

data was provided for female mice); consequently the safety margin provided by female mice would be expected to be higher than that for male mice.

#### 2.6.6.5.2 Rat carcinogenicity study

**Study title:** DVS-233: TWO-YEAR ORAL (GAVAGE) CARCINOGENICITY STUDY IN RATS (PROTOCOL 02\_1252).

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

- Oral gavage doses: 0, 30, 100, and 300 mg/kg to male rats and 0, 50, 150, and 500 mg/kg to female rats for 2 years.
- MTD reached based on body weights, which were decreased throughout much of the study in MD and HD males ( $\leq 10\%$ ) and HD females ( $> 10\%$  for much of the study); no effects on mortality.
- Plasma levels: 3-8  $\mu\text{g/ml}$  at 1 hr after LD, 15-18  $\mu\text{g/ml}$  at 1 hr after MD and 30-40  $\mu\text{g/ml}$  at 1 hr after HD (M-F).
- Neