations, abortion rates, maternal body weight, weight gain, or gravid uterine weight; and only a slight effect on food consumption at the HD of 75 mg/kg in this study. Additionally, they note lack of embryo/fetal toxicity: no effects on hysterectomy findings (embryo/fetal mortality, live fetuses per litter, total implantations, corpora lutea), fetal body weight, fetal gender distribution, fetal morphology, or placental appearance.

They conclude that "...there was no evidence of teratogenicity in rabbits at dosages that product minimal to moderate maternal toxicity, as well as embryo-fetal lethality;" and that this is analogous to what was seen in rats. [It should be noted that there was no maternal or fetal toxicity evident in the pivotal study.]

#### 2.3.5 Their conclusions:

They conclude "... that another teratogenicity study in rats would not provide useful information..." and propose not to conduct the requested study.

#### 2.3.6 They accepted our recommendations about labeling:

We recommended that the no-observed-effect level (NOEL) for teratogenicity in rats be lowered to 100 mg/kg/day ( ) in the teratogenicity section of the proposed product label. The dosage of 100 mg/kg/day in rats is 1 times the maximum recommended human dose ( mg/day) on a mg/m<sup>2</sup> basis. Wyeth concurred with this, "...since 100 mg/kg/day is also the NOAEL for the fetal weight changes observed in rats" [quoted from page 9 of their 9-page submission from March 2007].

#### 2.4 This Reviewer's comments on the Sponsor's arguments:

In general, I agree with the Sponsor's current summary of the reproductive toxicity studies that they provided in their original submission of this NDA.

As in my original review, I still do not think an adequate test of teratogenicity has been provided (as described in detail in my original review and summarized in the Section 1.2 Basis for this request and section 2 Overall Conclusions of this review): 1) the embryo-fetal segment of their combined fertility/embryo-fetal development study in rats was compromised by lack of adequate number of litters/fetuses available for evaluation at the

HD; this was due to decreased (50%) pregnancy rate, as well as increased pre-implantation losses, effects that should not be allowed to impact evaluation of teratogenicity; and 2) the embryo-fetal study in rabbits was arguably adequate, since there was no maternal toxicity (and no treatment-related signs) and no embryo-fetal toxicity in the pivotal study.

The Sponsor has not provided any new data and I do not think their power analysis adds useful information. Firstly, the Sponsor misinterpreted the ICH guideline when they chose a group size of 16 litters for their power analysis. The S5A ICH guideline which they cited (in its original form, from September 1994; and in subsequent revisions) says (in clarification note #13) that "For all but the rarest events (such as malformations, abortions, total litter loss), evaluation of between 16 to 20 litters for rodents and rabbits tends to provide a degree of consistency between studies." This does not mean that the assessment of 16 litters per dose group is adequate for evaluation of rare events like malformations, i.e., teratogenicity; in fact the high end of the suggested range (i.e., 20 litters) would be more appropriate; and 20 litters is considerably more than 16, especially when compared with the 11 litters that were actually evaluated. Additionally, we are really only concerned about the small sample size of the high dose group; a small sample size in a lower dose group would only be a concern if we were trying to determine a NOEL, based on findings at higher doses; whereas, there were no teratogenic findings at lower doses, so the high dose is the most important for determining whether there are any teratogenic findings.

More importantly, the guideline also says (in clarification note #23) that we rely on biological plausibility, not statistical significance, for interpretation of results and that "'Significance' tests (inferential statistics) can be used only as a support for the interpretation of results." If the small sample size in the HD group was clearly due to losses during the period of organogenesis (after GD 6), that toxicity would be acceptable for limiting dosing, and the causes of fetal losses could probably be adequately assessed. However, the evaluation of the HD of 300 mg/kg for teratogenicity was compromised both by loss of numbers of litters due to the 50% pregnancy rate and by early losses of embryo-fetuses due to early dosing prior to implantation in this study. The dose that resulted in early embryo loss (and decreased fertility) was exactly the dose that might have resulted in teratology if dosing was started later in gestation (after implantation), as in a standard embryo-fetal development study. It should also be noted that the pivotal perinatal/postnatal toxicity study (RPT-56483), where dosing was started at GD 6, would support the use of 300 mg/kg as a high dose in a standard embryo-fetal toxicity study. In that study, maternal toxicity was minimal (slightly decreased maternal weights, decreased 6% compared with controls at GD 21) at the HD of 300 mg/kg and toxicity in the offspring was limited to slightly (~10%) decreased birth weights and decreased PND 4 survival; there were no effects on the number of live pups or dead pups per litter at birth. However, the lack of prenatal deaths at the HD should not be interpreted as evidence that there was no teratogenicity, since malformations are rare and might not be expected to be reflected in the average litter size. Additionally, although the cause of the early post-natal deaths could not be determined, it is conceivable that they were due to teratogenic effects that were fatal early after birth.

### 3 OVERALL CONCLUSIONS:

The only Pharmacology/Toxicology issue that would have influenced approval of this NDA in the initial review cycle was our request for a post-marketing commitment from the Sponsor to conduct a standard embryo-fetal toxicity study in rats, because their combined fertility/embryo-fetal development study was considered to inadequately assess desvenlafaxine's potential for teratogenicity (as communicated in our 1/22/07 AE letter).

In their current submission, the Sponsor proposes not to conduct the requested study. They have not provided any new studies; all the studies they reference were reviewed under the original submission. They contend that there is "...a significant body of evidence from the series of reproductive studies performed to conclude that desvenlafaxine does not present a teratogenic risk at any of the dosages evaluated in rats. Based on the totality of the available data, Wyeth believes that an additional teratogenicity study with dosing limited to the period of organogenesis is unlikely to provide any differing results beyond what have already been submitted in the NDA." Although they have not provided any new data, they have conducted a power analysis, which they say demonstrates that "...the ability to detect a statistically significant increase in the incidence of a malformation is minimally different when the litter size/dosage group is set at 16 compared with the actual litter size/dosage in the pivotal combined fertility/developmental toxicity study in rats." However, their choice of 16 litters per group was based on a misreading/misinterpretation of the ICH S5 guideline and 20 litters per group would have been a more appropriate group size for comparison; their too-small test group size of 16 would underestimate the value of conducting another study, with a larger and more appropriate number of litters and fetuses available for evaluation. More importantly, we do not require statistical significance for evaluation of rare events like teratogenicity, but base our evaluation on biological plausibility (as also stated in the ICH S5 guideline).

The basis for our previous request remains the same; this Reviewer concluded that the potential for embryo-fetal toxicity, including teratogenesis, was not adequately addressed in the combined fertility/embryo-fetal developmental study in rats, because the number of litters available for evaluation at the HD of 300 mg/kg was only 11 (~half the number in the lower dose groups and ~half the number recommended for assessment in the ICH guideline). Since both causes of decreased numbers of assessable litters/fetuses, namely 50% decrease in pregnancy rate and increased pre-implantation losses, occurred (and had impact) prior to implantation, they could be avoided by conducting a standard embryo-fetal toxicity study, where dosing starts at GD 6, after implantation. This would allow a more reliable assessment of teratogenic potential, uncompromised by effects on fertility.

It is especially important to have an adequate rat study, because the apparent safety margin for teratogenicity, based on the high dose of 300 mg/kg in the currently available study, although relatively high (15 times the MRHD of 200 mg/day), is not reliable. Additionally, the high dose used in the pivotal rabbit study (75 mg/kg, which is 7 times the MRHD of 200 mg/day) was not clearly adequate: it did not produce maternal toxicity

(or any drug-related signs) or any embryo-fetal toxicity in that study, although that same dose resulted in decreased body weight gain and was  $\sim 1/10^{\text{th}}$  the dose (675 mg/kg) that was lethal in a dose-range finding study. The original decision to ask for another embryo-fetal toxicity study in the rat, rather than rabbit, was based on the more complete dosing information available for rats, which would make adequate dose-selection simpler, and the more complete reproductive toxicity data available for rats, which suggested that the combined embryo-fetal study was not adequate.

Nonetheless, the decision to require an additional embryo-fetal toxicity study was not a simple one. Based on the currently available combined fertility/embryo-fetal toxicity study in rats, this Reviewer feels that teratogenicity has only been adequately tested up to 100 mg/kg and that teratogenicity was not evident at that dose. Other reproductive toxicities also have NOELs of 100 mg/kg (or less); however, those NOELs are based on toxicities that were actually observed at higher doses: decreased fertility (NOEL = 30 mg/kg); increased pre-implantation losses, slightly decreased embryo-fetal weights (NOEL = 100 mg/kg); and decreased birth weights and decreased PND 4 survival (NOEL = 100 mg/kg). Teratogenicity is such an important reproductive end point that it should also be very well tested; citing a NOEL of 100 mg/kg without a relevant limiting toxicity at that dose or the higher dose of 300 mg/kg does not seem adequate. If the Sponsor conducts another embryo-fetal toxicity study, the results are likely to either: 1) raise the NOEL for teratogenicity 3-fold to 300 mg/kg (to 15 times the MRHD of 200 mg) or 2) maintain the NOEL at 100 mg/kg (or possibly lower it) based on actual teratogenic findings at 300 mg/kg (or lower doses); whatever the results, the information would be important to provide to patients and clinicians. However, we are allowing this to be addressed as a post-marketing commitment, because of the other reproductive toxicity data discussed above.

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#### **4 RECOMMENDATIONS:**

Our recommendations are the same as those based on the original review (and communicated in the 1/22/07 AE letter). From a Pharmacology/Toxicology perspective, this NDA may be approved if the Sponsor commits to conducting a standard embryo-fetal toxicity study in rats; this study may be conducted after approval.

The Sponsor has agreed to our previous request that revised the labeling to reflect a lower NOEL for teratogenicity of 100 mg/kg, the highest dose for which there were adequate numbers of litters/fetuses for analysis; 100 mg/kg is  $\frac{1}{10}$  times the MRHD on a mg/m<sup>2</sup> basis.

#### **5 INFORMATION TO BE COMMUNICATED TO THE SPONSOR:**

##### **PHARMACOLOGY/TOXICOLOGY POST-MARKETING COMMITMENTS:**

We have considered your proposal to not conduct a standard embryo-fetal toxicity study in rats, as we had requested in our AE letter dated 1/22/07. However, we do not find your arguments compelling. Consequently, we again ask that you commit to conducting a standard embryo-fetal toxicity study in rats; this may be done after drug approval.

#### **6 LABELING:**

Changes to labeling as previously proposed by the Reviewer have been accepted by the Sponsor.

#### **7 SIGNATURES**

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

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



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

## PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-992  
SERIAL NUMBER: N-000  
DATE RECEIVED BY CENTER: 12/22/05  
PRODUCT: Desvenlafaxine succinate (extended-release tablets)  
INTENDED CLINICAL POPULATION: Adults with major depressive disorder.  
SPONSOR: Wyeth Pharmaceuticals, Inc.  
DOCUMENTS REVIEWED: electronic submission (e-CTD)  
REVIEW DIVISION: Division of Psychiatry Drug Products (HFD-130)  
PHARM/TOX REVIEWER: Linda H. Fossom, Ph.D.  
PHARM/TOX SUPERVISOR: Barry Rosloff, Ph.D.  
DIVISION DIRECTOR: Thomas Laughren, M.D.  
PROJECT MANAGER: Renmeet Grewal, Pharm. D.

Date of review submission to Division File System (DFS): 1/22/07.

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## *EXECUTIVE SUMMARY*

### **I. Recommendations**

- A. Recommendation on approvability: From a Pharmacology/Toxicology perspective, this NDA may be APPROVED.
- B. Recommendation for nonclinical studies: The potential for embryo-fetal toxicity, including teratogenesis, was not adequately addressed in rats. The Sponsor should be asked to commit to conducting a standard embryo-fetal toxicity study in rats; this may be done after approval.
- C. Recommendations on labeling: Labeling proposed by the Reviewer has been included in the relevant sections of this review and has also been provided to the Review Team to form a part of the Agency's proposed labeling, which will be communicated to the Sponsor. Pivotal changes are: 1) lowering the no effect level for teratogenicity in rats, because the high dose was not adequate due to >50% fetal loss; and 2) the decision that the in vivo rat chromosomal aberration assay is negative, not positive as it was previously considered when reviewed in support of NDAs for venlafaxine (and included in the Effexor IR and XR labeling).

### **II. Summary of nonclinical findings**

- A. Brief overview of nonclinical findings: Desvenlafaxine was adequately assessed in non-clinical studies to support its approval for adults with major depressive disorder. In general toxicity studies in rats (up to 6 month duration) and dogs (up to 9 month duration), desvenlafaxine appeared to be devoid of toxicity up to doses that caused convulsions and/or death. Desvenlafaxine was not genotoxic, in the standard genotoxicity battery. Desvenlafaxine was not carcinogenic in rats or mice, in standard 2-year studies.

Desvenlafaxine's reproductive toxicity appeared to be limited to decreased fertility in rats and decreased fetal weights in rats. There was no evidence of teratogenicity in either rats or rabbits; however, the adequacy of maternal dosing was questionable in both species. Of particular concern is that teratogenicity was inadequately assessed in the combined fertility and embryo-fetal development study in rats, because the sensitivity at the high dose, where effects would most likely be seen, was compromised due to loss of half the fetuses because of the decreased (50%) fertility and increased pre-implantation loss in that group. These pre-implantation issues would be avoided in a standard embryo-fetal study, where dosing of pregnant rats begins after implantation.

- B. Pharmacologic activity: Desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI), with no MAOI activity, and no apparent affinity ( $>10\mu\text{M}$ ) for muscarinic cholinergic, H1 histaminergic, alpha 1- adrenergic receptors or ion channels including calcium, potassium and sodium.
- C. Nonclinical safety issues relevant to clinical use: Desvenlafaxine has potential for deleterious effects on fertility and embryo-fetal development: 1) adversely affected fertility in rats; 2) decreased fetal weights in rats, but did not appear to be teratogenic; 3) crossed the placental barrier in pregnant rats; and 4) was excreted in the milk of lactating rats.

**Appears This Way  
On Original**

## 2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

### 2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: NDA 21-992.

Review number: 1.

Sequence number/date/type of submission: N-000, original submission; stamp-dated 12/22/05.

Information to sponsor: Yes.

Sponsor and/or agent: Wyeth Pharmaceuticals, Inc.

Manufacturer for drug substance: \_\_\_\_\_

Reviewer name: Linda H. Fossom, Ph.D.

Division name: Psychiatry Products.

HFD #130.

Review completion date: 1/19/07.

#### Drug:

Trade name: (Proposed) Pristiq Extended-Release Tablets.

Generic name: desvenlafaxine succinate; *O*-desmethylvenlafaxine succinate.

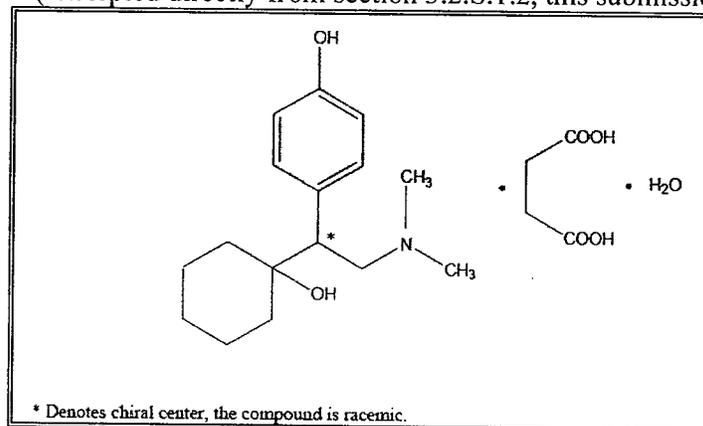
Code name: WY-45233 succinate monohydrate; WY-45233-1, ODV succinate·H<sub>2</sub>O.

Chemical name: 1-[(1*R,S*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl] cyclohexanol hydrogen butanedioate monohydrate. [Developed as an approximate 50/50 racemic mixture of R(-) and S(+) enantiomers.]

CAS registry number: 386750-22-7.

Molecular formula/molecular weight: C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>·C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>·H<sub>2</sub>O / 399.48 (as the succinate, monohydrate) / 263.38 (as the free base).

Structure (excerpted directly from section 3.2.S.1.2, this submission):



Impurities: For the drug substance, the specification for the \_\_\_\_\_ identified impurity, namely venlafaxine, has been set at \_\_\_\_\_, specification for any unspecified impurity has been set at \_\_\_\_\_ and the specification for total organic impurities has been set at \_\_\_\_\_. For the drug product, the specification for each

unspecified degradant has been set at         . None of these specifications for impurities/degradants is a cause for concern from a Pharmacology/Toxicology perspective; none would require lowering or necessitate qualification.

**Relevant INDs/NDAs/DMFs:** Desvenlafaxine is under several active INDs: IND 64,552 (for treatment of depression)         

         NDA           
(for treatment of          associated with menopause), sponsored by Wyeth.

Venlafaxine, which could be considered a pro-drug for desvenlafaxine in humans, has been approved under 2 NDAs (as the HCl salt): as Effexor IR tablets (NDA 20-151; approved 12/28/93) for treatment of Depression; and as Effexor XR capsules (NDA 20-699; approved 10/20/97) for Major Depressive Disorder, Generalized Anxiety Disorder, and Social Anxiety Disorder (Social Phobia); both NDAs were sponsored and marketed by Wyeth.

The Sponsor has obtained authorization from          for the Agency to refer to DMF Type II, No.          regarding the drug substance (desvenlafaxine succinate) for the current submission.

**Drug class:** inhibitor of reuptake transporters for serotonin (SERT) and norepinephrine (NET); an SNRI.

**Intended clinical population:** adults with Major Depressive Disorder.

**Clinical formulation:** 100- and 200-mg extended-release tablets;          formulation, with hypromellose (hydroxypropyl methylcellulose)         . According to the ECT Summary, the once-daily recommended dose is 100 mg, with no titration necessary. According to the Nonclinical Overview, individual patients         

[According to the Nonclinical Overview, throughout this NDA document, doses and concentrations refer to the desvenlafaxine free base.]

**Route of administration:** oral.

**Disclaimer:** Tabular and graphical information are constructed by the reviewer unless cited otherwise.

**Studies reviewed within this submission:** all non-clinical studies that are considered necessary for approval of a drug to be administered chronically to adults: pharmacology/pharmacodynamic studies to support labeling claims; chronic general toxicity studies; genotoxicity standard battery, and supporting studies; carcinogenicity; reproductive and developmental studies.

## 2.6.2 PHARMACOLOGY

### 2.6.2.1 Brief summary

In humans, desvenlafaxine is the major active metabolite of venlafaxine, which is marketed as Effexor for major depressive disorder. Desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI), with no MAOI activity, and no apparent affinity ( $>10\mu\text{M}$ ) for muscarinic cholinergic, H1 histaminergic, alpha1-adrenergic receptors or ion channels including calcium, potassium and sodium.

[The Sponsor's tabulated summary for Pharmacology is provided below.]

### 2.6.2.2 Primary pharmacodynamics

[The Sponsor's tabulated summary for primary and secondary pharmacodynamics is provided at the end of this section.]

Mechanism of action: Desvenlafaxine is thought to exert its antidepressant action by potentiating serotonergic and noradrenergic activity at synapses in the central nervous system by inhibiting the reuptake of these neurotransmitters. Desvenlafaxine increased 5-HT and NE in expected brain areas in rats. Desvenlafaxine was active in several animal models predictive of antidepressant activity: reversed of reserpine-induced hypothermia in mice, decreased immobility time in the mouse tail suspension test, and reduced aggressive behavior of resident rats in the resident-intruder test.

Drug activity related to proposed indication: Both enantiomers of desvenlafaxine inhibit SERT with much higher affinity ( $\sim 100\text{ nM}$ ) than NET ( $5\text{-}10\text{ }\mu\text{M}$ ). Based on the NovaScreen in vitro assays (see report RPT-43823), the S(+) enantiomer (WAY-120197) had slightly ( $\sim 2$ -fold) higher affinity for hSERT than did the R(-) enantiomer (WAY-120198);  $K_i$  for the S(+) enantiomer was  $48\text{ nM}$ , compared with  $95\text{ nM}$  for the R(-) enantiomer. Conversely, the R(-) enantiomer had ( $\sim 4$ -fold) higher affinity at hNET than did the S(+) enantiomer;  $K_i$  for the R(-) enantiomer was  $0.855\text{ }\mu\text{M}$ , compared with  $3.55\text{ }\mu\text{M}$  for the S(+) enantiomer. The affinity of each enantiomer was much higher for than for hNET: 74-fold for the S(+) and 9-fold for the R(-).

### 2.6.2.3 Secondary pharmacodynamics

Based on the NovaScreen (see report RPT-43823) in vitro screening assay of 96 targets (including receptors, transporters, enzymes, and channels, tested at  $10\text{ nM}$ ,  $100\text{ nM}$ , and  $10\text{ }\mu\text{M}$ ), desvenlafaxine at  $10\text{ }\mu\text{M}$  showed significant activity (i.e., inhibition of binding by  $\geq 50\%$ ) at only SERT and NET; inhibition of binding to DAT was only 30% at  $10\text{ }\mu\text{M}$  (and apparently not further investigated). The sites for which desvenlafaxine appeared to lack affinity also included: muscarinic cholinergic, H1 histaminergic, alpha1-adrenergic receptors or ion channels including calcium, potassium and sodium.

#### 2.6.2.4 Safety pharmacology

Neurological effects (in rats): Single oral doses of desvenlafaxine at 0, 100, 500, or 1000 mg/kg to male Sprague-Dawley rats did not produce significant effects on CNS: no deaths, no clinical observations, no effects on sensory, motor, or behavioral function as assessed in the Functional Observational Battery; mean rectal body temperature was slightly decreased (~1 degree C) at 500 and 1000 mg/kg, but were within published values for control rats (see report RPT-45379).

Desvenlafaxine at intraperitoneal (ip) doses up to 30 mg/kg (in 0.25% Tween 80) was not anticonvulsant or proconvulsant in the minimal/maximal electroshock test (transcorneal shock) in male (CF-1 and/or CD-1) mice; at 100 mg/kg ip, all mice showed clonic convulsions and died within 10 min; imipramine (at 100 mg/kg ip) also produced convulsions, but rarely death. Desvenlafaxine at up to 30 mg/kg ip was not sedative; it did not alter hexobarbital sleep time in rats like diazepam (at 30 mg/kg ip) did (see report GTR-16323).

Cardiovascular effects:

##### **In vitro studies:**

- hERG assay: desvenlafaxine (ODV) or NODV at 10 uM did not alter hERG channel activity (see reports RPT-55402 and RPT-56898); higher concentrations of ODV inhibited hERG, with 23% inhibition at 65 uM and 42% inhibition at 195 uM, with IC50 calculated as >195 uM (i.e., >51.3µg/ml) (see report RPT-57604). These affinities for the hERG channel do not signal special concern for QT-prolongation.
- Purkinje fiber assay (isolated from dog): desvenlafaxine at 10 uM did not decrease peak upstroke velocity (indirect measure of Na channel blockade) or alter APDs (indirect measures of K and/or Ca channel blockade) (see report RPT-15331).

##### **In vivo dog studies:**

- Escalating-dose iv study in anesthetized, ventilated, open-chest dogs: desvenlafaxine (as the butenedioate salt) at cumulative iv dosages of 1, 2.5, 5, 7.5, and 10 mg/ iv doses up to 10 mg/kg in pentobarb anesthetized (ventilated, open-chest) dogs did not alter atrial or ventricular effective refractory periods or stimulus impulse conduction through atrium or ventricle, but mean arterial blood pressure was slightly decreased after 7.5 and 10 mg/kg (↓12-18% compared with pre-dose values (see report GTR-16320).
- Single oral dose study in conscious dogs: single po (gavage) doses of 100 and 300 mg/kg (but not 30 mg/kg) increased MABP (95-110 mm Hg above baseline) and HR (65-101 bpm above baseline), but with no evidence of ventricular arrhythmia, QT prolongation or abnormal cardiac conduction times; the 2 dogs at 300 mg/kg

collapsed ~2 hr after dosing, with clonic convulsions and were euthanized (see report GTR-45496).

- Single oral dose study in dogs: desvenlafaxine at 100 mg/kg by gavage or SR tablets (in capsules) increased MABP and HR, with differences in peak and duration of effects that seem to correlate with PK differences with the 2 formulations; there was no evidence of ventricular arrhythmia, QTc prolongation, or abnormal cardiac conduction times (see report RPT-45497).
- Repeated-dose studies in dogs and rats: there were no effects on EKG or macro- or microscopic changes in hearts of dogs (see reports GRT-17194, RPT-49456, RPT-57597, RPT-59762) and no changes in hearts of rats (see reports GRT-17272, RPT-49309).

Pulmonary effects (in rats): Single oral gavage doses of DVS at 0, 100, 500, or 1000 mg/kg to male Sprague-Dawley rats resulted in slight, dose-related increases in respiratory rate (<25%) and corresponding decreases in minute volume, as early as 45 min after dosing and persisting for up to 4 hr at the high dose; without changes in tidal volume (see report RPT-45370).

Single iv doses of desvenlafaxine (as fumarate salt) up to 10 mg/kg to Guinea pigs did not alter pulmonary function or heart rate, but produced dose-related increases in MABP at > 1 mg/kg (see report GTR-15786).

Renal effects (in rats): only small effects on pH and osmolality of 30 mg/kg (see report GTR-15798).

Gastrointestinal effects (in rats): no effect of 30 mg/kg (see report RPT-15786).

Abuse liability: apparently not done (based on lack of findings for search of Nonclinical Overview for “abuse” and liability).

Other: no effect of 30 mg/kg on glucose levels in fed or fasted rats (see report GTR-15949).

#### **2.6.2.5 Pharmacodynamic drug interactions**

As a selective inhibitor of SERT and NET, with no apparent binding activities at other receptor sites, desvenlafaxine would be expected to have additive effects with other inhibitors of SERT and/or NET, such as SSRIs or SNRIs. Desvenlafaxine could also interact with drugs that act at serotonergic or noradrenergic receptors.

#### **2.6.2.6 Sponsor’s proposed labeling for pharmacodynamics:**

### **CLINICAL PHARMACOLOGY**

#### **Pharmacodynamics**



**2.6.2.7 Approved labeling for venlafaxine (Effexor):**

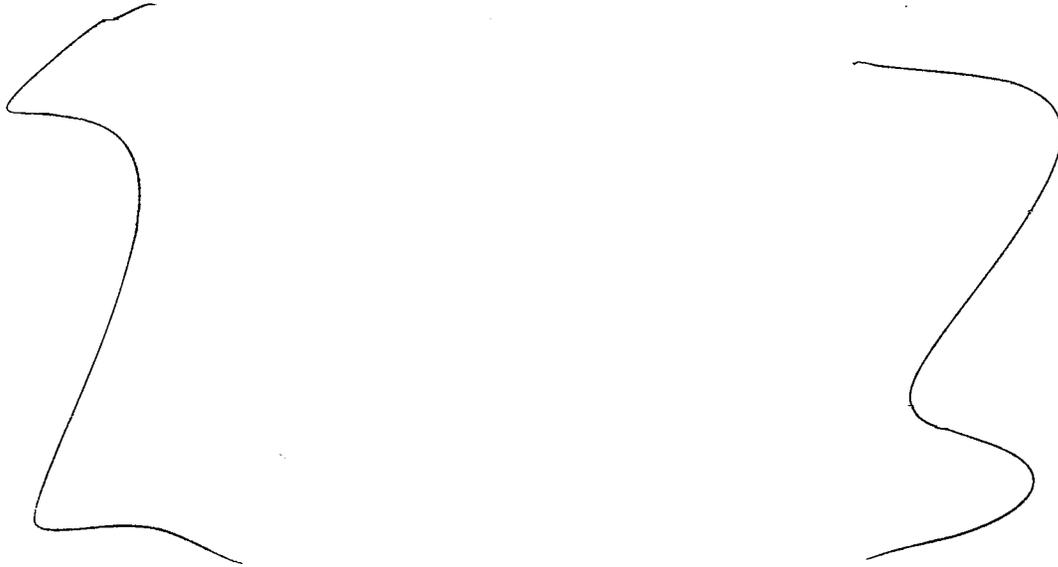
Effexor IR labeling:

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or  $\alpha$ -1 adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Effexor XR labeling:

The mechanism of the antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic cholinergic, H<sub>1</sub>-histaminergic, or  $\alpha$  1 -adrenergic receptors in vitro. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

**2.6.2.8 Labeling for pharmacodynamics proposed by this Reviewer:**



**2.6.3 PHARMACOLOGY TABULATED SUMMARY**

The Sponsor provided (42 pages of) tabulated summaries for Pharmacology, including primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology (Table 1.0, section 2.6 Nonclinical Written and Tabulated Summaries, pp 2-9); Safety Pharmacology, including CNS, respiratory, cardiovascular, renal/urinary, gastrointestinal, and hormonal/glucose metabolism (Table 2.1, section 2.6 Nonclinical Written and Tabulated Summaries, pp 10-42); and Safety Pharmacology of N,O-didesmethylvenlafaxine, limited to a hERG assay (Table 2.2, section 2.6 Nonclinical Written and Tabulated Summaries, p 43).

Below, I have excerpted (from the Sponsor's Table 1.0: Pharmacology: Overview from 2.6 Nonclinical Written and Tabulated Summaries, 2.6.3 Pharmacology Tabulated Summary) the information on studies that might be used to support pharmacology/pharmacodynamic labeling claims (because they were not reviewed here).

2   Page(s) Withheld

  X   Trade Secret / Confidential

       Draft Labeling

       Deliberative Process

Withheld Track Number: Pharm/Tox-   1

## 2.6.4 PHARMACOKINETICS/TOXICOKINETICS

[The review of the pharmacokinetics/toxicokinetics in this section was conducted by Amy Avila, Ph.D, Pharmacologist.]

### 2.6.4.1 Brief summary

Pharmacokinetic studies of desvenlafaxine as either the free base or succinate salt form (DVS-233) were conducted in mice, rats, dogs, and humans. Desvenlafaxine was rapidly absorbed in all species ( $\sim t_{1/2}$  4 hr), extensively and rapidly distributed to tissues, and rapidly eliminated. Exposure to desvenlafaxine (both AUC and  $C_{max}$ ) increased greater than dose proportionally for both rats and dogs. There was no accumulation of desvenlafaxine after 14-day repeat exposure in both rats and dogs. Metabolism was similar across all species including humans, and *in vitro* metabolism was reflective of *in vivo* metabolism. The predominant pathway of desvenlafaxine metabolism was glucuronidation via various UDPGT isoforms to form the O-glucuronide metabolite. All major and minor metabolites formed in humans were also formed in either rats or dogs. Oxidative metabolism to form N-desmethyl desvenlafaxine (NODV) was a minor pathway and was mediated mainly by CPY3A4. Urinary excretion was the major route of elimination with fecal excretion only a minor component. Protein binding was relatively low in all species (<40% in mice, rats dogs, and rabbits) and  $\sim 29\%$  in human plasma. Desvenlafaxine was a weak inhibitor of CYP2D6, but did not show any inhibition or induction of any other CYP isoforms tested. Desvenlafaxine was also not a substrate of the P-gp transporter nor did it inhibit the P-gp-efflux transporter.

[Note added by L. Fossom: In people administered desvenlafaxine at the maximum recommended human dose (MRHD) of 200 mg, the systemic exposure based on AUC was approximately 10  $\mu\text{g}\cdot\text{hr}/\text{ml}$  and based on  $C_{max}$  was approximately 0.5  $\mu\text{g}/\text{ml}$  (extrapolated from pooled human data from single and repeated dosing with DVS SR in healthy subjects who participated in Phase 1 studies, normalized to 100 mg, in Table 9, page 22 of Dr. Kofi Kumi's Clinical Pharmacology and Biopharmaceutics Review for this NDA, dated 10/26/06).]

### 2.6.4.2 Methods of Analysis

The methods of analysis were not reviewed in detail; however relevant information was included in each individual section when appropriate. Briefly, desvenlafaxine was

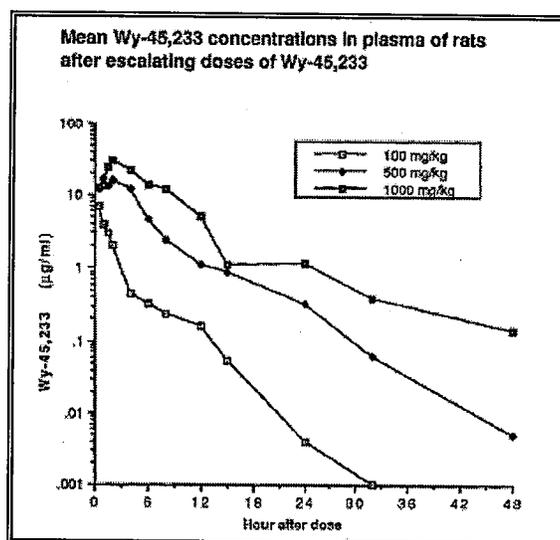
quantified by HPLC with UV detection and in some instances conjugated and total desvenlafaxine were quantified by LC/MS/MS.

### 2.6.4.3 Absorption

#### Single Dose Studies:

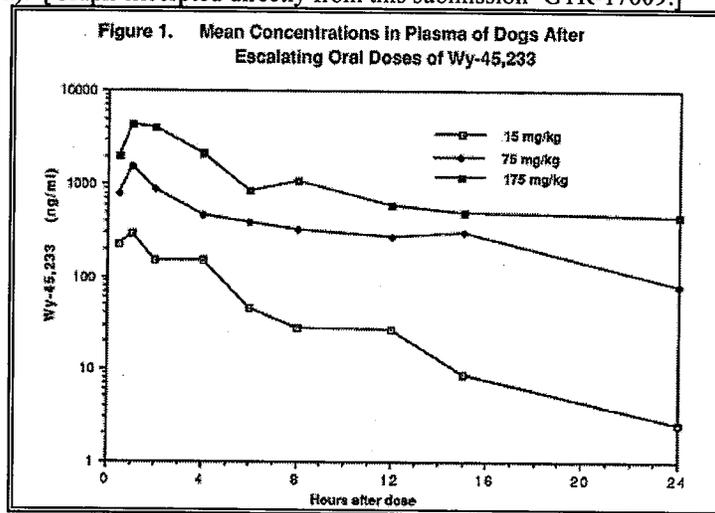
Single dose studies of desvenlafaxine as the free base were conducted in male S-D rats at doses of 100, 500 and 1000 mg/kg administered by oral gavage (GTR-15626, GTR-17423). Plasma samples were collected up to 48 hr after dosing. Absorption was rapid with  $t_{max}$  values between 0.5 and 2 hr.  $C_{max}$  and  $AUC_{0-\infty}$  values increased greater than dose proportional. Clearance slowed with increasing dose (132, 88, 78 ml/min/kg at doses of 100, 500 and 1000 mg/kg). There was a corresponding increase in  $t_{1/2}$  with increasing dose as well (3.0, 4.5 and 6.4 hr at 100, 500 and 1000 mg/kg). These data suggest the PK profile of desvenlafaxine in male rats is dose dependent.

**Figure 1.** Plasma curves for desvenlafaxine (Wy-45,233) levels in male S-D rats. Values are mean  $\pm$  SD (n=5/time point). [Graph excerpted directly from this submission- GTR-17423.]



Single dose studies of desvenlafaxine free base administered by oral capsule were conducted in male dogs at doses of 15, 75 and 175 mg/kg and plasma samples were collected up to 24 hr after dosing (GTR-15626, GTR-17609). Absorption was rapid with  $t_{max}$  values between 0.75 and 1.8 hr.  $C_{max}$  and  $AUC_{0-24}$  values increased greater than dose proportional, similar to rats.  $t_{1/2}$ , clearance and  $AUC_{0-\infty}$  could not be determined in study GTR-17609, however a  $t_{1/2}$  of 1.6 hr was calculated in study GTR-15626 for a 15 mg/kg single dose. The PK of desvenlafaxine is also dose dependent, similarly to rats, and there appears to be a reduction in clearance with increasing dose. Study GTR-15626 also measured the amount of glucuronide conjugated desvenlafaxine after a 15 mg/kg dose administered by oral gavage to dogs. The results demonstrated that desvenlafaxine is extensively conjugated in dogs with an AUC of 33.55  $\mu\text{g}\cdot\text{h}/\text{ml}$  for conjugated desvenlafaxine compared to an AUC of 1.08  $\mu\text{g}\cdot\text{h}/\text{ml}$  for desvenlafaxine after a 15 mg/kg oral dose.

**Figure 2.** Plasma curves for desvenlafaxine (Wy-45,233) levels in male Beagle dogs. Values are mean  $\pm$  SD (n=6/time point). [Graph excerpted directly from this submission- GTR-17609.]



A bioavailability PK study was conducted in male dogs comparing a single IV (25 mg) dose to 3 separate oral doses (solution, IR capsule, and MR tablet) each 75 mg/kg (RPT-43719). The oral bioavailability was similar between the oral solution, IR capsule and MR tablet (37, 42, 31% respectively). As expected, the MR tablet displayed a lower  $C_{max}$  and longer  $t_{max}$  than the other 2 oral doses. The total exposure, AUC, was similar between the oral solution, IR capsules and MR tablet doses (842, 921 and 707 ng.h/ml respectively). The total clearance and steady-state volume of distribution were calculated from the IV dose to be 2.65 L/h/kg and 3.36 L/kg respectively.

PK studies of DSV SR in humans revealed rapid absorption, however a much higher bioavailability (~80%), linear pharmacokinetics over a dose range of 100 to 600 mg, a longer  $t_{max}$  (6 to 10 hr after a single oral dose), and a mean  $t_{1/2}$  of 9-12 hr (CSR-54267).

A comparative PK study was conducted in female rats administered 100 mg/kg oral gavage doses from two batches of DSV-233 (succinate salt form), batch RB1636 and RB2691 (RPT-55852). This study was conducted in order to determine if there were any differences in exposure between the two batches, since a decrease in fertility was observed in a rat fertility study using batch RB1636 but not in a subsequent investigative rat fertility study with batch RB2691. The  $t_{max}$  was 0.5 hr for both batches and there was no significant difference between  $C_{max}$  and AUC, indicating that the differences seen in the two fertility studies were not attributed to differences in drug batch. This study also revealed that female rats have a higher exposure (~1.5-2-fold) than male rats at the 100 mg/kg dose.

3 separate single dose comparative PK studies were conducted in both male and female dogs to evaluate differences between salt forms, dosing vehicles, formulations, and exposures (RPT-45320, RPT-45321, RPT-45322, RPT-45323). There were no significant differences in exposure (AUC) between oral doses of either DSV-233 or



**Table 2.** Comparison of R(-) and S(+) enantiomers in rats, dogs, and humans. [Excerpted directly from Table 10.0-2 of the Pharmacokinetics Written Summary of the Sponsor's submission].

Species	Number	Sex	Dosage (mg/kg/day)	R(-)-Desvenlafaxine			S(+)-Desvenlafaxine		
				C <sub>max</sub> (µg/mL)	t <sub>1/2</sub> (h)	AUC (µg·h/mL)	C <sub>max</sub> (µg/mL)	t <sub>1/2</sub> (h)	AUC (µg·h/mL)
Rats	5 <sup>a</sup>	M	500 for 14 days	5.16 ± 1.99	3.5 <sup>b</sup>	16.3 <sup>bc</sup>	12.3 ± 2.7	3.9 <sup>b</sup>	68.5 <sup>de</sup>
Dogs	4	M	175 for 14 days	3.27 ± 2.61	1.4 ± 0.5	7.60 ± 5.16 <sup>d</sup>	1.41 ± 1.28	3.6 ± 4.5	2.98 ± 1.98 <sup>d</sup>
Humans <sup>e</sup>	14	M/F	100 mg for 1 day	0.077 ± 0.02	10.3 ± 1.9	1.92 ± 0.62	0.083 ± 0.022	10.2 ± 2.0	2.06 ± 0.64

Note: Results from 4.2.2.2: GTR-18702; GTR-18795 (rats and dogs, respectively).

a. N = 5 rats per time point.  
b. Calculated from the mean concentration-versus-time profile.  
c. AUC<sub>0-24</sub> hour value.  
d. AUC<sub>0-6</sub> hour value.  
e. Results from 5.3.1.1: CSR-54267.

AUC = Area under the concentration-versus-time curve; C<sub>max</sub> = Peak concentration; GTR = General Technical Report; N = Number of animals; SD = Standard deviation; t<sub>1/2</sub> = Apparent terminal half-life.

#### 2.6.4.4 Distribution

Organ and tissue distribution of [<sup>14</sup>C]DVS-233 was measured in male albino S-D rats by quantitative tissue distribution (QTD) and quantitative whole body autoradiography (QWBAR) after a single oral dose of 30 mg/kg [<sup>14</sup>C]DVS-233 (RPT-55853). The tissue distribution of radioactivity in selected melatonin-containing tissues was also measured in pigmented Long-Evans male rats. Absorption of radioactivity was rapid in all tissues (t<sub>max</sub> of 0.5 hr = the first sampling time) except for the large intestine (t<sub>max</sub> of 8 hr). Radioactivity tissue distribution was consistent with the oral administration of the drug. The highest amounts of radioactivity were found in the urinary bladder, liver, kidney medulla, small intestine, large intestine, stomach, whole kidney and kidney cortex. Radioactivity in the brain and spinal cord was low (tissue:plasma AUC ratio = 0.1). Radioactivity was also rapidly eliminated from all tissues with >99% (relative to the respective C<sub>max</sub>) eliminated by 120 hr. Radioactivity was much higher in the skin and uveal tract of Long-Evans (pigmented) rats indicating the drug has moderate affinity to melanin-containing tissues.

Plasma, hypothalamus and total brain (remainder of brain after dissection of hypothalamus) concentrations of DVS-233 were measured in male S-D rats (RPT-58120) and ovariectomized female S-D rats (RPT-55957) administered 30 mg/kg DVS-233. t<sub>max</sub> was reached in 0.5 hr for each tissue in both males and females, and t<sub>1/2</sub> ranged between 2.1 and 3.0 hr. Tissue:plasma AUC ratios were 1.8 and 1.3 in the hypothalamus of males and females respectively and 1.6 and 1.7 in the remainder of the brain for males and females respectively. The sponsor attributed the difference in brain:plasma ratios in the radioactive study vs. the brain penetration study to the majority of the radioactivity in plasma to desvenlafaxine metabolites and the active moiety (desvenlafaxine) having penetrated the brain and hypothalamus.

Protein binding of desvenlafaxine was measured by equilibrium dialysis and was relatively low in rat (39.6%), dog (26.0%) and human (29.8%) plasma (GTR-17425). Protein binding of [<sup>14</sup>C]DVS-233 was measured in mice and rabbit plasma and was also found to be relatively low (24.5 and 26.7% respectively for mice and rabbits) (RPT-49784). Protein binding in plasma from all species was independent of drug concentration.

The distribution of [<sup>14</sup>C]DVS-233 radioactivity to maternal and fetal tissues was measured in gestation day 17 female S-D rats administered a single oral dose of 100 mg/kg [<sup>14</sup>C]DVS-233 (RPT-58687). There was little distribution of radioactivity to the fetus; the tissue:plasma radioactivity AUC<sub>0-72</sub> ratios were 0.2, 0.2, and <0.1 for the placenta, amniotic fluid, and fetuses respectively. The concentration of radioactivity was below the limit of quantification by 48 hr after dosing for the placenta and fetus and was only 3.3% of the C<sub>max</sub> value for the amniotic fluid by 72 hr.

Distribution of [<sup>14</sup>C]DVS-233 into the milk of lactating female rats and into the plasma of nursing pups was measured in female S-D rats administered a single oral dose of 30 mg/kg [<sup>14</sup>C]DVS-233 (RPT-56443). Radioactivity readily distributed to the milk of lactating rats; the milk:plasma radioactivity ratios were 0.297, 0.880, 0.850 and 1.02 after 0.25, 1, 4 and 8 hr. Although radioactivity was rapidly transferred into the milk, the concentration of radioactivity in the plasma of nursing pups was very low; the AUC in the plasma of nursing pups was only 3.18% of the AUC from the plasma of lactating rats.

## 2.6.4.5 Metabolism

### 2.6.4.5.1 In vivo metabolism

Metabolism of desvenlafaxine was investigated *in vivo* in mice (RPT-49994), rats (RPT-47308) and dogs (RPT-47307) administered a single oral gavage dose of [<sup>14</sup>C]DVS-233 and measuring formation of metabolites in plasma, urine and feces over a 24-hr sampling period (see tables 2-4 below). Desvenlafaxine was rapidly metabolized in all species and the most abundant metabolite formed was the O-glucuronide metabolite (M7). The O-glucuronide metabolite accounted for 88.3% and 94.7% of the circulating radioactivity in plasma from mice, 87.7% and 93.6% in rats, and 77.5% and 96.4% in dogs at the 1 and 4-hr sampling times respectively (the actual data for individual metabolites in plasma from mice, rats, and dogs was NOT provided in the individual studies, only the % of total radioactivity for each metabolite was listed in the results section and PK tabulated summary tables). The O-glucuronide metabolite was excreted primarily in urine in all species. The second most abundant metabolite was N,O-didesmethylvenlafaxine (NODV) and was detected exclusively in feces. NODV accounted for 12.7%, 33.6%, and 11.8% of radioactivity in feces from mice, rats, and dogs respectively. The glucuronide metabolite of NODV (M13) was detected in a small amount in plasma and urine of mice and in urine of dogs. Unchanged desvenlafaxine was also detected and was excreted mainly in feces and urine. The oxidative metabolites (M1-M6) were detected in the urine and feces of rats only.

**Table 3. In vivo metabolic profile in mice. Single oral gavage dose of 30 mg/kg [<sup>14</sup>C]DVS-233 administered to 5 male mice. [Excerpted directly from Table 8.1 of the sponsor's Pharmacokinetic Tabulated Summary].**

Table 8.1: Pharmacokinetics: Metabolism In Vivo, Mice										Test Article: DVS-233	
Species: No. and Sex (M/F) of Animals:		Mice: 5 M (plasma, urine, feces)									
Feeding Condition:		Fed									
Vehicle/Formulation:		MC, polysorbate 80									
Method of Administration:		Single Dose Oral Gavage									
Dosage (mg/kg):		30									
Radionuclide:		<sup>14</sup> C									
Specific Activity:		144 µCi/mg									
Species	Sample	Sampling Time or Period (h)	% of Dosage in Sample	% of Radioactivity in Sample						Report No.	Cross-Reference
				ODV	O-glucuronide (M7)	NODV (M10)	O-glucuronide of NODV (M13)	M1-M6	Other		
Mice	Plasma	1	NA	4.2	88.3	ND	3.6	ND	ND	RPT-49994	4.2.2.4
		4	NA	ND	94.7 <sup>a</sup>	ND	2.8 <sup>a</sup>	ND	ND		
	Urine	0-24	102.4	17.3	75.9	ND	2.8	ND	ND		
	Feces	0-24	1.9	34.4	4.4	12.7	ND	ND	ND		
a. Average of 2 analyses.											
MC = Methylcellulose; NA = Not applicable; ND = Not determined; NODV = N,O-Didesmethylvenlafaxine; ODV = O-Desvenlafaxine; RPT= Report.											

**Table 4. In vivo metabolic profile in rats. Single oral gavage dose of 20 mg/kg [<sup>14</sup>C]DVS-233 administered to 3 male and female rats. [Excerpted directly from Table 8.2 of the sponsor's Pharmacokinetic Tabulated Summary].**

Table 8.2: Pharmacokinetics: Metabolism In Vivo, Rats										Test Article: DVS-233	
Species: No. and Sex (M/F) of Animals:		Rats: 3 M at 1, 4, 8, 24 h and 3 F at 1 and 8 h (plasma); 3 M at 0-8 and 8-24 h, 3 F at 0-8 h (urine); 3 M (feces)									
Feeding Condition:		Fed									
Vehicle/Formulation:		MC, polysorbate 80									
Method of Administration:		Single Dose Oral Gavage									
Dosage (mg/kg):		20									
Radionuclide:		<sup>14</sup> C									
Specific Activity:		144 µCi/mg									
Species	Sample	Sampling Time or Period (h)	% of Dosage in Sample	% of Radioactivity in Sample						Report No.	Cross-Reference
				ODV	O-glucuronide (M7)	NODV (M10)	O-glucuronide of NODV (M13)	M1-M6	Other		
Rats	Plasma	1	NA	<10	87.7 <sup>a</sup>	ND	ND	<2 <sup>a</sup>	ND	RPT-47308	4.2.2.4
		4 (M)	NA	<10	93.6	ND	ND	<2 <sup>a</sup>	ND		
	Urine	0-8 (M)	59.1	10.9	76.5	ND	ND	12.6 <sup>bc</sup>	ND		
		0-8 (F)	54.5	20.0	74.0	ND	ND	6.0 <sup>bc</sup>	ND		
		8-24	25.5	9.1	77.2	ND	ND	15.7 <sup>bc</sup>	ND		
	Feces	8-24	9.6	20.8	NA	33.6	ND	38.7 <sup>bc</sup>	7.1		
a. Average of two analyses.											
b. At 1, 4, 8, and 24 h postdose.											
c. Total of M1, M2, M3, M4, M5, and M6, if detected.											
MC = Methylcellulose; NA = Not applicable; ND = Not determined; NODV = N,O-Didesmethylvenlafaxine; ODV = O-Desvenlafaxine; RPT= Report.											

**Table 5. In vivo metabolic profile in dogs. Single oral gavage dose of 30 mg/kg [<sup>14</sup>C]DVS-233 administered to 4 male dogs. [Excerpted directly from Table 8.3 of the sponsor's Pharmacokinetic Tabulated Summary].**

Table 8.3: Pharmacokinetics: Metabolism In Vivo, Dogs										Test Article: DVS-233	
Species: No. and Sex (M/F) of Animals:		Dogs: 4 M at 1 and 4 h (plasma); 4 M at 0 - 24 and 8 - 24 h (urine); 4 M at 0 - 24 h (feces)									
Feeding Condition:		Fed									
Vehicle/Formulation:		MC, polysorbate 80									
Method of Administration:		Single Dose Oral Gavage									
Dosage (mg/kg):		30									
Radionuclide:		<sup>14</sup> C									
Specific Activity:		144 µCi/mg									
		-----% of Radioactivity in Sample-----									
Species	Sample	Sampling Time or Period (h)	% of Dosage in Sample	ODV	O-glucuronide (M7)	NODV (M10)	O-glucuronide of NODV (M13)	M1-M6	Other	Report No.	Cross-Reference
Dogs	Plasma	1	NA	< 22.5	77.5	ND	ND	ND	ND	RPT-47307	4.2, 2.4
		4	NA	< 3.6	96.4	ND	ND	ND	ND		
	Urine	0 - 8	< 0.1	ND	ND	ND	ND	ND	ND		
		8 - 24 <sup>a</sup>	74.8	5.8 <sup>b</sup>	84.6 <sup>b</sup>	ND	3.7 <sup>b</sup>	ND	2.3 <sup>b,c</sup>		
	Feces	0 - 24 <sup>a</sup>	3.0	75.9 <sup>b</sup>	ND	11.8 <sup>b</sup>	ND	ND	5.1 <sup>b,e</sup> 7.2 <sup>b,g</sup>		

a. Values for % of dose include 0 - 8 and 8 - 24 hour time points, but 0 - 8 hour collection contained < 0.1 % of the dose.  
b. Average of 2 analyses.  
c. Data for M11 metabolite.  
d. Data for M12 metabolite.  
e. At 24 h postdose, there was no fecal sample for 1 of 4 dogs, so collection continued until 48 h.  
f. Data for M14 metabolite.  
g. Data for N-oxide metabolite.

LCMS = Liquid chromatography/mass spectrometry; MC = Methylcellulose; NA = Not applicable; ND = Not determined; NODV = N,O-Didesmethylvenlafaxine; ODV = O-Desvenlafaxine; RPT= Report.

A mass-balance study of desvenlafaxine utilizing radioactive desvenlafaxine in humans was not conducted under this NDA, which would have quantified the amount of metabolites formed in humans. However, a mass-balance study was conducted previously for venlafaxine, in which 10 healthy males were administered a single 50 mg dose of [<sup>14</sup>C]-venlafaxine and blood, urine, and feces were analyzed for metabolites (GMR-17400). Over 87% of the dose was recovered in urine after 48 hr; 5% as unchanged venlafaxine, 30% of the dose was metabolized to desvenlafaxine, and 26% as O-glucuronide desvenlafaxine. The  $t_{1/2}$  for desvenlafaxine was 4.4 hr compared to 2.6 hr for venlafaxine, and the AUC for desvenlafaxine was ~4 times higher than that of venlafaxine.

Under this NDA the sponsor conducted an *in vivo* metabolism study of desvenlafaxine in healthy subjects (RPT-54416). The relative amount of metabolites formed in plasma was measured in healthy subjects after receiving either 300 or 600 mg single oral capsule doses of DVS SR. Plasma samples were analyzed 6, 12 and 24 hr after either a 300 or 600 mg oral dose. The metabolic profile was similar to that from human *in vitro* studies and animal *in vivo* studies. The major metabolic pathway was O-glucuronidation to the M7 metabolite. Plasma levels of the O-glucuronide metabolite (relative to plasma of unchanged desvenlafaxine levels) was highest at the 12-hr time point and in the 600 mg groups; O-glucuronide plasma levels ranged between 48-80% of desvenlafaxine plasma levels in the 600 mg groups at the 12-hr time point. Two additional metabolites were present predominantly in the 12 and 24 hr samples from the 600 mg dosages; they were N-desmethyl desvenlafaxine (NODV) (M10) and the O-glucuronide metabolite of M10 (M13). Plasma levels of each of these metabolites represented about <1% of the plasma

level of desvenlafaxine. All 3 metabolites present in human plasma were also present in mice, and dogs *in vivo*. In study CSR-54267, the major components recovered in urine after both oral and IV doses of DVS were unchanged DVS (46-52%) and conjugated DVS (19-22%), whereas urinary excretion of unconjugated and conjugated NODV only accounted for 3.5-3.6% of the administered dose.

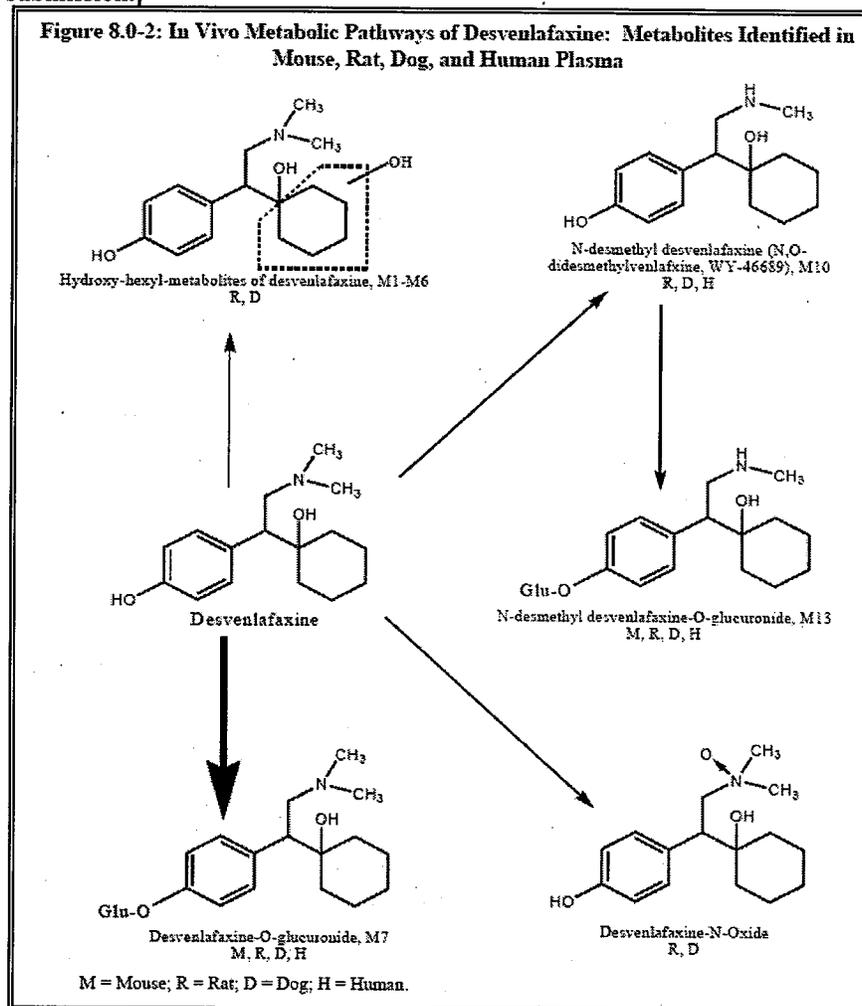
**Table 6. In vivo metabolic profile in humans. Single oral dose of 300 or 600 mg desvenlafaxine. [Excerpted directly from Table 1 of Study RPT-54416].**

Treatment Group and Subject Number	Dose	Time Point (hr)	Metabolite to Desvenlafaxine LC/MS Peak Area Ratio			Estimated Desvenlafaxine Concentration (ng/mL) <sup>a</sup>
			M13	M7	M10	
A (1,17)	300 mg	6	ND	0.29	ND	699
		12	0.007	0.65	ND	687
		24	0.011	0.44	ND	314
	600 mg	6	ND	0.36	ND	1393
		12	0.006	0.80	0.002	1194
		24	0.014	0.71	0.007	638
B (6,11,16,19) <sup>b</sup>	300 mg	6	ND	0.27	ND	625
		12	0.006	0.45	ND	499
		24	ND	0.35	ND	287
	600 mg	6	ND	0.33	ND	1301
		12	0.005	0.48	0.003	1269
		24	0.004	0.35	0.005	827
E (4,12,13,23)	300 mg	6	ND	0.21	ND	663
		12	ND	0.34	ND	621
		24	ND	0.23	ND	362
	600 mg	6	ND	0.31	0.002	1345
		12	0.004	0.48	0.003	1230
		24	0.005	0.28	0.005	787

a. Desvenlafaxine concentrations were estimated as described in section 2.3.1.1.  
 b. Subject 6 is included in the 300 mg samples but not the 600 mg samples.  
 ND indicates metabolite was not detected.

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Figure 3. In vivo metabolic pathway. [Excerpted directly from Nonclinical overview section of Sponsor's submission.]



#### 2.6.4.5.2 In vitro metabolism

Metabolism of desvenlafaxine was investigated *in vitro* in mice, rat, dog, and human liver microsomes and human hepatocytes (RPT-47306, RPT-45186). 10 metabolites were formed: 8 hydroxy metabolites (M1-M6, M8-M9), an O-glucuronide metabolite (M7), and an N-desmethyl metabolite (M10). Desvenlafaxine N-oxide was also formed in all species, but was determined to be a degradation product. All 10 metabolites were present in rat liver microsomes while only the O-glucuronide (M7) and N-desmethyl (M10) were formed in mice. All metabolites that were formed in either human liver microsomes or human hepatocytes were also formed in rat and dog liver microsomes. The major metabolic pathways were determined to be N-demethylation to M10, glucuronidation to M7, and oxidation. These metabolic pathways were similar to those previously identified for venlafaxine.

The major oxidative metabolites formed in human liver microsomes were formed by N-demethylation to generate N,O-didesmethylvenlafaxine, NODV (M10) and by hydroxylation on the benzyl ring (M9). Using recombinant CYP isozymes transfected in *E. coli* cells, it was determined that N-demethylation to NODV was catalyzed by CYP2C8, CYP2C9, CYP2C19, and CYP3A4, while hydroxylation to M9 was catalyzed by CYP2C8, CYP2C19, and CYP3A4. By using isozyme-specific chemical inhibitors, CYP3A4 and to a lesser extent CYP2C9 were responsible for N-demethylation to NODV, and CYP3A4 was responsible for hydroxylation (RPT-45184).

The major metabolic pathway in mice, rats, dogs and humans *in vivo* was determined to be glucuronidation to the O-glucuronide metabolite (M7). [<sup>14</sup>C]DVS-233 was used in human liver microsomes to identify UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17 as the isozymes responsible for formation of the M7 metabolite (RPT-58923).

**2.6.4.6 Excretion**

Excretion studies were performed in male mice (RPT-49994), rats (RPT-46556), and dogs (RPT-46462) administered oral gavage doses of [<sup>14</sup>C]DVS-233. Urinary excretion was the primary route for all species; 102%, 80.9%, and 68.1% of total radioactivity in mice, rats and dogs respectively. Fecal excretion accounted for only 1.9% in mice and slightly more in rats (13.1%) and dogs (11.7%). Excretion was complete and very rapid in mice with >100% of radioactivity being recovered within 24 hr. A total of 94.2% of radioactivity was recovered in rats after 120 hr (91.1% within 24 hr) and a total of 86.7% was recovered in dogs after 168 hr (85.4% within 72 hr).

Urinary excretion was also the major route of elimination in humans, with the majority of the administered DVS dose both after IV (76%) and after oral (69%) administration being recovered in the urine within 72 hr (CSR-54267).

Table 7. Excretion Profile in mice, rats, and dogs. [Excerpted directly from Table 3.4-1 of sponsor's Summary of Clinical Pharmacology section].

Species	% of Radioactive Dose		
	Urine	Feces	Total
Mice	102.4	1.9	104.3
Rat	80.9 ± 4.6	13.3 ± 3.0	94.3 ± 4.5
Dog	68.1 ± 15.1	13.6 ± 9.9	86.7 ± 5.4

**2.6.4.7 Pharmacokinetic drug interactions**

The inhibitory property of desvenlafaxine for CYP450 isozymes was evaluated in human liver microsomes (RPT-45185) and it was determined that desvenlafaxine does not

inhibit ( $IC_{50} > 100 \mu\text{M}$ ) CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP3A4. There was a slight inhibition of CYP2D6 ( $IC_{50}$  between 50-90  $\mu\text{M}$ ). Three follow-up studies to investigate desvenlafaxine's CYP2D6 inhibitory properties revealed no CYP2D6 inhibition at concentrations up to 100  $\mu\text{M}$  (RPT-57961, RPT-61024, GTR-23916). Taken together, desvenlafaxine is a very weak inhibitor of CYP2D6. A comparative CYP450 isozyme inhibitory study with 5 currently used SSRI/SNRI (venlafaxine, S,S-duloxetine, paroxetine, sertraline, and bupropion) was also conducted in human liver microsomes (RPT-57961).

DVS-233 only minimally inhibited P-glycoprotein (P-gp) mediated efflux of [ $^3\text{H}$ ]digoxin, <20% of control at 250  $\mu\text{M}$  (the highest concentration tested), in CACO-2 cells (RPT-59746).

Desvenlafaxine (DVS-233, the succinate salt) did not induce mRNA expression of CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5 at concentrations up to 20  $\mu\text{M}$  in human primary hepatocytes from 3 subjects (RPT-61379). Desvenlafaxine also did not induce enzyme induction of human CYP3A4 in human heptacarcinoma cells (HepG2) transfected with the human CYP3A4 promoter (RPT-56305).

#### 2.6.4.8 Other Pharmacokinetic Studies

There were not other pharmacokinetic studies in this submission.

#### 2.6.4.9 Discussion and Conclusions

Absorption of either desvenlafaxine as the free base or succinate salt form was rapid in both rats and dogs, with  $t_{1/2} \sim 4$  hr, however  $t_{1/2}$  did increase with increasing dose in rats. Female rats had  $\sim 1.5$ -2-fold higher exposure than male rats, while there was no sex difference in dogs. Desvenlafaxine exposure (both  $C_{\text{max}}$  and AUC) increased greater than dose proportional for both rats and dogs. There was however, no accumulation of drug after 14-day repeat exposures in both rats and dogs. There was a higher ( $\sim 4$ -fold) exposure to the S(+) enantiomer in rats after an oral dose of racemic desvenlafaxine, while there was equal exposure of the R(-) and S(+) enantiomers in dogs and humans given an oral dose of the racemate. [ $^{14}\text{C}$ ]DVS-233 was rapidly ( $t_{\text{max}}$  of 0.5 hr) and extensively distributed in rats with the highest amounts of radioactivity found in the urinary bladder, liver, kidney medulla, small intestine, large intestine, stomach, whole kidney and kidney cortex. There was also a moderate affinity towards melanin-containing tissues (skin and uveal tract of pigmented rats). There was good total brain and hypothalamus ( $< 2$ -fold) penetration of unlabeled DVS-233, accounting for the active moiety of desvenlafaxine penetrating the brain and hypothalamus, the proposed site of action. Although [ $^{14}\text{C}$ ]DVS-233 was readily distributed to the milk of lactating rats, there was very little exposure in plasma of nursing pups. Protein binding was relatively low in all species ( $< 40\%$  in mice, rats dogs, and rabbits) and  $\sim 29\%$  in human plasma. The major metabolic pathway for desvenlafaxine was O-glucuronidation to O-glucuronide desvenlafaxine (M7) and was similar among mice, rats, dogs, and humans. Several UGT

enzyme isoforms were found to be responsible for formation of the O-glucuronide metabolite in liver microsomes of mice, rats, dogs and humans (UGT1A1, UGT1A3, UGT2B4, UGT2B15, and UGT2B17) therefore drug inhibition of one isoform should not greatly impair the metabolism of DVS. Other minor metabolites found included the oxidative N-desmethyl metabolite (NODV) and the O-glucuronide metabolite of NODV. In humans, the major component found in plasma and urine was unchanged DVS, while in all animal species the major component was the O-glucuronide metabolite. The N-desmethyl and its O-glucuronide detected in humans but at levels <1% of DVS. All major and minor metabolites formed in humans were also formed in rats and dogs and to a greater extent than in humans, therefore no further qualification of these metabolites is necessary. Urinary excretion was the major route of elimination in rats and dogs as well as humans and was the major route of elimination for the O-glucuronide metabolite. The oxidative metabolite (NODV) was excreted exclusively in the feces of rats and dogs. CYP3A4 is the major oxidative enzyme responsible for formation of NODV. DVS was found to be a weak inhibitor of CYP2D6 (in 1 of 3 assays) while DVS did not inhibit or induce any of the other CYP isozymes tested. Desvenlafaxine was a weak inhibitor of CYP2D6, but did not show any inhibition or induction of any other CYP isoforms tested. Desvenlafaxine was also not a substrate of the P-gp transporter nor did it inhibit the P-gp-efflux transporter.

#### 2.6.4.10 Tables and figures to include comparative TK summary

**Table 8. Rat PK summary table. [Excerpted directly from the Pharmacokinetics Written Summary of the Sponsor's submission.]**

Table 10.0-1: Mean $\pm$ SD Pharmacokinetic Parameters for Desvenlafaxine in Male Rats after Single or Repeat (2 Weeks) Oral (Gavage) Dosages of Desvenlafaxine Free Base or DVS-233								
No. of Animals	Route	Compound Administered	Dosage <sup>a</sup> (mg/kg/day)	Study Day	C <sub>max</sub> ( $\mu$ g/mL)	t <sub>1/2</sub> (h)	AUC ( $\mu$ g $\cdot$ h/mL)	Report No.
<b>Single- and Repeat-dose PK Studies With Early Lots/Batches</b>								
5 <sup>b</sup>	Oral (gavage)	Desvenlafaxine free base	100	1	4.77 $\pm$ 0.49	2.1 <sup>c</sup>	15.4 $\pm$ 4.4 <sup>c,d</sup>	GTR-15626
5 <sup>b</sup>	Oral (gavage)	Desvenlafaxine free base	100	1	6.92 $\pm$ 0.97	3.0 <sup>c</sup>	12.6 <sup>c,d</sup>	GTR-17423
5 <sup>b</sup>			500	1	17.0 $\pm$ 3.9	4.5 <sup>c</sup>	94.9 <sup>c,d</sup>	
5 <sup>b</sup>			1000	1	30.7 $\pm$ 14.1	6.4 <sup>c</sup>	213 <sup>c,d</sup>	
5 <sup>b</sup>	Oral (gavage)	Desvenlafaxine free base	500 for 1 day	1	14.5 $\pm$ 3.3	4.1 <sup>c</sup>	87.2 <sup>c,d</sup>	GTR-16974
5 <sup>b</sup>			500 for 14 days	14	17.4 $\pm$ 4.6	3.8 <sup>c</sup>	84.7 <sup>c</sup>	
<b>Comparative PK Studies With Recent Lots/Batches</b>								
4	Oral (gavage)	Desvenlafaxine free base	30	1	0.727 $\pm$ 0.275	2.4 $\pm$ 0.5	1.18 $\pm$ 0.41 <sup>d</sup>	RPT-45320
4			100	1	4.77 $\pm$ 0.75	2.9 $\pm$ 0.6	8.35 $\pm$ 1.14 <sup>d</sup>	
4	Oral (gavage)	DVS-233	30	1	0.79 $\pm$ 0.23	2.0 $\pm$ 0.2	1.10 $\pm$ 0.21 <sup>d</sup>	RPT-55852
4			100	1	2.82 $\pm$ 0.79	3.1 <sup>a</sup>	5.99 <sup>d,e</sup>	
4F	Oral (gavage)	DVS-233 (batch RB1636)	100	1	3.67 $\pm$ 0.87	3.6 $\pm$ 0.5	13.7 $\pm$ 2.3 <sup>d</sup>	RPT-55852
4F		DVS-233 (batch RB2691)	100	1	3.59 $\pm$ 0.78	3.7 $\pm$ 0.3	13.0 $\pm$ 2.3 <sup>d</sup>	
<p>a. Dosages are reported as the active moiety.  b. N = 5 rats at each time point.  c. Estimated from the mean concentration-versus-time profile.  d. AUC<sub>0-<math>\infty</math></sub> value.  e. N = 2.</p>								
<p>AUC = Area under the concentration-versus-time curve; C<sub>max</sub> = Peak concentration; DVS-233 = Desvenlafaxine succinate; GTR = General Technical Report; N = Number of animals; PK = Pharmacokinetics; RPT = Report; SD = Standard deviation; t<sub>1/2</sub> = Apparent terminal half-life.</p>								

**Table 9. Dog summary table. [Excerpted directly from the Pharmacokinetics Written Summary of the Sponsor's submission.]**

Table 10.0-4: Mean ± SD Pharmacokinetic Parameters for Desvenlafaxine in Dogs after Single or Repeat Oral Dosages of Desvenlafaxine Free Base or DVS-233											
Sex	N	Route	Compound Administered	Dosage <sup>a</sup> (mg/kg/day)	Study Day	C <sub>max</sub> (µg/mL)	Dose Normalized <sup>b</sup> C <sub>max</sub>	t <sub>1/2</sub> (h)	AUC (µg·h/mL)	Dose Normalized <sup>b</sup> AUC	Report No.
Single- and Repeat-dose PK Studies With Early Lots/Batches (Conducted Under the Venlafaxine Development Program)											
M, F	4	Oral (neat powder in capsule)	Desvenlafaxine free base	15	1	0.47 ± 0.14	0.031	1.6 ± 0.9	1.08 ± 0.38 <sup>c</sup>	0.072	GTR-15626
M	6	Oral	Desvenlafaxine free base	15	1	0.356 ± 0.185	0.024	ND <sup>d</sup>	1.19 ± 0.70 <sup>e</sup>	0.079	GTR-17609
M	6	(neat powder	free base	75	1	1.60 ± 0.85	0.021	ND <sup>d</sup>	8.68 ± 3.35 <sup>e</sup>	0.116	
M	6	in capsule)		175	1	5.36 ± 3.65	0.031	ND <sup>d</sup>	26.5 ± 11.8 <sup>e</sup>	0.151	
M	4	Oral	Desvenlafaxine free base	175 for 1 day	1	4.1 ± 4.6	0.023	ND <sup>d</sup>	16.9 ± 9.1 <sup>e</sup>	0.097	GTR-16978
M	4	(neat powder in capsule)		175 for 14 days	14	4.65 ± 3.91	0.027	ND <sup>d</sup>	14.8 ± 6.9 <sup>e</sup>	0.085	
Comparative PK Studies With Recent Lots/Batches (Conducted Under the DVS SR Tablet Development Program)											
M	4	Oral	Desvenlafaxine free base	30	1	3.73 ± 0.81	0.124	3.1 ± 1.4	11.1 ± 2.0 <sup>e</sup>	0.370	RPT-45321
M	4	(neat powder in capsule)		100	1	12.4 ± 6.2	0.124	4.8 ± 1.8	47.7 ± 3.5 <sup>e</sup>	0.477	
M	4	Oral	DVS-233	30	1	3.52 ± 1.22	0.117	3.2 <sup>f</sup>	7.57 <sup>e,f</sup>	0.252	
M	4	(neat powder in capsule)		100	1	10.3 ± 2.1	0.103	3.9 <sup>f</sup>	52.5 <sup>e,f</sup>	0.325	
M	4	Oral	DVS-233	100	1	16.6 ± 3.5	0.166	3.1 ± 0.4	55.3 ± 16.0 <sup>e</sup>	0.553	RPT-45322
F	4	(suspension by gavage)		100	1	20.8 ± 12.1	0.208	3.2 ± 0.7	53.2 ± 5.4 <sup>e</sup>	0.532	
Comparative PK Studies With Recent Lots/Batches (Conducted Under the DVS SR Tablet Development Program) (cont'd)											
M	4	Oral	Desvenlafaxine free base	100	1	10.5 ± 2.1	0.105	3.8 ± 1.1	55.0 ± 18.4 <sup>e</sup>	0.550	
F	4	(suspension-filled capsule)		100	1	17.9 ± 3.0	0.179	3.1 ± 0.6	60.3 ± 5.8 <sup>e</sup>	0.603	
M, F	4	Oral (suspension by gavage)	DVS-233	100	1	25.3 ± 3.0	0.253	3.7 <sup>f</sup>	79.9 <sup>e,f</sup>	0.799	RPT-45323
M, F	4	Oral (SR tablets in capsule)	DVS-233	100	1	3.55 ± 0.84	0.036	5.1 ± 4.0	43.5 ± 7.5 <sup>e</sup>	0.435	

a. Dosages are reported as the active moiety.  
b. Dose-normalized value = C<sub>max</sub> or AUC divided by dosage.  
c. AUC<sub>0-∞</sub> value.  
d. Could not be calculated due to the shape of the plasma concentration-versus-time curve.  
e. AUC<sub>0-24</sub> hour value.  
f. N = 2.

AUC = Area under the concentration-versus-time curve; C<sub>max</sub> = Peak concentration, DVS-233 = Desvenlafaxine succinate; GTR = General Technical Report; N = Number of animals; ND = Not determined; PK = Pharmacokinetics; RPT = Report; SD = Standard deviation; SR = Sustained-release; t<sub>1/2</sub> = Apparent terminal half-life.

**2.6.5 PHARMACOKINETICS TABULATED SUMMARY**

[Note added by L.Fossom: The Sponsor provided (62 pages of) tabulated summaries for Pharmacokinetics, comprising 12 tables, including Absorption (15 reports), Distribution (7 reports), Metabolism (16 reports), and Excretion (3 reports).]

## 2.6.6 TOXICOLOGY

### 2.6.6.1 Overall toxicology summary

General toxicology: Desvenlafaxine was tested for general toxicity in repeated-dose studies in rats (up to 6 months) and Beagle dogs (up to 9 months).

There were essentially no drug-related findings short of decreased body weights and, at higher doses, death when desvenlafaxine was administered by oral gavage to rats. Oral LD50s were calculated as 3158 mg/kg and 3533 mg/kg for males and females, respectively. In the 6-month rat study, the NOAEL was 100 mg/kg for male rats, based on based on decreased body weights at 300 mg/kg (6-10% lower than controls, from week 13); and HD of 300 mg/kg for females (with no limiting toxicity). The decreased body weights in HDM at 300 mg/kg corroborated the same finding at 500 mg/kg (but not at 100 mg/kg) in the 3-month study. Additionally, the HD of 300 mg/kg is  $\sim 1/3^{\text{rd}}$  the lethal dose of 1000 mg/kg (for both males and females) in the 3-month study.

In dogs, the only limiting toxicity appeared to be convulsions and/or death, with NOELs for these findings of 100 mg/kg in 2 3-month studies using the suspension formulation; and a NOEL for these findings of 200 mg/kg in a 3-month study using the SR tablets. There was also some evidence of effects on the liver at the high doses: increases in liver enzymes, but without histopathologic correlates. The chronic (9-month) study in dogs was conducted with administration by oral gavage up to a high dose of 50 mg/kg, which is half the MTD determined in the shorter studies. It should be noted that higher systemic exposures could have been achieved using SR tablets at the MTD of 200 mg/kg determined in 3-month study. However, the 50 mg/kg dose used in the chronic dog study covers the C<sub>max</sub> (7-fold) and AUC (1.6-fold) for humans at the MRHD of 200 mg/day.

Genetic toxicology: Desvenlafaxine was negative for mutagenicity in the Ames test and for in vitro clastogenicity in a chromosomal aberration assay in CHO cells.

Desvenlafaxine was assessed for clastogenicity in 2 in vivo studies: a rat chromosomal aberration assay, which had been previously reviewed for approval of venlafaxine and considered to be positive, plus a mouse micronucleus assay that had not been previously reviewed. After reexamination of the in vivo rat chromosomal aberration assay results, it is this Reviewer's opinion the assay cannot be considered positive, because the only positive finding was for males (not females) at the high dose (of 3 doses) at the 6 hour time point (but not at 18- or 24-hr time points) and reduced to the 5 rats in that dose group having 0, 0, 4, 8, 12% cells with aberrations, compared with 0, 0, 0, 4, 8% cells with aberrations in the control group, and the aberrations in that HDM were largely chromatid breaks. Additionally, the in vivo mouse micronucleus assay was negative.

Finally, desvenlafaxine was not mutagenic in a CHO/HPRT forward gene mutation assay and was negative in the BALB/c-3T3 transformation assay.

**Carcinogenicity:** Desvenlafaxine was not carcinogenic in 2-year studies in mice at oral gavage doses up to 500/300 mg/kg (dose lowered at week 46 due to mortality) and rats at doses up to 300 mg/kg in males and 500 mg/kg in females.

**Reproductive toxicology:** Fertility was assessed in rats, with both males and females treated with desvenlafaxine at doses up to 300 mg/kg (for 4 weeks and 2 weeks prior to cohabitation, respectively). The NOAEL for fertility was considered to be the LD of 30 mg/kg (with only disrupted estrus cycles and doubling of time to mate). At  $\geq 100$  mg/kg, the fertility index was decreased (50%) and pre-implantation loss was increased. At 300 mg/kg, gravid uterine weight was decreased.

Embryo-fetal toxicity was assessed in rats and rabbits. This assessment in rats was an extension/combination with the fertility study: decreased fetal weights were seen at 300 mg/kg (but not at 100 mg/kg), but there was no indication of teratogenesis at any dose tested (up to 300 mg/kg). The high dose of 300 mg/kg could be considered adequate based on decreased food consumption during GD 0-5 (pre-implantation) and throughout gestation (GD0-20) and decreased body weight gain during gestation. However, it should be noted that the number of fetuses available for assessment was approximately half that at the lower doses (due to decreased fertility and increased pre-implantation loss); consequently the sensitivity for identifying malformations was severely compromised at the high dose, where they might be most likely to occur. Assessment of embryo-fetal toxicity in rabbits was conducted in a standard study, at doses up to 75 mg/kg; the NOEL for developmental effects including teratogenicity was the high dose of 75 mg/kg; this was also the NOEL for maternal toxicity, however, this high dose could be considered acceptable based on mortality at less than 10-fold that dose in a supporting study.

Prenatal and postnatal development was assessed in progeny of pregnant rats, treated at doses up to 300 mg/kg from implantation (GD 6) through lactation and weaning (PND 21). The NOAEL for maternal toxicity was 100 mg/kg based on transient weight loss from GD 6-7, which resulted in 18% decreased weight gain (compared with controls) during gestation (GD 6-21), accompanied by decreased food consumption, and slightly increased gestation duration at 300 mg/kg. The NOAEL for perinatal/postnatal toxicity was also considered to be 100 mg/kg, based on lower pup birth weights and decreased viability through PND 4 at 300 mg/kg; there were no other drug-related effects on the progeny.

## 2.6.6.2 Single-dose toxicity

### 2.6.6.2.1 Single-dose toxicity in rats

Study report GTR-15230 (dosing in October 1987; Wyeth-Ayerst): oral gavage LD-50 study (8½-week old male and female CD Charles River; 10/sex/group; 0, 2500, 3000, 3500, and 4000 mg/kg (doses of the base (WY-45,233; W.I.C. No. W32-87), but administered as fumarate salt), 20 ml/kg, as suspension in 0.5% CMC + 0.25% Tween 80 in sterile water for injection; monitored for 10 days): deaths at all doses (see table,

below); oral LD50s were calculated as 3158 mg/kg and 3533 mg/kg for males and females, respectively.

**Table 10. Mortality data for male and female rats administered single oral doses of desvenlafaxine. [Tables excerpted directly from this study report, pages 14-15.]**

DAILY MORTALITY INCIDENCE - MALES												
DOSE (MG/KG)	D A Y										NO. OF DEATHS/ TOTAL NO. IN GROUP	
	1		2	3	4	5	6	7	8	9		10
	0-4 H	4-24 H										
0	0	0	0	0	0	0	0	0	0	0	0	0/10
2500	1	0	0	0	0	0	0	0	0	0	0	1/10
3000	2	0	0	0	0	0	0	0	0	0	0	2/10
3500	5	1	0	0	0	0	0	0	0	0	0	6/10
4000	4	2	0	0	0	0	0	0	0	0	0	6/10

H = Hours after dosing

DAILY MORTALITY INCIDENCE - FEMALES												
DOSE (MG/KG)	D A Y										NO. OF DEATHS/ TOTAL NO. IN GROUP	
	1		2	3	4	5	6	7	8	9		10
	0-4 H	4-24 H										
0	0	0	0	0	0	0	0	0	0	0	0	0/10
2500	0	0	0	0	0	0	0	0	0	0	0	0/10
3000	0	4	0	0	0	0	0	0	0	0	0	4/10
3500	4	0	0	0	0	0	0	0	0	0	0	4/10
4000	2	4	1	0	0	0	0	0	0	0	0	7/10

H = Hours after dosing

Study report GTR-15466 (dosing in September 1987; Wyeth-Ayerst; conducted by Ayerst Research Laboratories): preliminary oral gavage LD-50 study (7-9-week old male and female CD Charles River; 2/sex/group; 0, 200, 300, 400, 500, 800, 1100, 1500, 2000, 2500, 2800, 3200, and 4000 mg/kg (doses of the base, but administered as fumarate salt): only 2 deaths: 1/2 males (4-24 hr after dosing) at 2500 and 1/2 females (0-4 hr after dosing) at 4000 mg/kg.

Study report 44840 (dosing in November 2001; Wyeth-Ayerst): acute ip study (7-week old, male and female CD VAF rats; 3/sex/group; 0, 200, 700, 2000 mg/kg (DVS-233, lot RB1636), in 0.25% polysorbate 80 + 0.5% methylcellulose in purified water, 10 ml/kg; monitored for 14 days): at ≥700 mg/kg, all rats were found dead or euthanized within 4 hr of dosing on day 1, with tremors, convulsions, ataxia, decreased motor activity, immobility (at MD only), dyspnea, and Straub tail; but no macroscopic changes that indicated cause of death; some injections at HD were into the cecum or ilium (as verified by white material at necropsy) and there were some intestinal perforations evident in other rats at the MD and HD; at 200 mg/kg, no mortalities and no clinical or macroscopic signs.

**2.6.6.2.2 Single-dose toxicity in mice**

Study report GTR-15229 (dosing in October 1987; conducted by Wyeth-Ayerst): oral gavage LD-50 study (8-week old male and female CD Charles River; 10/sex/group; 0,

1600 (F), 1800, 1900 (F), 2100, 2400, 2700, and 3000 mg/kg (doses of the base (WY-45,233; W.I.C. No. W32-87), but administered as fumarate salt), 20 ml/kg, as suspension in 0.5% CMC + 0.25% Tween 80 in sterile water for injection; monitored for 10 days): deaths at  $\geq$  1800 mg/kg; drug-related effects included bradypnea, clonic convulsions, dyspnea, hyper- and hyp-activity, immobility, low carriage, straub tail, and tremors; **oral LD50s were calculated as 2489 mg/kg and 1985 mg/kg for males and females, respectively.**

Study report GTR-15170: (dosing in September 1987; conducted by Wyeth-Ayerst): preliminary oral gavage LD-50 study (7-9-week old male and female CD-1 mice, Charles River ~~\_\_\_\_\_~~; 7-8 weeks old; 2/sex/group; 0, 200, 300, 400, 500, 800, 1100, 1500, 2000, 2500 mg/kg (doses of the base, based on fumarate salt, 66.26% strength): deaths in first 24 hr (but not later up to 4 days) at  $\geq$  2000 mg/kg: 1/2 females at 2000 and 2/2 males and 2/2 females at 2500 mg/kg; clinical signs including ataxia, tremors, low carriage, and hypoactivity in males at  $\geq$ 2000 mg/kg and females at  $\geq$ 1500 mg/kg. Recommended doses of 1800, 2100, 2400, 2700, and 3000 mg/kg for definitive study.

1-day DRF study (RPT-48797; dosing on 12/13/02): [Originally planned as 13-week study, but was terminated after 1 day due to severe clinical signs and deaths after first dose.] doses of 0, 1000, 2000 mg/kg of DVS-233 (based on active moiety; by gavage as suspension in 0.25% polysorbate + 0.5% methylcellulose in purified water) to ~~\_\_\_\_\_~~ CD-1 mice (from ~~\_\_\_\_\_~~ 10/sex/dose + 18/sex at 1000 and 2000 mg/kg for TK, but HD mice were not dosed and no blood samples were collected); evaluation based on mortality, clinical observations (body weight and food consumption were planned but not conducted). Results: Based on the Sponsor's conclusions, there were 11 unscheduled deaths (8 toxicology mice, 1 LDM, 1 HDM, 6 HDF; and 3 TK mice, all LDF); clinical observations in these and other dosed mice included: tremors, decreased motor activity, and convulsions; MTD < 1000 mg/kg.

**Table 11. Incidences for mortality and clinical signs in mice treated acutely with DVS-233. [Complied from Sponsor's tables, pages 16-20 of the study report.]**

FINDING	0 mg/kg		1000 mg/kg		2000 mg/kg	
	M	F	M	F	M	F
<b>Mortality</b>	0% (0/28)	0% (0/28)	4% (1/28)	11% (3/28)	10% (1/10)	60% (6/10)
Convulsions/Clonic	0% (0/28)	0% (0/28)	0% (0/28)	4% (1/28)	20% (2/10)	10% (1/10)
Convulsions/General	0% (0/28)	0% (0/28)	0% (0/28)	0% (0/28)	0% (0/10)	30% (3/10)
Tremors	0% (0/28)	0% (0/28)	11% (3/28)	36% (10/28)	50% (5/10)	80% (8/10)
↓ activity	0% (0/28)	0% (0/28)	4% (1/28)	21% (6/28)	10% (1/10)	40% (4/10)

The subchronic (2 weeks to 3 months) studies in mice were used as the basis for choosing doses for the mouse carcinogenicity study and are not reviewed for this NDA.

#### 2.6.6.2.2 Single-dose toxicity in dogs

None conducted.

### 2.6.6.3 Repeat-dose toxicity

#### 2.6.6.3.1 Repeat-dose toxicity in rats

##### 2.6.6.3.1.1 Subacute and subchronic exposures in rats

The 7-day DRF study in rats: (GTR-15463): doses of 500, 1000, 2000 mg/kg of desvenlafaxine (WY-45,233C, lot 8455-268-X; W.I.C. no 31-87) by oral gavage as a suspension to CD rats (3/sex/dose): all rats survived; decreased body weight gain (HD rats weighed 4-6% less than controls) and decreased (15-25%) food intake at HD considered limiting.

1-month oral gavage study in rats (GTR-16369; Wyeth-Ayerst; GLP/QA; 1988): doses of 0, 75, 225, and 675 mg/kg of desvenlafaxine (WY-45,233, lot C-13877) by oral gavage as suspension to CD rats (20/sex/dose): all rats survived (except 1 HDF found dead in week 1, attributed to gavage trauma, with necropsy finding of perforated esophagus); decreased body weight ( $\downarrow$ 6-10% in HDM and  $\downarrow$ 6% in HDF in weeks 2-4) and food intake at HD; clinical signs limited to increased salivation at HD; changes in clinical chemistry parameters (slight increases in ALP and K at MD and HD, slight decrease in Ca at HD) and absolute organ weights were unremarkable; there were no treatment-related changes in ophthalmology or hematology, and no gross or microscopic lesions.

3-month oral gavage study in rats (GTR-17272; Wyeth-Ayerst; GLP/QA; 1988): Methods: doses of 0, 100, 500, 1000 mg/kg of desvenlafaxine (WY-45,233, lots C-13892, C-13912, C-13877) by oral gavage as suspension (in 0.5% Natrasol) to CD rats (20/sex/dose); clinical chemistry and hematology on 10/sex/group pre-test and at weeks 6 and 13; full histopathology on all groups.

Results: deaths at HD (2 HDM: 1 found dead in week 12, 1 killed in extremis in week 6; neither HDM showed decreased body weight (measured weekly) prior to death and cause of death was not determined; and 1 HDF: found dead in week 12; with weight loss in the week prior to death, but no cause of death determined) were attributed to "drug-related acute functional toxicity," but the details of what this meant were not provided (presumably the lack of necropsy evidence of gavage error; CNS signs were not provided for individual rats) [deaths of 5 other rats (apparently 1 MDM, 1 control female, and 3 HDF) were attributed to gavage and/or bleeding trauma (all but 1 HDF had necropsy evidence of esophageal perforation)]; decreased body weights in MDM (from week 2,  $\downarrow$ 10% at week 13), HDM (from week 1,  $\downarrow$ 16% at week 13), and HDF (from week 1,  $\downarrow$ 12% at week 13), with decreased food intake in HDM (from week 1); slight increases in fibrinogen (at MD and HD), and in triglycerides and cholesterol in all dose female groups were unremarkable; there were no treatment-related changes in ophthalmology, organ weights, and no gross or microscopic lesions. "The no effect level was 100 mg/kg, although only minor adverse effects occurred at 500 mg/kg."

Conclusions: It is assumed that the 3 deaths (2 males and 1 female) at 1000 mg/kg were drug-related; decreased body weights in males at  $\geq$  500 mg/kg and females at 1000 mg/kg

could be considered dose-limiting; no other evidence of limiting (or any) toxicity was apparent. NOAEL = 100 mg/kg (<500 mg/kg) for males and 500 mg/kg (<1000 mg/kg) in females.

#### 2.6.6.3.1.2 Chronic exposure (6-month study) in rats

**Study title:** DVS-233 SUCCINATE: TWENTY-SIX WEEK ORAL (GAVAGE) TOXICITY STUDY IN RATS (PROTOCOL 01\_0535).

##### **Key study findings:**

- Doses: 0, 30, 100, and 300 mg/kg/day of desvenlafaxine by oral gavage for 26 weeks.
- Treatment-related findings were minimal: decreased body weights at 300 mg/kg (6-10% lower than controls, from week 13) in males, only; slight decreases in prostate weights in HD males and pituitaries in HD females, but with no histopathological correlates.
- The decreased body weights in HDM at 300 mg/kg corroborate the finding at 500 mg/kg in the 3-month study; the HD of 300 mg/kg is  $\sim 1/3^{\text{rd}}$  a lethal dose in the 3-month study.
- NOAEL = 100 mg/kg for males, based on decreased body weights at 300 mg/kg (6-10% lower than controls, from week 13); and HD of 300 mg/kg for females, with no limiting toxicity in this study.

**Study no.:** RPT-49309.

**Volume #, and page #:** electronic submission, 564 pages.

**Conducting laboratory and location:** Wyeth European DSM Research Center, Catania, Italy.

**Date of study initiation:** dosing started on 6/7/2002.

**GLP compliance:** yes, see page 198

**QA report:** yes, see pages 200-201.

**Drug, lot #, and % purity:** DVS-233 (WAY-45233 succinate monohydrate) micronized; lot/batch nos: RB2608; RB2637 (from June 20, 2002); no impurities detected in RB2608, total impurities = — in RB2637 (see C of As, pages 140-141).

##### **Methods**

Doses: 0, 30, 100, and 300 mg/kg of desvenlafaxine once daily for 26 weeks [HD based on decreased body weights in fertility study].

Species/strain: CD@ (SD) IGS BR rats

Number/sex/group (main study): 20/sex/group.

Route, formulation, volume, and infusion rate: oral gavage in 0.25% polysorbate 80 + 0.5% methylcellulose (4000 cps) in deionized water (10 ml/kg); vehicle and drug formulations prepared fresh every 1-2 weeks and stored refrigerated and protected from light; pH of control was 5.90-6.96, pH of drug formulations was

4.62-5.70; drug formulations were assessed for drug content and found to range from 95.3-103.3% of nominal concentration; homogeneity was not analyzed, but previous data was referenced.

Satellite groups used for toxicokinetics: additional 9/sex at LD, MD, and HD for TK.

Age: Approximately 6 weeks old at dose initiation.

Weight: 173.0-244.6 grams males; 133.1-192.4 grams females on the first day of dosing.

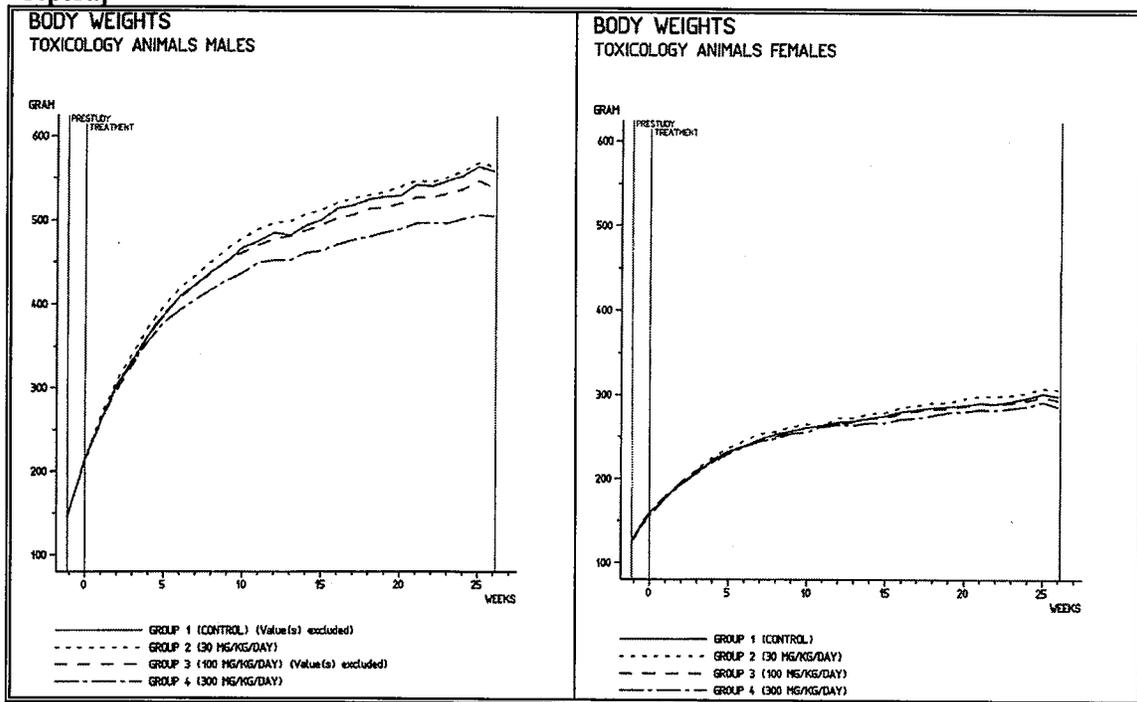
**Results:**

Mortality: There was no drug-related mortality, but 4 unscheduled deaths (3 premature deaths were attributed to gavage error: control male #2, found dead on day 83; LDM #38 and HDF #191, found dead on day 104); MDM #66 was euthanized on day 33, after prolonged, marked weight loss and deterioration, COD was confirmed at necropsy as lower urinary tract spontaneous disease (urinary and prostate inflammation).

Clinical signs: drug-related clinical signs were limited to salivation (esp at HD), other signs (e.g. Staub tail) were rare or sporadic and considered incidental.

Body weights and food consumption: Body weights decreased (see figure, below) in HDMs from week 13 (6-10%), with parallel decrease in food consumption from week 6. There was no effect on body weights of females at any dose.

**Figure 4. Decreased body weight in male rats (but not females) treated with 300 mg/kg desvenlafaxine for 26 weeks. [Sponsor's graphs excerpted directly from pages 53-54 of the study report.]**



Ophthalmoscopy (indirect; pre-test and at weeks 13 and 26): only scattered abnormalities were detected during the course of the study; and were considered incidental and not related to treatment. Choroidal vascular anomaly was not present at pre-test, but was detected in 2 control males, 1 MDM, and 2 HDF; chromodacryorrhea was detected in 1 MDF.

EKG: not conducted.

Hematology and coagulation (at weeks 13 and 26; 4-5/sex/group): drug-related changes were limited to (significantly) decreased number of reticulocytes in males at MD (44% lower than controls) and HD (46% lower than controls) at week 26, but not at week 13. There were no alterations in coagulation parameters (PT, APTT, or fibrinogen).

Clinical chemistry (at weeks 13 and 26; 5 /sex/group): drug-related changes were limited to (significantly) increased BUN/creatinine ratio in HDM (30% greater than controls) at week 13 only, with non-significantly decreased creatinine and non-significantly increased BUN.

Urinalysis: not conducted.

Gross pathology: no treatment-related effects.

Organ weights: in males at MD and/or HD, absolute weights of several organs (adrenals, heart, kidney, liver, prostate) were decreased compared to controls (whose terminal body weights were decreased, 11% lower than controls); only prostate weight at HD was still decreased when normalized to both body weight and brain weight (decreased 25% abs, 17% vs body weight, 24% vs brain weight). Decreased pituitary weights in HD females (whose terminal body weights were also decreased, 5% lower than controls) also remained decreased when normalized to both body weight and brain weight (decreased 21% abs, 16% vs body weight, 19% vs brain weight).

Histopathology: Adequate Battery: yes.

Peer review: yes, see certification on page 564.

There were no apparent differences between controls and HD rats. Because there was a decrease in prostate weights in HD males and pituitary in HD females, I have provided the microscopic findings in those (and related) organs. In the prostate, the incidence of mononuclear cell inflammation was slightly higher at HD (12/20) compared with control (8/19); but this was also seen in liver for HDM (16/20) compared with controls (12/19). A single HDM had (moderate, bilateral) tubular degeneration in testes and (moderate, bilateral) luminal cellular debris in epididymides, but no findings in prostate. There were no findings in pituitaries (or adrenals) of HDF.

Toxicokinetics: conducted during the 4<sup>th</sup> month of the study (at day 102), samples were drawn at 0.5, 1, 2, 4, 10, and 24 hours after dosing from 3 TK rats/sex/group/time point, with each rat sampled twice. AUCs (see table, below) were greater for females, especially

at LD and MD; and increased with increasing dose. At the HD of 300 mg/kg (the NOAEL, based on slightly decreased body weights in males), AUCs were 56 µg/hr/ml for males and 77 µg.hr/ml for females.

**Table 12. Systemic exposures to desvenlafaxine after 102 days of dosing at 30, 100, and 300 mg/kg by oral gavage to rats. [Sponsor's table, excerpted directly from page 32 of study report.]**

MEAN (±SE) ODV PHARMACOKINETIC PARAMETERS						
Dosage (mg/kg/day)	Sex	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (ng•hr/mL)	t <sub>1/2</sub> <sup>a</sup> (hr)	AUC/Dose
30	M	892±254	0.5	3364±384	3.0	112±13
30	F	1619±130	1.0	6441±300	3.4	215±10 <sup>b</sup>
100	M	2060±217	2.0	11238±695	ND	112±7
100	F	3579±241	1.0	25568±2350	3.4	256±24 <sup>b</sup>
300	M	6675±1067	0.5	56409±6428	3.3	188±21 <sup>c</sup>
300	F	8234±1472	0.5	76860±6433	6.1	256±21 <sup>b</sup>

a: Determined from the mean concentration-time profiles  
b: Significantly higher than the corresponding value in males  
c: Significantly higher than the corresponding value at both the lower dosages  
ND: Not determined due to insufficient data in the terminal phase

### 2.6.6.3.2 Repeat-dose toxicity in dogs

#### 2.6.6.3.2.1 Subacute and subchronic exposures in dogs:

The Sponsor has provided several repeated-dose studies in dogs of 1 week to 3 months duration, administering desvenlafaxine orally in 3 formulations: capsules containing drug substance, SR tablets like the clinical formulation, and as a suspension in 0.25% polysorbate 80 + 0.5% methylcellulose. The findings in these studies are summarized in the table, below. The only limiting toxicity appeared to be convulsions and/or death, with NOELs for these findings of 100 mg/kg in 2 3-month studies using the suspension formulation; and a NOEL for these findings of 200 mg/kg in a 3-month study using the SR tablets. [The chronic study in dogs was of 9-month duration and desvenlafaxine was administered by oral gavage.]

**Table 13. Comparison of oral doses, systemic exposures (at NOAEL), and toxicities in dog studies (NDA 21-992). [Compiled from information for each study, as summarized below.]**

STUDY	FORM	DURATION	DOSES (mg/kg)	NOAEL (mg/kg)	C <sub>max</sub> ug/ml M/F	AUC ug.hr/ml	LIMITING TOXICITY?
GTR-15148 (~8-month old dogs)	Powder in capsules	7 days	50, 150, 250	250	n/d	n/d	(Mydriasis; surmountable ↓food consumption)
RPT-58721 (25-67 month old dogs)	Tablets in capsules	7 days	200, 400	400	n/d	n/d	(Surmountable ↓food consumption; ↑ALT/ALP in 1/1 HDF)
GTR-16363 (15-35)	Powder in capsules	1 month	15, 75, 175	175	n/d	n/d	(Mydriasis)

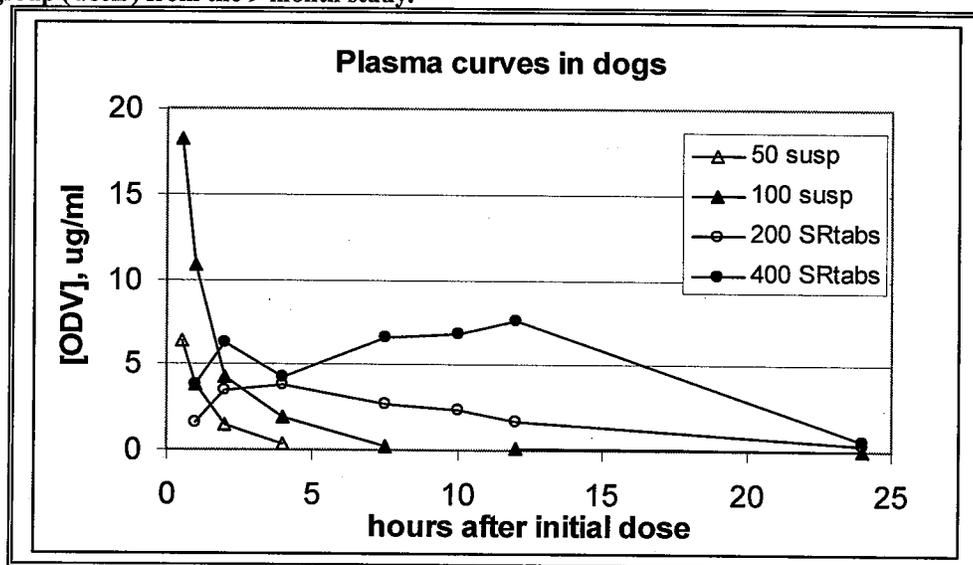
STUDY	FORM	DURATION	DOSES (mg/kg)	NOAEL (mg/kg)	Cmax ug/ml M/F	AUC ug.hr/ml	LIMITING TOXICITY?
month old dogs)							
GTR-17194 (15-20 month old dogs)	Suspension in capsules (450 mg/ml)	3 months	100, 200, 300	100	n/d	n/d	Death of 1/3 HDF at wk 9 (↑ALT/AST/LDH at wk 6, normal at wk 7; no liver findings); <b>convulsions</b> 1/3 MDF (wk12), at least 1/3 HDM (≥wk 1), at least 1/3 HDF (≥wk 5).
RPT-57597 (7-month old dogs)	Suspension (≤100 mg/ml)	13 weeks	100, 300, 500	100	8.5/11	22/25	<b>Convulsions</b> after 1 <sup>st</sup> MD and HD: doses discontinued. CNS signs at LD diminished after ~1 wk.
RPT-59762 (7-8 month old dogs)	Tablets in capsules	13 weeks	200, 400	200	5.2/4.2	37/27	1 grand mal <b>convulsion</b> in 1/3 HDM (day 3); ↑ALT/ALP in 1/1 HDM (day 7, only; no liver findings).
RPT-49456 (6-8 month old dogs)	Suspension	9 months	5, 15, 50	50	6.5/7.3	16/15	None (HD)

Convulsions occurred approximately 0.5- 1 hr after single doses of desvenlafaxine that produced plasma concentrations  $\geq$  ~30  $\mu$ g/ml (2/2 at 500 mg/kg; 2/6 at 300 mg/kg), but not at  $\leq$  ~20  $\mu$ g/ml (0/6 at 100 mg/kg) in a 13-week (oral suspension) gavage study (RPT=57597). In a 13-week study using SR tablets (in capsules), the HD of 400 mg/kg did not produce convulsions on the first day of dosing and the highest plasma concentration measured was ~10  $\mu$ g/ml (and ~13  $\mu$ g/ml on day 91); however, 1 dog at this dose had a single grand mal seizure on day 3 of dosing. At the lower dose of 200 mg/kg as SR tablets, the highest plasma concentration measured on 1 (or 91) was ~6  $\mu$ g/ml and no seizures were observed throughout the study.

Based on this information from single dose exposures in the 13-week studies, it seems that convulsions would limit the high dose, particularly for a (gavage) suspension formulation. Dosing for a chronic study in dogs would be limited to a HD of less than 300 mg/kg based on convulsions (and other CNS effects) observed after single doses in the 13-week study; a dose of 100 mg/kg for a chronic study would seem reasonable, as it was considered a NOAEL in the 13-week study and is only 1/3 the dose (300 mg/kg) where 2/6 of the dogs had convulsions and 1/2 the dose where 1 dog died after 9 weeks of dosing in another 3-month study.

It is not clear that a limiting dose was established using SR tablets (in capsules); at 400 mg/kg, the highest dose tested for up to 13 weeks, only a single convulsion (on day 3) was seen in 1/6 dogs and there were no other limiting toxicities. [The Sponsor considered the NOAEL to be 200 mg/kg based on this single seizure at 400 mg/kg in the 13-week study.] Consequently, the dose of 400 mg/kg (or even a higher dose) could be considered appropriate for a chronic (9-month) study using SR tablets. No doses higher than 400 mg/kg in this formulation appear to have been tested in dogs.

Figure 5. Plasma curves for desvenlafaxine after oral administration at doses of 50 mg/kg (9-month study) and 100 mg/kg (13-week study) as a suspension and 200 and 400 mg/kg as SR tablets (13-week study). Values represent averages for 6 dogs per group (3/sex) from the 13-week studies and 8 dogs per group (4/sex) from the 9-month study.



In conclusion, based on studies of up to 3 months' duration, the MTD for oral gavage dosing is 100 mg/kg and that for SR tablets is 200 mg/kg. The chronic (9-month) study in dogs was conducted with administration by oral gavage up to a high dose of 50 mg/kg, which is half the MTD determined in the shorter studies. It should be noted that higher systemic exposures could have been achieved using SR tablets at the MTD of 200 mg/kg determined in 3-month study (see table, below). However, the 50 mg/kg dose used in the chronic dog study covers the C<sub>max</sub> (7-fold) and AUC (1.6-fold) for humans at the MRHD of 200 mg/day.

Table 14. Systemic (AUC) exposures to desvenlafaxine after oral administration at doses of 50 mg/kg (9-month study) and 100 mg/kg (13-week study) as a suspension and 200 and 400 mg/kg as SR tablets (13-week study). Values represent averages for 6 dogs per group (3/sex) from the 13-week studies and 8 dogs per group (4/sex) from the 9-month study.

STUDY	FORMULATION	DOSE mg/kg	C <sub>max</sub> ug/ml	C <sub>max</sub> vs MRHD	AUC µg.h/ml	AUC vs MRHD
Pooled human data <sup>1</sup>	SR tablets	200 mg/day	0.5		10	
RPT-49456 (9-mo)	Suspension	50	7	14X	16	1.6X
RPT-57597 (13-wk)	Suspension	100	10	20X	24	2.4X
RPT-59762 (13-wk)	SR tablets	200	5	10X	32	3.2X
RPT-59762 (13-wk)	SR tablets	400	10	50X	77	7.7X

<sup>1</sup>: In people administered desvenlafaxine at the maximum recommended human dose (MRHD) of 200 mg, the systemic exposure based on AUC was approximately 10 µg.hr/ml and based on C<sub>max</sub> was approximately 0.5 µg/ml (extrapolated from pooled human data from single and repeated dosing with DVS SR in healthy subjects who participated in Phase 1 studies, normalized to 100 mg, in Table 9, page 22 of Dr. Kofi Kumi's Clinical Pharmacology and Biopharmaceutics Review for this NDA, dated 10/26/06).

**Summaries of the subacute/subchronic studies in dogs:**

1-week oral (powder in capsules) dog DRF study (GTR-15148; first day of dosing 10/6/87; non-GLP; 15 pages): (non-naive) Beagles (~8 months old), 3/sex, 1/sex/dose, WY-45,233 orally in capsules at 50, 150, or 250 mg/kg/day (based on weight of fumarate salt) for 7 days and observed for 3 more days.

Results: clinical signs included mydriasis, no pupil response, and slow pupil response to light at all doses, diarrhea/loose feces at  $\geq 150$  mg/kg; "no toxic limiting effects." Decreased food consumption and body weights were not considered dose-limiting as they were improved by feeding wet food. The HD of 250 mg/kg was considered a MFD, because it required 2-3 capsules per dog per dose. Doses of 25, 125, and 250 mg/kg were recommended for the future 1-month study.

1-week oral (tablets in capsules) dog study (RPT-58721; conducted at \_\_\_\_\_ first day of dosing 3/29/05; non-GLP; 83 pages): adult Beagles (25-67 months old), 2/sex, 1/sex/dose, DVS-233 orally at 200, or 400 mg/kg/day (as DVS-233 200mg SR FCT \_\_\_\_\_ tablets packed into gelatin capsules) for 7 days.

Results: clinical signs included: at  $\geq 200$  mg/kg, salivation, decrease/absent feces; at 400 mg/kg, head shaking, tremors, and dilated pupils; but "were not considered dose limiting based on the low frequency of occurrence and/or low severity." Decreased food consumption and body weights were not considered dose-limiting as they were improved by feeding wet food; after 7 days of dosing, all dogs had lost 7-15% of their starting weights, but "there was an indication that body weight was stabilizing following supplementation of the diet with canned food from day 4 to day 8. Clinical chemistry: increased ALT (1093%) and ALP (348%) compared with pretest in the HDF, which was not considered limiting based on lack of histopathology confirmation and only 1 dog affected. The MTD for longer studies was considered to be 400 mg/kg, because the decreases in body weights and food consumption at that dose could be tolerated with food supplementation.

1-month oral (powder in capsules) dog study (GTR-16363; first day of dosing 3/2/88; GLP (presumably, but no statement)/QA; 237 pages): Beagles (15-35 months old), 3/sex/dose, WY-45,233 orally in capsules at 0, 15, 75, or 175 mg/kg/day (based on weight of fumarate salt) for 28 or 29 days.

Results: apparently the only drug-related findings were dose-related mydriasis and slightly decreased glucose at weeks 2 and 4 in HDM. (Plasma levels only determined 24 hr after final dose and only detectable in 2/3 MDM (0/3 MDF) and 3/3 HDM and 2/3 HDF.)

3-month oral (suspension in capsules) dog study (GTR-17194; first day of dosing 3/2/88; GLP (presumably); 256 pages): Beagles (15-20 months old), 3/sex/dose, WY-45,233 orally as a suspension in gelatin capsules at 0, 100, 200, and 300 mg/kg/day (based on weight of active moiety) for 13 weeks.

Results: apparently the only drug-related findings were: 1 HDF (#24, 300 mg/kg) who died during week 9, with CNS signs (chorea-like movements and stereotypy) and body

weight loss; clonic or tonic convulsions (noted as usually occurring during or immediately after involving handling and noise, such as at weighing detailed physical exams, etc) at HD (individual dogs not identified, just number of dogs/sex/dose with sign each week; no more than 1 dog/sex showed clonic/tonic convulsions in any week so it is unclear how many of each sex actually had convulsions; earliest incidences were week 1 for 1 HDM and week 5 for 1 HDF) and in 1 MDF (#17 in week 12, 200 mg/kg); slight decrease in body weight in HDF; salivation before and after dosing and conditioned salivation at other times at MD and HD; emesis at all doses; mydriasis at all doses, particularly during weeks 1-2; slightly decreased MCV in some males at all doses and females at MD and HD. NOEL=100 mg/kg, with only minor or sporadic effects at 200 mg/kg. (Plasma levels determined at 2, 4, and 24 hr after dosing during week 13; AUC/Cmax not determined.) [HDF#24 had markedly elevated ALT, AST, LDH values in week 6, which were within normal range when re-tested in week 7; died with clinical signs and decreased body weight in week 9, with no macro or microscopic pathology, liver was among tissues listed as normal, no PK was done on this dog.]

13-week oral (suspension) dog study (RPT-57597; conducted at \_\_\_\_\_  
\_\_\_\_\_ ; first day of dosing 3/9/05; GLP/QA; 425 pages): Beagles (7 months old), 3/sex/dose, except 1/sex at HD, DVS-233 orally by gavage at 0, 100, 300, and 500 mg/kg/day (based on weight of active moiety; suspended in 0.25% polysorbate 80 + 0.5% methylcellulose in deionized water; 5 ml/kg → ≤100 mg/ml) for up to 13 weeks.

Results: MD and HD groups (≥300 mg/kg) were discontinued after the first dose, due to the nature and severity of the clinical signs: convulsions (1/3 MDM and 1/3 MDF at ~30-50 µg/ml; HDM and HDF at ~50-65 µg/ml), agitated behavior, and/or aggression; rigid limbs, tremors, dilated pupils, abnormal gait and decreased activity and/or increased respiratory rate still present up to 24 hr. [Convulsions were not noted for LD dogs on day 1, <30 µg/ml, or anytime during the study.] At LD of 100 mg/kg, signs included limb rigidity, abnormal posture and gait, decreased activity, chewing action, head shaking, tremors, uncoordinated movement, dilated pupils, salivation, and deep breathing in both sexes; and excessive licking, hunched posture, increased respiration rate and emesis in females; these signs occurred mainly in week 1 and decreased in severity with longer dosing; after the first week only limb rigidity, abnormal posture and gait, decreased activity, chewing action, dilated pupils, emesis and salivation, which generally decreased in frequency and incidence. No other effects were seen at the LD; consequently, "the clinical signs were not considered adverse at 100 mg/kg/day" and this dose was considered the NOAEL. On day 78, mean AUC was 21.5 µg.hr/ml for LDM and 24.9 µg.hr/ml for LDF; mean Cmax was 8.5 µg/ml for LDM and 11 µg/ml for LDF.

3-month oral (tablets in capsules) dog study (RPT-59762; first day of dosing 5/11/05; conducted at Wyeth Research, Drug Safety, Chazy, NY; GLP/QA; 457 pages):  
Methods: Beagles (7-8 months old), 3/sex/dose, DVS-233 orally at 0, 200, or 400 mg/kg/day (as DVS-233 200mg SR film-coated tablets packed into gelatin capsules) for 91/92 days.

**Results:** CNS signs: ataxia, decreased motor activity, and tremors primarily on days 2 and/or 3 in 1/3 LDM, 2/3 LDF and 3/3/sex at HD (mostly between 3 and 8 hr after dosing); a single (brief) grand mal convulsion in 1 HDM (#15) on day 3; mydriasis in all dosed dogs throughout the study; lacrimation in 8/12 in one or both eyes and 11/12 had pink or red discoloration of the eye(s), which subsided by the end of week 2, only 1 HDM (#13) required artificial tears; decreased food consumption and body weights that normalized by week 5, with canned food supplementation;  $\uparrow$ ALT (2207% of pretest value) and ALP (152%) in 1 HDM at day 7 (but not at weeks 4, 8, or 13), without histopathologic findings in liver.

**Conclusions:** NOAEL= LD of 200 mg/kg, based on grand mal seizure in a male at 400 mg/kg. On day 91, mean AUC was 37  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for LDM and 27  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for LDF; mean  $C_{\text{max}}$  was 5.2  $\mu\text{g}/\text{ml}$  for LDM and 4.2  $\mu\text{g}/\text{ml}$  for LDF. On day 91, mean AUC was 91  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for HDM and 63  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for HDF; mean  $C_{\text{max}}$  was 12  $\mu\text{g}/\text{ml}$  for HDM and 8  $\mu\text{g}/\text{ml}$  for HDF. [No plasma concentration was greater than 15  $\mu\text{g}/\text{ml}$  at either dose or either day; measured at 1, 2, 4, 7, 10, 12, 24 hr after dosing.]

#### 2.6.6.3.2.2 Chronic exposure in dogs (9-month study):

**Study title:** DVS-233: THIRTY-NINE WEEK ORAL (GAVAGE) TOXICITY STUDY IN DOGS (WYETH RESEARCH PROTOCOL NO. 01\_0482).

##### Key study findings:

- Doses: 0, 5, 15, and 50 mg/kg/day by oral gavage for 13 weeks.
- Drug-related findings: limited to decreased activity at HD on day 1; reddened abdomens at MD and HD and reddened ears/muzzle at HD throughout the study, with frequency and severity generally diminished after 1 month.
- NOAEL: HD of 50 mg/kg; systemic exposures (after 38 weeks): mean AUC = 16.0  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for HDM and 15.0  $\mu\text{g}\cdot\text{hr}/\text{ml}$  for HDF; mean  $C_{\text{max}}$  = 6.5  $\mu\text{g}/\text{ml}$  for HDM and 7.3  $\mu\text{g}/\text{ml}$  for HDF.

**Study no.:** RPT-49456.

**Volume #, and page #:** electronic submission, 274 pages.

**Conducting laboratory and location:** \_\_\_\_\_

**Date of study initiation:** first day of dosing 3/18/02.

**GLP compliance:** yes, see pages 4-6.

**QA report:** yes, see page 7.

**Drug, lot #, and % purity:** DVS-233 (WY-45233 succinate monohydrate, \_\_\_\_\_)  
lot/batch # RB2608; active moiety = \_\_\_\_\_ "use at" value = \_\_\_\_\_ total impurities =  
none detected, with report limit of \_\_\_\_\_ (see Investigational Raw Material Record  
Form, pages 260-263).

##### Methods

**Doses:** 0, 5, 15, and 50 mg/kg/day (doses for the active moiety, by oral gavage for 39 weeks).

Species/strain: male and female Beagle dogs (

Number/sex/group: 4/sex/dose.

Route, formulation, volume, and infusion rate: oral gavage in 0.25% polysorbate 80 + 0.5% methylcellulose (4000 cps) in deionized water (5 ml/kg); vehicle and drug formulations prepared fresh weekly and stored refrigerated and protected from light; pH of all drug and control solutions and concentrations of all drug solutions assessed weekly for 1 month, then every 3 weeks to end of study: pH of control was ~6.60-7.88, pH of drug formulations was ~4.65-4.97; drug formulations were assessed for drug content and found to range from ~93-104% of nominal concentration; homogeneity was analyzed for LD and HD solutions from the 1<sup>st</sup> preparation (approximately 2 and 3 weeks after preparation), and samples from top, middle and bottom of the suspensions ranged from 93-105% (previous tests of this formulation had also shown homogeneity).

Satellite groups used for toxicokinetics or recovery:

Age: 6 and 8 months of age at the initiation of dosing.

Weight: 5.8 to 8.7 kg (on the day of group assignment, study day -4).

Housing: individually, in stainless steel cages; tap water ad lib; acclimated to feeding for 2-4 hr feeding interval, daily in late morning or early afternoon, no earlier than 1 hr after dosing; dry diet

, supplemented with canned or dry food ( , when required to treat diarrhea or to stimulate appetite and increase body weight (LDMs 202, 204); with exercise at least once per week, acclimatized for 18 days prior to initiation of dosing; assigned to treatment groups by sex and body weight on day -4.

Sampling times:

Unique study design or methodology (if any): standard study.

## Results

Mortality: no premature deaths; all dogs survived to scheduled termination.

Clinical signs: decreased activity at HD on day 1 only (4/4 HDM, 1/4 HDF); slightly reddened abdomens post-dosing at MD (8/8) and HD (8/8), continued throughout the study, but with decreased incidence after 1 month; sporadic occurrence of reddened ears (1/4 HDF) or muzzle (1/4 HDM) at HD; occasional emesis, but not dose-related (occurred in all dogs).

Body weights: (weekly) no treatment-related effects on body weights: group means for males ranged from 7.8-7.9 kg on day 1 of dosing and were 10.0 (control males), 9.6 (LDM), 11.0 (MDM), and 11.3 (HDM) kg on day 267, near the end of dosing; group means for females ranged from 6.4-6.5 kg for females on day 1 and were 8.2 (control females), 8.2 (LDM), 8.8 (MDM), and 8.0 (HDM) kg on day 267, near the end of dosing.

Food consumption: (assessed daily, by visual inspection) no treatment-related effects on food consumption. [Two LDM received supplemental feeding: LDM 202, from day 144-273, presumably to treat diarrhea that started on day 95 and continued through day 274, but with no decrease in body weight or food consumption apparent; LDM 204, from day 166-228, presumably to treat emesis and diarrhea, but with no decrease in body weight or food consumption apparent.]

Ophthalmoscopy: (at days -19 and 270; individual results provided) no treatment-related effects on eye findings: in males, 1 LDM and 1 MDM had mild unilateral epiphora at the end of dosing that wasn't seen pre-dosing; 2 HDF that had only mild epiphora at pre-dosing, had mild epiphora at the end of dosing, with small, translucent opacities on both corneas in one HDF and persistent papillary membrane across the upper portion of the iris (right eye) in the other HDF, both findings probably resulting from the pre-existing epiphora.

EKG: (twice pre-test and during weeks 26 and 39 at 1-2 hr after dosing; EKGs were evaluated by \_\_\_\_\_ DVM, PhD, DACVIM (cardiology); blood pressure and heart rate, by a veterinary physiologist; individual data not provided; group mean data for HR and BP provided) no treatment-related effects on heart rate or blood pressure; and no treatment-related effects on EKGs; quoting the cardiologist's review (in its entirety), "All ECG's are within limits of normal. One dog (animal 351 week 26) with a slow heart rate had occasional junctional escape beats, and many had changes in configurations of component deflections, however, these do not appear to be related to the test article."

Hematology: (on days -21, -14, 88, 178, 274; group mean and individual data provided) no treatment-related effects on hematology: the few statistically significant differences from controls were slight in magnitude and not dose-related. No treatment-related effects on coagulation parameters (PT, APTT, fibrinogen).

Clinical chemistry: (on days -21, -14, 88, 178, 274; ALP, AST, ALT, GGT, total bilirubin, direct bilirubin, total protein, albumin, glucose, BUN, creatinine, Ca, Ph, TAGs, cholesterol, Na, K, Cl, globulin, A/G ratio, indirect bilirubin, amylase, lipase, thyroxine, BUN/creatinine ratio; group mean and individual data provided) no treatment-related effects on clinical chemistry: the few statistically significant differences from controls were slight in magnitude and not dose-related.

Urinalysis: (on days -14/13 and 274; group mean and individual data provided) no treatment-related effects on urinalysis parameters ().

Gross pathology: no treatment-related gross findings.

Organ weights: no treatment-related effects on organ weights: heart weights (absolute and normalized to body weight or brain) were increased ~20% in LDF, but not at higher doses or in males.

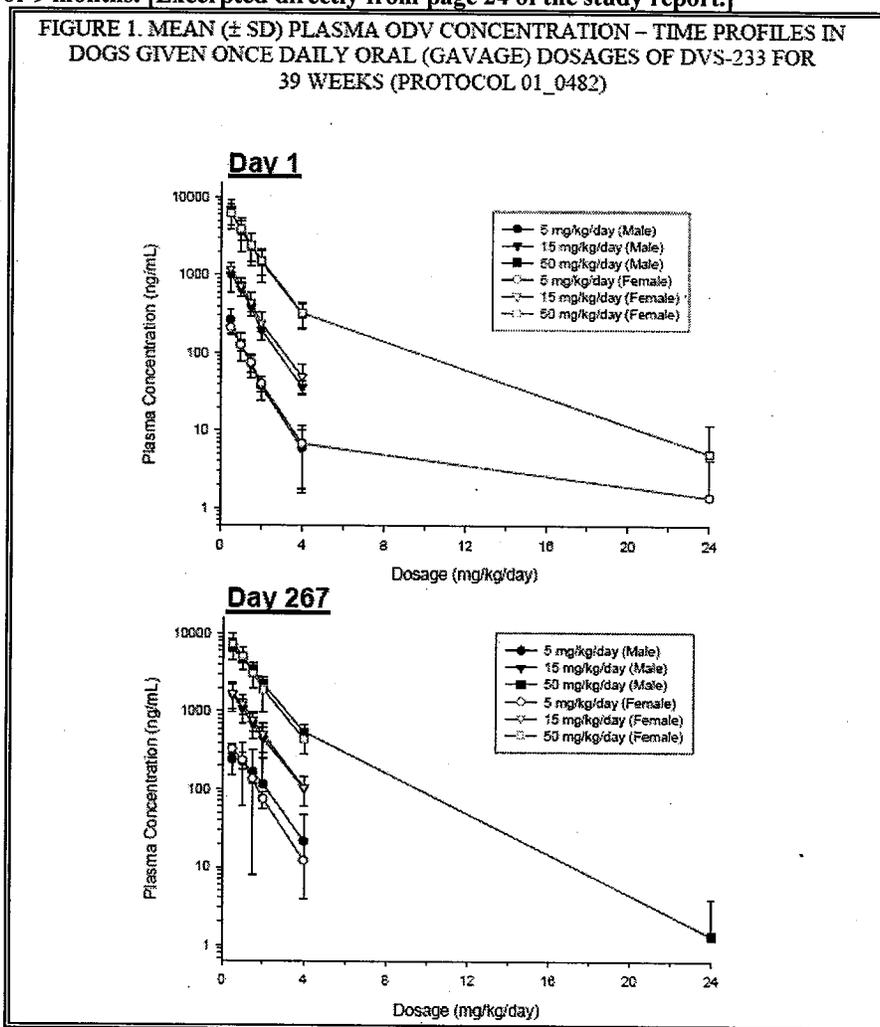
Histopathology: Adequate Battery:            yes.

Peer review: yes, see page 258 (performed by a Wyeth Research pathologist on all tissues from control male 104, control female 153, HDMs 402 and 404, and HDF 452 and 453).

(group and individual data provided) no treatment-related microscopic findings; the prolonged diarrhea in LDM 202 was attributed to mild chronic ileal inflammation.

Toxicokinetics: (on day 1 and during week 39; on blood samples drawn at 0, 0.5, 1, 1.5, 2, 4, and 24 hr after dosing; provided in report RPT-49108): Although the no samples were analyzed between 4 and 24 hr, the levels at 4 hr were less than 1/10 those at the C<sub>max</sub> at all doses (see figure, below), so AUC calculations (see table, below) may be reasonably accurate.

Figure 6. Sponsor's figure showing plasma curves for desvenlafaxine in male and female dogs treated for 1 day or 9 months. [Excerpted directly from page 24 of the study report.]



**Table 15. Sponsor's summary table of PK parameters in male and female dogs treated with desvenlafaxine for 1 day or 9 months. [Excerpted directly from page 25 of the study report.]**

TABLE 13. SUMMARY OF MEAN ( $\pm$ SD) ODV PHARMACOKINETICS IN DOGS FOLLOWING ONCE DAILY ORAL (GAVAGE) ADMINISTRATION OF DVS-233 FOR 39 WEEKS (PROTOCOL 01_0482)							
Day	Dosage (mg/kg/day)	Sex	C <sub>max</sub> (ng/mL)	t <sub>max</sub> (hr)	AUC <sub>0-24</sub> (ng·hr/mL)	AUC <sup>a</sup> /Dose	R
1	5	M	265 $\pm$ 90	0.5 $\pm$ 0.0	343 $\pm$ 142	ND	NA
1	5	F	211 $\pm$ 41	0.5 $\pm$ 0.0	342 $\pm$ 74	ND	NA
1	15	M	1018 $\pm$ 376	0.6 $\pm$ 0.3	1665 $\pm$ 258	ND	NA
1	15	F	1179 $\pm$ 252	0.5 $\pm$ 0.0	2004 $\pm$ 593	ND	NA
1	50	M	6601 $\pm$ 2757	0.5 $\pm$ 0.0	11516 $\pm$ 4525	ND	NA
1	50	F	6179 $\pm$ 1767	0.5 $\pm$ 0.0	11720 $\pm$ 3568	ND	NA
267	5	M	292 $\pm$ 143	0.6 $\pm$ 0.3	695 $\pm$ 597	139 $\pm$ 119	1.81 $\pm$ 0.94
267	5	F	327 $\pm$ 45	0.5 $\pm$ 0.0	573 $\pm$ 153	115 $\pm$ 31	1.68 $\pm$ 0.34
267	15	M	1622 $\pm$ 646	0.5 $\pm$ 0.0	3382 $\pm$ 1292	225 $\pm$ 86	2.01 $\pm$ 0.62
267	15	F	1684 $\pm$ 634	0.5 $\pm$ 0.0	3620 $\pm$ 1284	241 $\pm$ 86	1.80 $\pm$ 0.18
267	50	M	6521 $\pm$ 1891	0.6 $\pm$ 0.3	16039 $\pm$ 1505	321 $\pm$ 30	1.56 $\pm$ 0.61
267	50	F	7329 $\pm$ 2735	0.6 $\pm$ 0.3	14982 $\pm$ 4749	300 $\pm$ 95	1.32 $\pm$ 0.44

a: AUC<sub>0-∞</sub> for Day 1; AUC<sub>0-24</sub> for Day 267  
 NA: Not Applicable  
 ND: Not Determined  
 R: AUC<sub>0-24</sub> (day 267)/AUC<sub>0-24</sub> (day 1)  
 Note: AUC<sub>0-∞</sub> values were not determined.

**2.6.6.3.3 Repeat-dose toxicity in mice**

The subchronic (2 weeks to 3 months) oral gavage studies in mice were used as the basis for dose-selection for the 2-year mouse carcinogenicity study and have not been reviewed for this NDA.

Studies using dietary administration of desvenlafaxine to mice have not been reviewed for this NDA.

#### 2.6.6.4 Genetic toxicology

Several genetic toxicity tests for desvenlafaxine have already been reviewed under NDA 20-151 for venlafaxine HCl immediate-release tablets (Effexor) and/or NDA 20-699 for venlafaxine HCl extended-release capsules (Effexor XR). In the current review, these tests have been reassessed.

##### 2.6.6.4.1 Ames test

**Ames test summary:** Between the 2 studies submitted here, all the strains currently required for an adequate test were assessed; there was no evidence of mutagenicity in any strain (with or without metabolic activation) to the high concentrations of 3330 or 5000 µg/plate; some cytotoxicity was noted at 5000 µg/plate in several strains. The current labeling for venlafaxine, “Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria...” agrees with this conclusion.

Required strains: TA98 and TA 100 and TA 1535; TA1537 or TA97 or TA97a; TA102 or E. coli WP2uvrA ±pKM10 [ICH Guidance S2A (1996) and CFSAN Redbook (2000)].

**Study id: GTR-14871:** (1987; Ayerst Labs; 25-page report; previously reviewed under NDA 20-151 and considered negative and included in labeling as “Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria...”): **Methods:** plate-incorporation method (48-hr incubation; counted by Colony Counter); in TA 97a, 98, 100, 102, 104 (but **lacking TA1535**; required strains underlined); concentrations of WY-45,333 (ethanedioate salt) in DMSO (0.1 ml/plate): 0.5, 5, 50, 500, and 5000 µg/plate; ± Aroclor 1254-induced S-9 (43 mg protein/ml; 0.08 ml added per ml mixture); duplicate experiments, each with 3 plates for spontaneous revertants and 2 plates for each other condition/concentration (3 positions were counted for each plate); positive controls linked to strain (same ±S9): ICR-191 for TA97a (mutagenic -S9, but not much +S9), sodium azide for TA100 (mutagenic -S9, but not +S9), cumene hydroperoxide for TA102 (mutagenic ±S9), methylglyoxal for TA104 (mutagenic ±S9), 2AF (requires metabolic activation) for TA98 (mutagenic +S9, but not much -S9); their rationale was that 2AF (in TA98) was a test for S9 activity. **Results:** They noted drug was “partially inhibitory to strains TA98, TA100, TA102, and TA104 at 5000 µg/plate with and without metabolic activation.” Values for individual plates were not provided, but mean values and SD were provided for each experiment and for the 2 experiments combined. There was **no indication of mutagenicity at any concentrations tested** (although the report said this was true at noninhibitory concentrations.) [This study appears to have been conducted adequately, although there was no GLP statement; there is a QA statement for inspection of the final report on 10/8/87; an amendment to the protocol states that the study was completed on September 14, 1987.] This study was reviewed in support of NDA 20-151 (for venlafaxine) and considered negative (and adequate) at that time.

**Study id: GTR-23717:** (1993; conducted at \_\_\_\_\_ GLP and QA; 50-page report): **Methods:** plate-incorporation method (48-hr incubation; counted manually); in TA 98, 100, 1535, 1537, and 1538, which is like TA 98, (but **missing a strain for TAA base pair substitution, such as TA102 or E. coli WP2uvrA**; required strains underlined); concentrations of WY45333 (free base; lot C13913) in DMSO (0.1 ml/plate; stock solution at 20 mg/ml, but 33 mg/ml with sonication): 66.7, 99.9, 333, 667, 999, and 3330 µg/plate (based on preliminary toxicity testing in TA100, with no cytotoxicity from 3.3 up to 2000 µg/plate, ±S9); ± Aroclor 1254-induced S-9 (43 mg protein/ml; 0.10 ml added per ml S9 mixture; ±500 ul S9 mix + 100 ul drug/vehicle + 100 ul tester strain per plate was added to 2 or 2.5 ml top agar); positive controls chosen for each stain and activation condition: +S9, all strains were tested with 2-AA, -S9, strains TA98 and TA1538 with 2-nitrofluorene, TA100 and TA1535 with sodium azide, and TA1537 with ICR-191; triplicate plates for each condition/dose; independent replicate study at same concentrations; bacterial lawn was evaluated for estimate of cytotoxicity. **Results:** no evidence of cytotoxicity reported for any strain under any condition; **no evidence of mutagenicity for WY45333 in any strain**, with or without metabolic activation; positive controls gave strong signals.

#### 2.6.6.4.2 In vitro chromosomal aberration test

**In vitro chromosomal aberration summary:** desvenlafaxine was negative for in vitro clastogenicity (chromosomal aberrations) in CHO cells under the conditions tested.

**Study id: GTR-15984;** report no. 15984; study no. 61097-05; protocol no. 88521: (1988; conducted by \_\_\_\_\_ apparently GLP, based on a statement in the text under "Objective of the Study" (see page 8), but no signed statement provided; QA, see page 6; 33-page report; previously reviewed under NDA 20-151 and considered negative and included in labeling as "ODV was not clastogenic in the in vitro Chinese hamster ovary cell chromosomal aberration assay...").

**Methods:** in vitro test in CHO cells; concentrations of WY-45,333C (it is not clear which salt this is, although the MW was listed as \_\_\_\_\_ and solubility in DMSO = ~357 mg/ml was noted; lot # 9529-96E) in DMSO (0.1 ml/plate; stock solution at 20 mg/ml, but 33 mg/ml with sonication): 1, 3, 10, 30, 100, 300, 1000, 3000 µg/ml, without activation; 0.83, 2.5, 8.3, 25, 83, 250, 833, 2500 µg/ml and 1, 3, 10, 30, 100, 300, 1000, 3000 µg/ml for 10- and 20-hr assays, respectively, with activation; stock solutions of 250 and 300 mg/ml were appropriately diluted with DMSO, suggesting 1/100 dilutions (of drug and DMSO) into cell medium; apparently the high concentrations of 3 and 2.5 µg/ml were based on solubility in DMSO (noted as ~357 mg/ml) and a maximum DMSO concentration of 1% in the cell culture medium; ± Aroclor 1254-induced S-9 (20 ul per ml in each flask, but protein concentration not provided); drug-exposure and sampling times were 10 and 20 hrs (in serum-containing medium) for non-activated samples; drug-exposure time was 2 hrs (in serum-free medium), followed by 8 or 18 hrs (for growth in serum-containing medium) for activated conditions; vinblastine (at final concentration of

0.26 µg/ml) was added approximately 2 hr before harvesting; positive controls were mitomycin C (0.3 µg/ml) without activation and cyclophosphamide (50 µg/ml) with activation. Mitotic index (percentage of cells in metaphase) was determined from at least 500 total cells (presumably per flask). Metaphase cells were analyzed microscopically using a 100X oil objective; controls and test article samples were analyzed from duplicate flasks, with at least 100 metaphase cells per flask from at least 3 selected test article concentrations and negative controls; at least 25 cells were analyzed from positive controls; the following types of aberrations were counted/calculated: chromatid gaps, chromatid breaks, chromosome gaps, chromosome breaks, quadriradials, triradials, interstitial deletions, dicentric chromosomes, cells with at least one pulverized chromosome, complex rearrangements, rings, double minute chromosomes, cells with >10 aberrations, number of aberrations per cell (with and without gaps), number/percentage of cells with aberrations (excluding gaps); apparently polyploidy and endoreplication were not recorded. The negative control frequency was expected to range from 1 to 5% of cells (with aberrations excluding gaps); a test sample was considered negative if less than 9% aberrant cells were observed.

**Results:** There was **no indication of clastogenicity with desvenlafaxine under the conditions of the assay:** none of the treatments with desvenlafaxine that were analyzed had more than 3.5% of mitotic cells with aberrations (excluding gaps) and no single duplicate had more than 4% of mitotic cells with aberrations (excluding gaps). The following concentrations were analyzed for aberrations: 1) without activation, 10-hr treatment, 300, 1000, 3000 µg/ml, with mitotic index decreased 36% at 1000 and 45% at 3000 µg/ml; 2) without activation, 20-hr treatment, 100, 300, 1000 µg/ml, with mitotic index decreased 22% at 1000 and 88% at 3000 µg/ml; 3) with activation, 2-hr treatment, assessed at 10 hr, 250, 833, 2500 µg/ml, with no decreases in mitotic index; and 4) with activation, 2-hr treatment, assessed at 20 hr, 300, 1000, 3000 µg/ml, with no decreases in mitotic index. **The assays were generally valid:** negative controls were within the range of historical controls (1-5% of mitotic cells having aberrations, not including gaps); and positive controls gave robust signals (13-19-times the respective negative controls, except for mitomycin for 20 hr without activation which was 74-times the negative control value). However, the duration of exposure to desvenlafaxine in the presence of metabolic activation (i.e., 2 hr) was less than the usual duration of 3-6 hr; and there was inadequate indication of toxicity, based on decreased mitotic index, especially in the presence of metabolic activation. Nonetheless, it could be argued that the high concentrations of 2500-3000 µg/ml were maximum feasible doses, based on solubility. **Overall, the assays probably adequately tested desvenlafaxine for in vitro clastogenicity and were negative.**

#### 2.6.6.4.3 In vivo chromosomal aberration tests

The current labeling for venlafaxine includes information on clastogenic findings with desvenlafaxine in the in vivo rat study (see below). According to the Effexor (IR) tablets labeling, "There was a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m<sup>2</sup> basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg)

or 17 time (mg/m<sup>2</sup>) the human dose.” According to Effexor XR labeling, “[ODV] elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow.” However, this Reviewer does not find this study to provide compelling evidence of clastogenicity. Additionally, in the current NDA submission, the Sponsor has also provided an in vivo mouse micronucleus assay, which was valid and negative.

Study id: GTR-17770: In vivo chromosomal aberration assay in rats with WY-45,233 base. (1988/1989; conducted by \_\_\_\_\_ previously reviewed under NDA 20-151 and considered positive for male rats at the high dose).

**Methods:** WY-45,233 base (lot # C-13892; \_\_\_\_\_ pure) administered to male and female Sprague-Dawley rats (\_\_\_\_\_ 8-9 weeks old) at doses of 150, 500, and 1500 mg/kg (based on toxicity in a preliminary study at doses of 500, 1000, 2000 and 3000 mg/kg (death of 1/2 females at doses of 1000 and 3000 mg/kg and bloody mouth and/or stomach in 1/2 males at 2000 mg/kg and 2/2 males at 3000 mg/kg; 24 hr test) and LD50 data supplied by the Sponsor: oral LD50s were calculated as 3158 mg/kg and 3533 mg/kg for males and females, respectively, with deaths occurring within 24 hr of dosing); an aqueous solution of 0.25% Tween 80 + 0.5% carboxymethyl cellulose served as the vehicle and the negative control; cyclophosphamide (30 mg/kg) served as the positive control; all treatments by oral gavage at 10 ml/kg, with food withheld for 2-3 hr before and after dosing; rats (6/sex) at each dose were sacrificed at 6, 18, and 24 hr after dosing, except for the positive control which was for 24-hr treatment only; metaphase cells were analyzed for chromatid gaps, chromatid breaks, chromosome gaps, chromosome breaks, quadriradials, triradials, interstitial deletions, dicentric chromosomes, double minute chromosome, rings, complex rearrangements, rings, double minute chromosomes, cells with at least one pulverized chromosome, cells with >10 aberrations, number of aberrations per cell (with and without gaps), number/percentage of cells with aberrations (excluding gaps); % mitotic index (% of total cells that were in metaphase) was calculated for each rat, based on at least 500 total cells.

**Results:** Most rats survived to scheduled sacrifice, with premature deaths of females at 1500 mg/kg (only 2/6 survived at the 6 hr time point and only 5/6 at the 24 hr time point). [A dose of 3000 mg/kg was included for toxicity, but was not analyzed for chromosomal aberrations: only 2/5 females at this dose survived for 24 hr, but all 5/5 males survived.] A summary of the findings (excluding gaps) is presented in the table below. Cyclophosphamide, the positive control (at 24 hr, only), gave strong signals for both mean aberrations per cell and percentage of cells with aberrations (26 and 28% of cells with aberrations in males and females, respectively); inspection of the individual rat data showed that most of the aberrations were chromatid breaks and chromosome breaks (and chromatid gaps). The negative controls gave low signals at all time points ( $\leq$  2.4% of cells with aberrations). The only condition where WY-45,233 produced a concentration-related response that was higher than the concomitant negative control was for males after 6 hr at the high dose of 1500 mg/kg (4.8% of cells with aberrations, compared with 2.4% for the negative controls); inspection of the individual rat data showed that this difference between treated and untreated groups was due to a single treated rat: the 5 control rats had 0, 0, 0, 4, 8% of cells with aberrations, the 5 males treated with 1500

mg/kg WY-45,233 for 6 hr had 0, 0, 4, 8, 12% cells with aberrations; the rat with the highest % of cells with aberrations also had the highest mean aberrations per cell; this difference could be attributed to 6 total chromatid breaks for that rat, compared with a high of 3 chromatid breaks among the controls. [It should be noted that only 2 female rats were analyzed at the high dose of 1500 mg/kg for the 6 hr point.]

**Conclusions:** The study report (Study Director, not the Sponsor) concluded that this assay was positive for male rats after 6 hr at the high dose of 1500 mg/kg, based on the increase in the percentage of aberrant cells, and judged WY-45,233 to be a possible clastogen in Sprague-Dawley rats. It is this Reviewer's opinion that this assay appears (generally) adequate and negative.

**Table 16. Summary of findings (excluding gaps) for male and female rats treated for 6, 18, or 24 hr with WY-45,233 (desvenlafaxine) or 24 hr with cyclophosphamide as a positive control. [Excerpted directly from table 17 (males) and table 16 (females) of the study report.]**

SEX	FINDINGS								
	DOSE TIME	TREATMENT	DOSE	TOTAL # ANIMALS	TOTAL # CELLS	TOTAL # ABERRATIONS	ABERRATIONS PER CELL	% CELLS WITH ABERRATIONS	
Males	6-HOUR	CNC / Tween 80	10 ml / kg	5	250	0	0.032	2.4	
		WY-45,233 Base	150 mg / kg	5	250	3	0.012	1.2	
			500	5	250	3	0.012	1.2	
			1500	5	250	14	0.056	4.8	
	18-HOUR	CNC / Tween 80	10 ml / kg	5	250	0	0.032	2.4	
		WY-45,233 Base	150 mg / kg	5	250	0	0.000	0.0	
			500	5	250	0	0.000	0.0	
			1500	5	250	0	0.000	0.0	
	24-HOUR	CNC / Tween 80	10 ml / kg	4	250	0	0.000	0.0	
		Cyclophosphamide	30 mg / kg	5	250	198	0.792	26.4	
			WY-45,233 Base	150 mg / kg	5	250	13	0.052	2.8
				500	5	250	1	0.004	0.4
		1500	5	250	0	0.000	0.0		
Females	6-HOUR	CNC / Tween 80	10 ml / kg	5	250	0	0.000	0.0	
		WY-45,233 Base	150 mg / kg	5	250	0	0.000	0.0	
			500	3	190	3	0.016	1.6	
			1500	2	236	2	0.008	0.8	
	18-HOUR	CNC / Tween 80	10 ml / kg	5	236	7	0.030	1.7	
		WY-45,233 Base	150 mg / kg	5	250	1	0.004	0.4	
			500	5	218	0	0.000	0.0	
			1500	4	243	1	0.004	0.4	
	24-HOUR	CNC / Tween 80	10 ml / kg	5	250	5	0.020	2.0	
		Cyclophosphamide	30 mg / kg	6	300	254	0.847	28.0	
			WY-45,233 Base	150 mg / kg	5	241	1	0.004	0.4
				500	5	250	2	0.008	0.8
		1500	3	200	4	0.020	1.5		

Study id: GTR-23718: In vivo mouse micronucleus assay of WY45233 (1993; conducted by \_\_\_\_\_, GLP and QAed):

**Methods:** WY-45,233 (lot # C-13913; \_\_\_\_\_, pure) administered to adult male and female CD-1 (\_\_\_\_\_) mice (\_\_\_\_\_) 8 weeks old; weights were 28.8-36.2 g for males, 22.6-28.7 g for females) at doses of 450, 900, and 1800 mg/kg (specified by the Sponsor, based on LD50 data: oral LD50s were calculated as 2489 mg/kg and 1985 mg/kg for males and females, respectively, with deaths occurring within 24 hr of dosing at doses ≥1800 mg/kg); an aqueous solution of 0.25% Tween 80 + 0.5%

carboxymethyl cellulose served as the vehicle (WY-45,233 stock was a suspension at 90 mg/ml) and the negative control; cyclophosphamide (80 mg/kg) served as the positive control; all treatments by oral gavage at 20 ml/kg (10 ml/kg for positive control); mice (5/sex) at each dose were sacrificed at 24, 48, and 72 hr after dosing, except for the positive control which was for 24-hr treatment only (extra mice were treated at HD to replace any premature mortalities); slides for each mouse were scored for micronuclei (based on 1000 PCEs per mouse) and the polychromatic (PCE) to normochromatic (NCE) ratio (based on the first 1000 erythrocytes per mouse); the normal frequency of micronuclei in this mouse strain was noted as about 0.0-0.4%.

**Results:** Toxicity at the HD was noted as death of 1 HDM immediately after dosing and ataxia in all HD mice ~1.5 hr after dosing; and deaths of 5 (more) HDM and 15 HDF within 18 hr of dosing. Cyclophosphamide, the positive control, gave strong signals in both male and female mice (see table, below). Treatment with WY-45,233 did not produce a dose-related increase the frequency of micronuclei; although micronuclei were statistically significantly increased in HDM at the 24-hr time point, compared with concomitant controls; at this dose and time point there as also a tendency for the PCE:NCE ratio to be decreased relative to control (values for 5/5 HDM were lower than 4/5 vehicle controls). It should be noted that 5 mice per group were analyzed, except for HDF, where 4, 3, and 3 were analyzed at 24, 48, and 72 hr, respectively, due to excessive deaths; based on premature deaths, the HD exceeded an MTD for both males and females.

**Conclusions:** The study report (Study Director) considered WY-45,233 to be negative in this in vivo mouse micronucleus test; and this Reviewer agrees, since there were no positive findings at doses up to 900 mg/kg, a dose which could be considered an MTD, due to the deaths at the higher dose of 1800 mg/kg.

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**Table 17. Summary of micronuclei findings for male and female rats treated for 24, 48, or 72 hr with WY-45,233 (desvenlafaxine) or 24 hr with cyclophosphamide as a positive control. [Excerpted directly from the study report.]**

TABLE 1 MICRONUCLEUS DATA SUMMARY TABLE SPONSOR: Wyeth-Ayerst Research ASSAY: 15853 TEST ARTICLE: WY45233							
TREATMENT	DOSE	HARVEST TIME (HR)	MICRONUCLEATED PCEs MEAN OF 1000 PER ANIMAL ± S.E.			RATIO PCE:ICE MEAN ± S.E.	
			MALES	FEMALES	TOTAL	MALES	FEMALES
VEHICLE CONTROL 0.5%CMC/0.25%VEENA20	20 ml/kg	24	0.02 ± 0.02	0.02 ± 0.02	0.02 ± 0.01	1.08 ± 0.16	0.88 ± 0.17
		48	0.04 ± 0.02	0.14 ± 0.05	0.09 ± 0.03	0.82 ± 0.11	1.02 ± 0.21
		72	0.08 ± 0.04	0.04 ± 0.02	0.06 ± 0.02	0.87 ± 0.14	0.91 ± 0.15
POSITIVE CONTROL CP	80 mg/kg	24	2.82 ± 0.50*	2.48 ± 0.23*	2.65 ± 0.26*	0.68 ± 0.07	0.69 ± 0.13
TEST ARTICLE	450 mg/kg	24	0.12 ± 0.04	0.08 ± 0.02	0.10 ± 0.02	0.90 ± 0.18	0.59 ± 0.12
		48	0.08 ± 0.02	0.06 ± 0.02	0.07 ± 0.02	0.66 ± 0.10	0.70 ± 0.12
		72	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.04	0.76 ± 0.08	0.77 ± 0.14
	900 mg/kg	24	0.10 ± 0.03	0.14 ± 0.04	0.12 ± 0.02	0.82 ± 0.11	0.54 ± 0.23
		48	0.06 ± 0.02	0.04 ± 0.02	0.05 ± 0.02	0.85 ± 0.21	0.65 ± 0.16
		72	0.08 ± 0.04	0.04 ± 0.04	0.06 ± 0.03	0.83 ± 0.08	0.91 ± 0.14
	1800 mg/kg	24	0.14 ± 0.02*	0.13 ± 0.08	0.13 ± 0.03	0.52 ± 0.09	0.72 ± 0.04
		48	0.08 ± 0.02	0.10 ± 0.06	0.09 ± 0.02	0.73 ± 0.08	0.77 ± 0.21
		72	0.05 ± 0.05	0.13 ± 0.09	0.09 ± 0.05	0.80 ± 0.18	0.65 ± 0.28

\* Significantly greater than the corresponding vehicle control, p<0.05.

**2.6.6.4.4 Other genetic toxicity tests**

**Summary of other genetic toxicity findings:** Desvenlafaxine was not mutagenic in a CHO/HPRT forward gene mutation assay; it was negative in BALB/c-3T3 transformation assays.

Study id: GTR-17647: CHO/HGPRT cell mutation assay (conducted by \_\_\_\_\_ 1988) (previously reviewed under NDA 20-151 and considered negative and included in labeling as “Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in ...the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay.”)

Study id: GTR-16898: BALB/c-3T3 cell transformation assay with venlafaxine and desvenlafaxine (conducted by \_\_\_\_\_ 1988) (previously reviewed under NDA 20-151 and considered “weakly positive” \_\_\_\_\_ (see Dr. Fitzgerald’s memo date 7/30/1993) as “it [ODV] induced a weak positive transformation response in the absence of metabolic activation in the in vitro BALB/c-3T3 cell transformation assay.” \_\_\_\_\_ this finding/assay

with desvenlafaxine (ODV) \_\_\_\_\_: It should be noted that a valid assay in the presence of metabolic activation was not achieved in this study and it was suggested that the Sponsor should repeat the assay "under more rigorous conditions so that a definitive result may be obtained" (see Dr. Fitzgerald's memo). The following studies appear to have been intended to address this concern.

Study id: GTR-25405: BALB/c-3T3 cell transformation assay (conducted by \_\_\_\_\_)

**Methods:** WY-45,233 (lot # C-13913; suspended in DMSO at 125 mg/ml; final concentrations up to 313 µg/ml were soluble when added to medium, but precipitation was seen at ≥ 625 µg/ml) at 37.5 to 300 µg/ml (preliminary toxicity testing showed severe toxicity (relative cloning efficiency <2%) at ≥313 µg/ml); without metabolic activation; 3-day exposure without activation, 4 hr exposure with activation; 20-methylcholanthrene (MCA; 5.0 µg/ml) served as positive control.

**Results:** In Trial 1, concentrations of 75, 100, 150, 200, 250, and 300 µg/ml (0.83-1.24 foci per culture; 17-18 cultures per concentration) did not differ from DMSO control (0.97 foci per culture; 36 cultures), but a strong signal was seen with the positive control (16.4 foci per culture; 18 cultures; relative survival was 17%). In this trial, relative survival was decreased at WY-45,233 concentrations ≥ 100 µg/ml (93, 90, 63, 68, 30, 28, and 0% of controls, at 37.5, 75, 100, 150, 200, 250, and 300 µg/ml, respectively). Trial 2 was terminate due to unacceptable cytotoxicity. In trial 3, concentrations of 75, 100, 150, 200, 250, and 300 µg/ml were again tested, with small but significant increases seen at ≥200 µg/ml (1.28, 0.67, and 0.89 foci per culture at 200, 250, and 300 µg/ml, respectively; 18 cultures/concentration; relative survival was also decreased at these concentrations, 62, 18, and 3 % of controls, respectively), but not at lower concentrations (0.28-0.39 foci per culture; 18 cultures per concentration; relative survival was 86-94%), compared with DMSO control (0.33 foci per culture; 36 cultures); a strong signal was seen with the positive control (7.94 foci per culture; 18 cultures; relative survival was 34%).

**Conclusions:** WY45-233 was **negative up to 300 µg/ml, without metabolic activation** (but activation not tested).

Study id: GTR-28485: BALB/c-3T3 cell transformation assay (conducted by \_\_\_\_\_)

**Inadequate study:** The Study Director considered only 1 of the 4 transformation assays to be acceptable; the major problem was low positive control transformation frequencies (which would require evaluation of new lots of fetal bovine serum and S9 and require several months to complete). The test article was not positive in the acceptable trial and there was no evidence of transforming properties in the remaining 3 trials (up to the high concentration of 650 µg/ml).

Study id: GTR-28509: morphologic transformation of BALB/c-3T3 mouse embryo cells (conducted by \_\_\_\_\_)

**Methods:** WY-45,233 (\_\_\_\_\_ purity; suspended in distilled water; insoluble and not workable at >100 mg/ml; distilled water was chosen, based on solubility and compatibility with target cells, versus DMSO, ethanol, acetone) at 125, 250, 500, and 1000 µg/ml (the high concentration was expected to produce 80% survival (relative

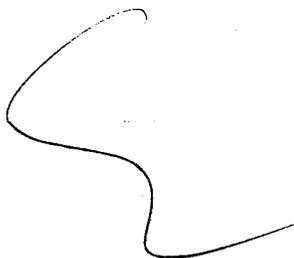
cloning efficiency) based on a preliminary toxicity test up to 1000 µg/ml); ± metabolic activation (S9 from Aroclor-induced rat liver); triplicate dishes; 3-day exposure without activation, 4 hr exposure with activation; MNNG (0.5 µg/ml; without activation) and DMN (8 µl/ml; with activation) served as positive controls.

**Results:** for the test article, survival at highest concentration was 81% without activation, 71% with activation. There were no increases in transformation frequency with test article (< ~0.2 per 10<sup>4</sup> surviving cells; 0 transformed foci per 14-15 dishes, except 1 transformed foci out of 14 dishes at 125 µg/ml with activation), essentially the same as negative controls (< 0.16 per 10<sup>4</sup> surviving cells; 0 transformed foci per 15 dishes); positive controls gave transformation frequencies of 5.83 and 8.89 per 10<sup>4</sup> surviving cells (7 and 8 foci per 15 dishes each), for MHHG and DMN, respectively.

**Conclusions:** WY-45-233 was negative, at concentrations up to 1000 µg/ml, with or without metabolic activation.

#### 2.6.6.4.5 Sponsor's proposed labeling (submitted 4/24/06) for mutagenicity

##### MUTAGENESIS



#### 2.6.6.4.5 Labeling for mutagenicity proposed by this Reviewer:

**[Reasons for changes to Sponsor's Mutagenesis labeling:** We have presented the results of tests from the standard battery first and other tests later. Additionally, we have determined that desvenlafaxine was not positive for clastogenicity in the in vivo chromosome aberration assay in rats.]



[Supporting information: It is this Reviewer's opinion that DVS was negative in the in vivo rat chromosomal aberration assay, for reasons detailed above. However, the "possibly positive" findings were included in the labeling for venlafaxine (see below):

**Mutagenicity [for Effexor IR tablets, bolding added]**

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic in the in vitro BALB/c3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured CHO cells, or the in vivo chromosomal aberration assay in rat bone marrow. **ODV was not mutagenic in the in vitro CHO cell chromosomal aberration assay. There was a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow in male rats receiving 200 times, on a mg/kg basis, or 50 times, on a mg/m<sup>2</sup> basis, the maximum human daily dose. The no effect dose was 67 times (mg/kg) or 17 times (mg/m<sup>2</sup>) the human dose.**

**Mutagenesis [for Effexor XR capsules, bolding added]**

Venlafaxine and the major human metabolite, O-desmethylvenlafaxine (ODV), were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was also not mutagenic or clastogenic in the in vitro BALB/c3T3 mouse cell transformation assay, the sister chromatid exchange assay in cultured Chinese hamster ovary cells, or in the in vivo chromosomal aberration assay in rat bone marrow. **ODV was not clastogenic in the in vitro Chinese hamster ovary cell chromosomal aberration assay, but elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow.**

Consequently, the labeling for both Effexor IR and Effexor XR should be changed to reflect this decision.

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## 2.6.6.5 Carcinogenicity

### 2.6.6.5.1 Mouse carcinogenicity study

**Study title:** DVS-233:TWO-YEAR ORAL (GAVAGE) CARCINOGENICITY STUDY IN MICE (PROTOCOL 02\_1452). Toxicology study report RPT-57595; TK RPT-59615.

#### **Key study findings:**

- Oral gavage doses: 0, 50, 150, and 500/300 mg/kg (HD lowered at week 46) for 2 years.
- MTD reached based on increased mortality and decreased body weights ( $\leq 10\%$ ) in HD group: HD was decreased from 500 to 300 mg/kg at week 46, due to higher mortality at week 45.
- Plasma levels: 4-6  $\mu\text{g/ml}$  at 1 hr after LD, 20-40  $\mu\text{g/ml}$  at 1 hr after MD and 60-70  $\mu\text{g/ml}$  at 1 hr after HD (M-F). [compare with rats for retinal findings]
- Neoplastic findings (in all mice):
  - No findings considered biologically significant.

#### Adequacy of the carcinogenicity study and appropriateness of the test model:

Adequate and appropriate: This was a standard 2-year study in CD-1 mice, using doses approved by the E-CAC (see below), based on MTD in shorter studies. The HD was lowered (from 500 to 300 mg/kg) at week 46 due to increased mortality (this action was approved by the Division); the slight decrease in body weights in this dose-group were  $\leq 10\%$  and would not be expected to complicate the analysis of tumors.

#### Evaluation of tumor findings: Negative.

- 1) There were no significant tumor findings in female mice; the finding of increased incidence of ovarian cystadenoma at the LD, only, appears to be spurious, since it was not seen at higher doses.
- 2) The findings of non-dose-related increased incidence of lung bronchiolo-alveolar adenomas (at all doses) in male mice only, do not seem convincing, because they are accompanied by a parallel (non-statistically significant) decrease in carcinomas and no effect on combined adenomas and carcinomas. This apparent shift from carcinoma to adenoma tumor type suggests a drug-related decrease in the severity of the tumors, rather than a simple increase in adenomas. Alternatively, based on the apparently variable historical incidence of this tumor, it seems likely that the incidence of adenomas in the control group is low (or the incidence of carcinomas is high), rather than incidence of adenomas in all the dosed-groups being high (and the incidence of carcinomas in all the dosed-groups being low).
- 3) The slightly increased incidence of multisystemic histiocytic sarcomas in MD and HD males (2/65=3% and 3/65=5%, respectively, compared with 0/130 and 0/65 in controls and LDM respectively) is statistically significant; however, the

incidence is fairly low and within the range of historical control values for this strain and supplier. Additionally, the incidence of this tumor in was higher in control female mice and was not increased with drug treatment: incidence was 10% in control females (13/130) and 8% (5/65), 11% (7/65), and 8% (5/65) in LDF, MDF, and HDF, respectively. The Sponsor provided some historical control data from their facility that indicated that incidences up to 5% were seen in control males of this strain. Finally, the Sponsor argued that female mice have a higher spontaneous incidence of this tumor type compared with males and appear to be more sensitive than males to increased incidence in response to other xenobiotics (based on literature and the NTP database). Consequently, it seems likely that the apparently (slightly) increased incidence of histocytic sarcomas in MD and HD male mice is due to random variation in a low incidence tumor.

**Study no.:** RPT-57595 (2983 pages); TK in RPT-59615.

**Conducting laboratory and location:** Wyeth Research, Drug Safety, 641 Ridge Road, Chazy, NY 12921.

**Date of study initiation:** first dosing on 4/25/03.

**GLP compliance:** yes (see page 2921).

**QA report:** yes (see pages 2923-2983).

**Drug, lot #, and % purity:** DVS-233 (desvenlafaxine succinate monohydrate), lot/batch numbers RB2691 (———% total impurities) and RB4605 (———total impurities).

**CAC concurrence:** According to the minutes from the 3/25/03 meeting (faxed to the Sponsor on 3/27/03):

“Based on the review of data submitted by the sponsor, the Committee concurred with the proposed doses of 50, 150, and 500 mg/kg/day, assuming that the 2 deaths at 500 mg/kg/day in the 13-week oral toxicity study were not compound related.” However, “The Committee noted that only summaries were received for the mouse (13-week toxicity and a single dose tolerability) ... studies. Therefore, the recommendations of the Committee are contingent on the receipt of the final study reports and on FDA's agreement with the summary upon which these recommendations are based.”

## Methods

Doses: 0, 0, 50, 150, 500/300 mg/kg (HD lowered from 500 to 300 mg/kg after week 45).

Basis of dose selection (MTD, MFD, AUC etc.): MTD, based on a 13-week study at doses up to 500 mg/kg and a single-dose study at 1000 and 2000 mg/kg.

Species/strain: ~~CD-1~~ BR mice (from —————)

Number/sex/group (main study): 65/sex/group (130/sex total in combined control groups).

Route, formulation, volume: oral gavage in 0.25% polysorbate 80 + 0.5% methylcellulose (4000 cps) in purified water (10 ml/kg).

Frequency of dosing: daily.

Satellite groups used for toxicokinetics or special groups: none.

Age: ~7 weeks old at start of dosing.

Animal housing: individually in plastic solid-bottom cages with contact bedding.  
 Restriction paradigm for dietary restriction studies: food and water *ad libitum*.

Drug stability/homogeneity: Stability and homogeneity had been established previously for concentrations 1 and 200 mg/ml, with stability for at least 21 days when refrigerated and protected from light; uniformity of formulation had been confirmed prior to the start of the study for 2 concentrations, sampled from top, middle, and bottom (3 times in Jan/Feb 2002 for 1 mg/ml and twice in Nov/Dec 2001 for 200 mg/ml), and ranged from 96.4-103% and 98.8-105% of the intended concentrations, respectively; dosing formulations used in the study (assayed weekly for the first month, then monthly) were determined to be 88.7-102% of the intended concentrations; pH range of formulations was 4.5-4.8 for drug and 6.3-8.4 for control.

Dual controls employed: yes.

Interim sacrifices: no.

Deviations from original study protocol: minor.

**Observation times**

Mortality: at least twice daily.

Clinical signs: general monitoring at least once daily; detailed clinical exams weekly through week 13, then every 4 weeks.

Palpation for tissue masses: every 4 week for weeks 29-53, then every 2 weeks.

Body weights: weekly through week 13, then every 4 weeks.

Food consumption: weekly through week 13, then every 4 weeks.

Histopathology: original analyses by \_\_\_\_\_ DVM, Diplomate, ACVP (all male mice) and \_\_\_\_\_ DVM, MS, Diplomate, ACVP (all female mice); with peer review by \_\_\_\_\_ DVM, Diplomate, ACVP; all from \_\_\_\_\_

Toxicokinetics: on blood drawn (terminally from vena cava or abdominal aorta) 1 hr after dosing from 3/sex/group on day 729 (males) or 732 (females).

**Results**

Mortality: Because survival at the HD of 500 mg/kg was decreased after 45 weeks (i.e., 315 days) of dosing, compared with controls and lower dose groups (see table, below), the HD was lowered to 300 mg/kg for the remainder of the study (this action was approved by the Division in an e-mail dated 2/13/04).

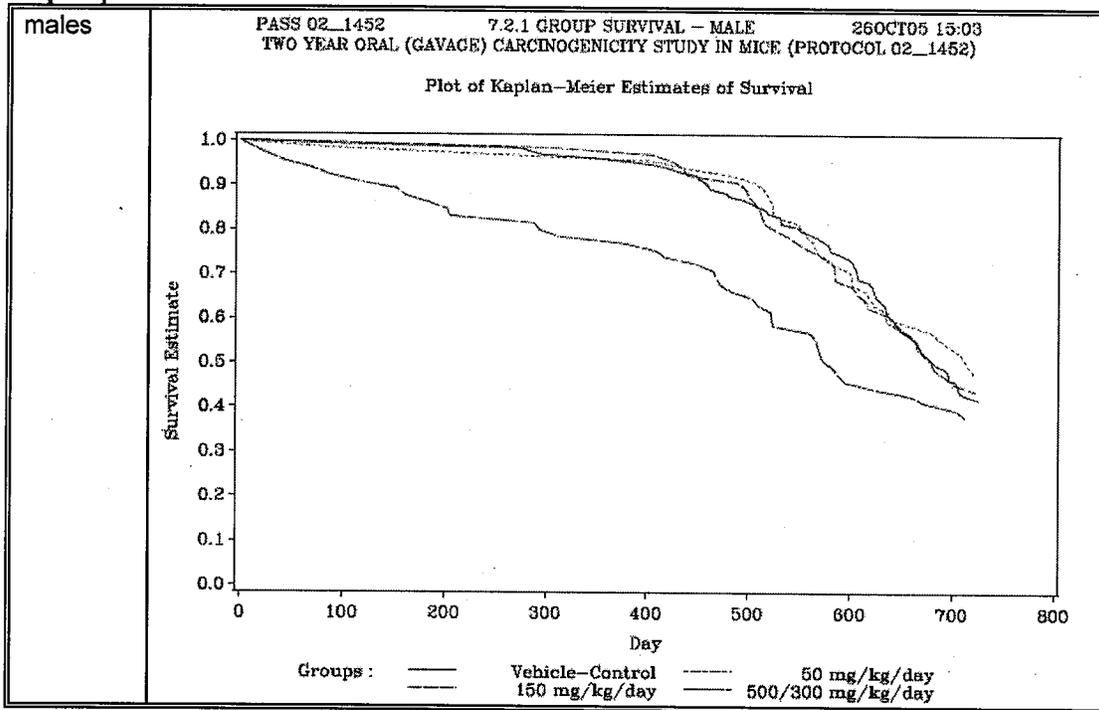
**Table 18. Survival of male and female mice after 45 weeks of dosing. [Excerpted directly from page 26 of the study report.]**

DVS-233 Dosage (mg/kg/day)	Number of Animals Remaining		Percentage of Animals Remaining	
	Males	Females	Males	Females
0	61	65	93.8	100
0	64	63	98.5	96.9
50	63	65	96.9	100
150	64	64	98.5	98.5
500/300 <sup>b</sup>	52	56	80.0	86.2

a. N = 65/sex/group at the start of the study  
 b. After week 45, the high dosage was decreased from 500 to 300 mg/kg/day.

During the remainder of the study, survival in HD males was lower than for other groups (see figure, below) and survival of HD females was lower than for other groups until ~ week 86 (see figure, below). At termination (~week 104), survival for HDM was 38% (24/65) compared with 42% (54/130) for controls; survival for HDF was 29% (19/65) compared with 26% (33/130) for controls (see table, below).

Figure 7. Kaplan-Meier estimates of survival in mice treated for 2 years with DVS-233; the HD was lowered from 500 to 300 mg/kg at day ~315. [Excerpted directly from pages 59 and 60 of the study report.]



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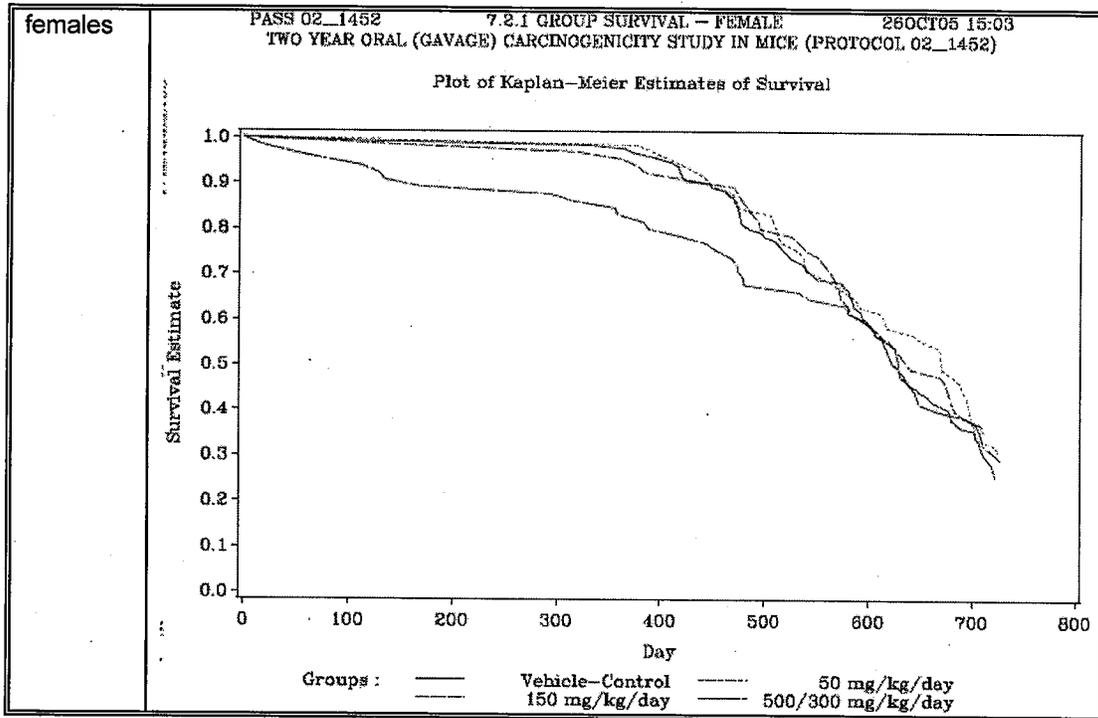


Table 19. Summary of mortalities in mice treated for 2 years with DVS-233 . [Excerpted directly from page 26 of the study report.]

Table 4.3-2: Survival

	Vehicle-Control	Dosage (mg/kg/day)			Total
		50	150	500/300	
<b>Males</b>					
Animals initially on study	130	65	65	65	325
Found dead	18	8	14	23	63
Electively euthanized	57	26	22	17	122
Accidental death	1	0	1	1	3
Animals surviving to study termination	54	31	28	24	137
Kaplan-Meier endpoint survival rate	42%	48%	44%	38%	-
<b>Females</b>					
Animals initially on study	130	65	65	65	325
Found dead	16	7	9	18	50
Electively euthanized	80	38	33	28	179
Accidental death	1	0	0	0	1
Animals surviving to study termination	33	20	23	19	95
Kaplan-Meier endpoint survival rate	26%	31%	35%	29%	-

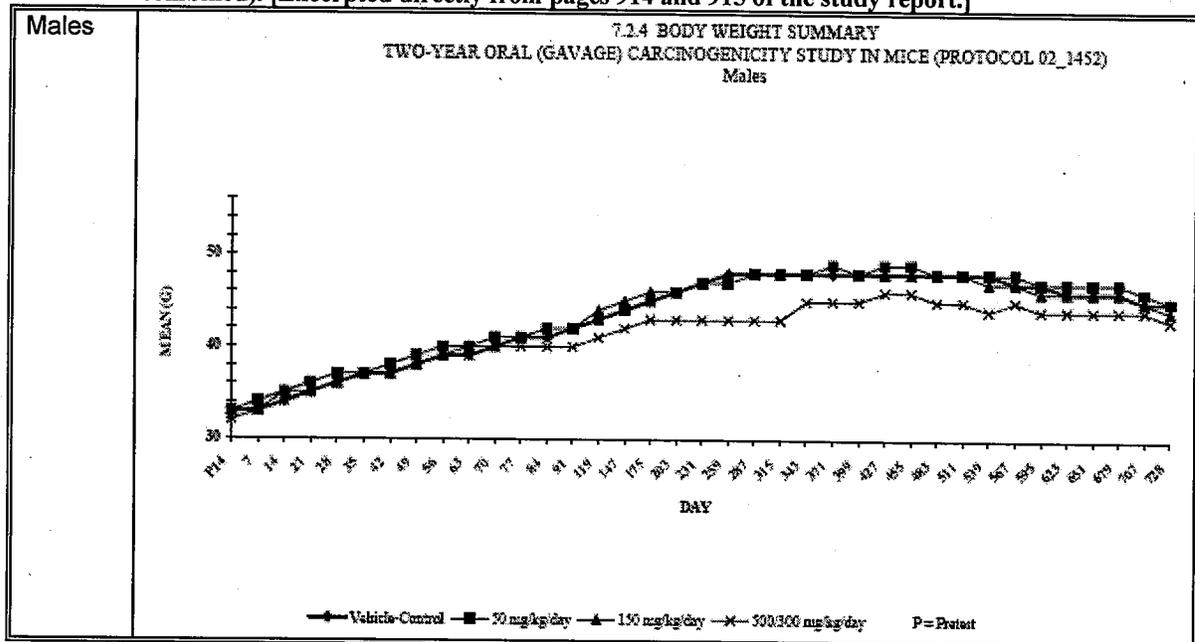
For unscheduled deaths of male mice (76/130 controls, 35/65 LDM, 40/65 MDM, 41/65 HDM), the major causes of death in all groups were neoplasia, amyloidosis, and undetermined: neoplasia accounted for fewer deaths at the HD (43% for controls, 57% for LDM, 43% for MDM, 24% for HDM); deaths due to amyloidosis affected the groups more equally (18% for controls, 14% for LDM, 30% for MDM, 15% for HDM); and more deaths in the HD group were of undetermined cause (17% for controls, 17% for LDM, 15% for MDM, 44% for HDM).

For unscheduled deaths of female mice (98/130 controls, 45/65 LDF, 42/65 MDF, 46/65 HDF), the major cause of death in all groups was neoplasia (58% for controls, 56% for LDF, 55% for MDF, 43% for HDF). More HDF died by undetermined mechanisms (8% for controls, 11% for LDF, 14% for MDF, 33% for HDF). Renal disease (14% for controls, 9% for LDF, 12% for MDF, 9% for HDF) and amyloidosis (7% for controls, 2% for LDF, 5% for MDF, 13% for HDF) affected the groups more equally.

**Clinical signs:** The only clinical signs that appeared to be treatment related were salivation and circling behavior. Convulsions and tremors were observed sporadically in drug-treated and control mice and were not considered drug-related. [Mydriasis was not noted, but the examinations probably were not adequate to detect it.]

**Body weights:** Body weights were decreased ( $\leq 10\%$ ) throughout much of the study in HD males and HD females, compared with controls (see figure, below). In male mice, body weights were significantly decreased compared with controls after 13 weeks of dosing at the HD ( $\downarrow 5\%$ ) and the decrease continued ( $\downarrow 3-10\%$ ) to nearly the end of the study (see table, below). In female mice, mean body weights of dosed groups tended to be slightly lower than controls from about 4 weeks of dosing, however, the largest effect was seen at the HD, where weights were decreased 4% after 4 weeks of dosing and continued lower ( $\sim 10\%$ ) than controls throughout most of the study (see table, below).

**Figure 8. Body weights of mice treated for 2 years with DVS-233 (data from the 2 control groups have been combined). [Excerpted directly from pages 914 and 915 of the study report.]**



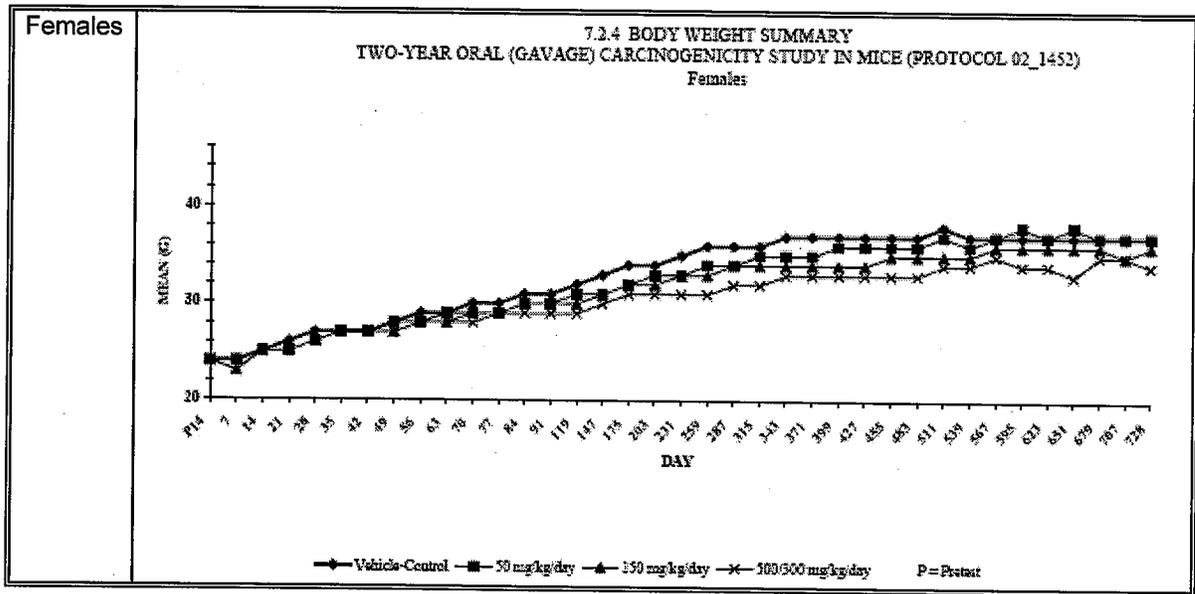


Table 20. Decreased body weights in mice treated for 2 years with DVS-233, compared with control mice. [Excerpted directly from page 28 of the study report.]

Table 4.4-1: Percent (%) Difference in Group Mean Body Weights from Controls<sup>a</sup>

Dosages (mg/kg/day)	Male			Female		
	50	150	500/300 <sup>b</sup>	50	150	500/300 <sup>b</sup>
Week 25	-	+ 1%	- 6% <sup>c</sup>	- 5% <sup>c</sup>	- 7% <sup>c</sup>	- 10% <sup>c</sup>
Week 45	-	-	- 10% <sup>c</sup>	- 4%	- 7% <sup>c</sup>	- 12% <sup>c</sup>
Week 53	+ 1%	+ 1%	- 7% <sup>c</sup>	- 5% <sup>d</sup>	- 8% <sup>c</sup>	- 11% <sup>c</sup>
Week 77	+ 1%	- 1%	- 7% <sup>c</sup>	- 1%	- 4%	- 8% <sup>c</sup>
Week 104	-	- 1%	- 3%	- 1%	- 4%	- 8%

a. N = 65/sex/group at the start of the study.  
b. After week 45, the high dosage was decreased from 500 to 300 mg/kg/day.  
c. Significantly different from controls, p ≤ 0.01  
d. Significantly different from controls, p ≤ 0.05

Food consumption: The small decreases in body weights were not accompanied by systematic decreases in food consumption.

Hematology: In 15/sex/group after ~1 year of dosing, there were no remarkable findings.

Gross pathology at final necropsy: There were no drug-related macroscopic findings in mice at final necropsy.

Histopathology:

Non-neoplastic at final necropsy: Drug-related findings in male mice consisted of: increased incidence of **retinal degeneration** of the eyes at MD and HD (13%=7/54 controls, 13%=4/30 LDM, 36%=9/25 MDM, 33%=8/24 HDM); slightly increased incidence of **dilatation of gallbladder** in dosed groups (2%=1/52 controls, 7%=2/30 LDM, 12%=3/25 MDM, 14%=3/21 HDM); and increased incidence of **diffuse hepatocellular hypertrophy** of the liver at HD (4%=2/54 controls, 7%=2/30 LDM, 4%=1/25 MDM, 13%=3/24 HDM).

Drug-related findings in female mice consisted of: increased incidence of **fibrous osteodystrophy of bone/joint** at all doses (9%=3/32 controls, 35%=7/20 LDF, 52%=12/23 MDF, 47%=9/19 HDF); increased incidence of **retinal degeneration** of the eyes at all doses (31%=10/32 controls, 40%=8/20 LDF, 43%=10/23 MDF, 63%=12/19 HDF); and increased incidence of **atrophy of the ovaries** at MD and HD (65%=20/31 controls, 55%=11/20 LDF, 83%=19/23 MDF, 84%=16/19 HDF).

The Sponsor attributed the increased retinal degeneration seen in both male and female mice given desvenlafaxine to increased light exposure of the retinas of dosed mice due to mydriasis, which is a pharmacological effect of the drug.

Neoplastic in all mice: In male mice, neoplastic changes were limited to: **bronchiolo-alveolar adenomas** and multisystemic **histiocytic sarcomas**.

The incidence of **bronchiolo-alveolar adenomas** of the lungs was increased at all doses, but not dose-relatedly: 7%=9/130 in controls, compared with 16%=10/64, 16%=10/64, and 19%=12/64 at LD, MD, and HD, respectively, with no increase in carcinomas or in combined adenomas and carcinomas (see table, below). [It should also be noted that according to the \_\_\_\_\_ (2005), the incidence of bronchiolo-alveolar adenomas in male mice ranged from 2.0 to 42%, based on 51 studies.]

**Table 21. Increased incidence of lung bronchiolo-alveolar adenomas, but not carcinomas, in male mice treated with DVS-233. [Excerpted directly from page 36 of the study report.]**

	Dosage (mg/kg/day)				Trend p-Value
	0	50	150	500/300	
Bronchiolo-alveolar Adenoma	9/130 (7%)	10/64 (16%)	10/64 (16%)	12/64 (19%)	0.002*
Bronchiolo-alveolar Carcinoma	26/130 (20%)	7/64 (11%)	8/64 (13%)	5/64 (8%)	0.932
Combined	33/130 (25%)	17/64 (27%)	18/64 (28%)	16/64 (25%)	0.286
Bronchiolo-alveolar Tumors		0.528	0.419	0.346	

\*. p-value ≤ 0.025 level  
 Pairwise one-sided comparisons to controls.  
 One-sided test for trend (minimum of ordinal and dose proportional scores p-values).

The incidence of multisystemic **histiocytic sarcomas** (also known as histiocytic lymphoma or fibrous histiocytoma) was slightly increased at MD and HD, compared with controls: 0%=0/130 in controls, 0%=0/65 at LD, but 3%=2/65 at MD and 5%=3/65 at HD (see table, below). Although the spontaneous incidence of this tumor in control males in the current study (0/130) suggests that this is a rare tumor, the incidence in control groups of this strain of male mice appears to be higher in general, ranging from 1.1-8.0%, as reported by \_\_\_\_\_ (reported in 2005, from 59 studies in 11 laboratories, initiated between 1987 and

2000: the incidence for this tumor in male CD-1 mice ranged from 1.1 to 8.0% in the 24 studies where this diagnosis was reported; see table, below). The incidences of 3 and 5% seen in MDM and HDM, respectively, are within the spontaneous range reported by \_\_\_\_\_ for 24 studies initiated between 1987 and 2000 (i.e., 1.1-8.00% (1/90-4/50), but slightly above the range for the 3 studies that were initiated between 1998 and 2000, within 5 years of the time of the initiation of the current study (mid 2003). Apparently multisystemic histiocytoma was also seen by this Sponsor (cited study reports for 2-year studies in mice: Wyeth Ayerst GTR-27668, from 1996, for tasosartan; and Wyeth Ayerst GTR-36596, from 1999, for Rapamune™) [the results of these studies were subsequently submitted and are discussed below].

**Table 22. Increased incidence of multisystemic histiocytic sarcomas in male mice treated with DVS-233. [Excerpted directly from page 37 of the study report.]**

	Dosage (mg/kg/day)				Trend p-Value
	0	50	150	500/300	
Histiocytic Sarcoma	0/130 (0%)	0/65 (0%)	2/65 (3%)	3/65 (5%)	0.004*
		0.999	0.116	0.023*	

\*. p-value ≤ 0.025 level  
Pairwise one-sided comparisons to controls.  
One-sided test for trend (minimum of ordinal and dose proportional scores p-values).

**Table 23. Comparison of incidence of multisystemic histiocytic sarcomas in male and female mice treated with DVS-233. [Excerpted directly from page 1175 of the study report.]**

SEX	CONTROLS	50 mg/kg	150 mg/kg	500/300 mg/kg
Male	0/130 (0%)	0/65 (0%)	2/65 (2%)	3/65 (5%)
Female	13/130 (10%)	5/65 (8%)	7/65 (7%)	5/65 (8%)

**Table 24. Comparison of spontaneous incidence of multisystem histiocytic sarcomas in male and female mice in the current study, the \_\_\_\_\_ data base (2005 report), and the 2 studies cited by the Sponsor.**

SOURCE	MALES	FEMALES
Current study	0% (0/130)	10% (13/130)
S Z	1.1-8.00% (1/90-4/50)	1.67-18.33% (1/60-11/60)
	1.4-3.1% (1/70-2/60)	3.64-10.77% (2/55-7/65)

<sup>1</sup> From studies reporting this diagnosis: 24/52 studies in male mice and 42/54 studies in female mice.

<sup>2</sup> From studies reporting this diagnosis and initiated between 1998 and 2000 (i.e., no more than 5 years earlier than the current study): 3 studies in males (1/70, 2/65, 2/60) and 4 studies in females (2/55, 4/60, 5/60, 7/65).

When the results of this study were presented to the E-CAC (10/10/06), they were concerned that only minimal information from only 2 historical control studies conducted at the current facility was provided by the Sponsor. Subsequently, the Division requested (in an e-mail sent 10/17/06) that the Sponsor submit all historical control data that they had for multisystem histiocytic sarcomas in male and female CD-1 mice from studies

conducted at their facility since approximately 1998; that is, all studies initiated within about 5 years of the one submitted to this NDA. In response, the Sponsor informed us (submission to NDA 21-992 stamp-dated 10/26/06) that the 2 studies mentioned in the NDA submission were the only relevant historical controls for the current study; all other studies conducted at their facility were of 18 months duration and conducted prior to 1987. Nonetheless, the Sponsor provided the incidences of this tumor type in both male and female CD-1 mice, for controls and treated groups, in these 2 studies (see table, below).

**Table 25. Sponsor's table comparing the supplier of mice, study start dates and durations, vehicle composition, and incidence of histiocytic sarcoma in the current study and the studies serving as historical controls. [Excerpted directly from the Sponsor's submission, page 7 out of 18.]**

Study/Compound	Source/Supplier	Study Start Date	Study Duration	Vehicle and Route of Administration	Incidence of Histiocytic Sarcoma	
					Male	Female
Study 1 (Rapamune)	}	12 Feb 1997	2 years	1.0% polysorbate 80, NF; 99.0% phosal 50 PG and purified (Class I) water; oral (gavage)	Controls: 0%, 5% Low dose: 2% Mid dose: 0% High dose: 0%	Controls: 8%, 7% Low dose: 2% Mid dose: 0% High dose: 5%
Study 2 (Tasosartan)		11 Jan 1994	2 years	0.08% polysorbate 80, NF; 1.0 % CMC sodium, 7HOF USP, and purified (Class I) water; oral (gavage)	Controls: 4%, 0% Low dose: 8% Mid dose: 6% Mid High dose: 0% High dose: 2%	Controls: 6%, 15% Low dose: 10% Mid dose: 18% Mid High dose: 8% High dose: 12%
DVS-233		25 Apr 2003	2 years	0.25% polysorbate 80, NF; 0.5% methylcellulose (4000 cps), mixed in purified (Type I) water; oral (gavage)	Controls: 0%, 0% Low dose: 0% Mid dose: 3% High dose: 5%	Controls: 14%, 6% Low dose: 8% Mid dose: 11% High dose: 8%

The incidence in controls in the other 2 studies ranged from 0 to 5%, when the replicate control groups were treated separately in each study and a similar range was seen in the drug-treated groups (0-6%), with no indication of drug dose-dependence (see table, below). In these studies, as in the DVS study currently under review, the incidence of this tumor in female mice was higher than in males, ranging from 6-15% in separate control groups and 8-18% in drug-treated groups, without apparent drug-dependency.

**Table 26. Comparison of incidence of multisystemic histiocytic sarcomas in male CD-1 mice treated with DVS-233 compared with male mice from 2 other studies with other drugs, but conducted by the Sponsor.**

STUDY	CONTROL-1	CONTROL-2	LD	MD	HMD	HD
DVS <sup>1</sup>	0/65 (0%)	0/65 (0%)	0/65 (0%)	2/65 (2%)	na	3/65 (5%)
Rapamune <sup>2</sup>	0/60 (0%)	3/60 (5%)	1/61 (2%)	0/61 (0%)	na	0/65 (0%)
Tasosartan <sup>3</sup>	2/50 (4%)	0/52 (0%)	4/51 (8%)	3/52 (6%)	0/52 (0%)	1/51 (2%)

- <sup>1</sup>: current study with DVS.
- <sup>2</sup>: study with Rapamune (Protocol 96047, GTR-36596).
- <sup>3</sup>: study with Tasosartan (Protocol 93118, GTR-27668).

The Sponsor also noted that there was no indication of increased incidence of this tumor type in their 2-year rat study (see details provided under review of the rat study, below). Finally, the Sponsor provided some evidence (from a review of the literature and search of the NTP database) that “the increased incidence of histiocytic sarcomas was

consistently detected in female mice, and less reliably in males.” They noted that although the NTP studies were conducted in B6C3F1 mice, which have lower spontaneous incidence of this tumor in both males and females, the females still had higher incidence than males in this strain. Nonetheless, the Sponsor was unable to find an example in the NTP database (or the literature) where male mice showed increased incidence of this tumor, but females did not; female mice were as much or more sensitive to xenobiotic-related increases in this tumor and that “a true positive signal is more likely to be expressed in females.” Consequently, particularly based on the variability in historical control data, it seems likely that the apparently (slightly) increased incidence of histocytic sarcomas in MD and HD male mice is due to random variation in a low incidence tumor.

**In female mice, there were no significant neoplastic findings** related to drug-treatment. The incidence of ovarian cystadenoma was increased at LD, but not at higher doses (2%=3/129 controls, 11%=7/65 LDF, 0%=0/64 MDF, 3%=2/64 HDF). [It should also be noted that according to the \_\_\_\_\_ report (2005), the incidence of ovarian cystadenoma ranged from 2.0 to 42%, based on 14 studies.]

There was no significantly increased incidence of palpable tumors in males or females.

**Toxicokinetics:** Based on samples drawn (only) 1 hr after dosing from (only) 3/sex/group at scheduled termination, the dosed groups appeared to have been exposed to dose-related amounts of drug, at least on the last day of dosing (see table, below).

**Table 27. Plasma levels of desvenlafaxine measured 1 hr after final dosing (in 3/sex/group) in the 2-year mouse carcinogenicity study. [Excerpted directly from page 40 of study report.]**

Dosage <sup>a</sup> (mg/kg/day)	Day of Study	Gender	Time after Dosing (hour)	C <sub>1 hour</sub> (ng/mL)
Vehicle-Control	729	Male	1	0.00 ± 0.00
Vehicle-Control	732	Female	1	0.00 ± 0.00
50 DVS-233	729	Male	1	4233 ± 243
50 DVS-233	732	Female	1	5860 ± 1470
150 DVS-233	729/732 <sup>b</sup>	Male	1	19047 ± 5052
150 DVS-233	732	Female	1	40284 ± 16028
500/300 DVS-233 <sup>a</sup>	729	Male	1	61620 ± 9473
500/300 DVS-233 <sup>a</sup>	732	Female	1	68861 ± 3135

a. After week 45, the high dosage was decreased from 500 to 300 mg/kg/day.  
 b. An additional male animal administered 150 mg/kg/day DVS-233 was bled on study day 732 due to an insufficient sample obtained from one animal at this dosage on study day 729.  
 SD. Standard deviation

However, in their submission dated 10/26/06, the Sponsor provided AUCs from their 3-month study: based on AUCs for male mice after 13 weeks of dosing at 150 and 500 mg/kg, the AUC estimated for 300 mg/kg would be ~52 µg.hr/ml. This would give approximately 5-fold coverage for the ~10 µg.hr/ml AUC in humans at the 200-mg dose (the maximum recommended human daily dose). Female mice appeared to have (~1.6-fold) higher exposures, based on AUC at the dose of 150 mg/kg (the only dose for which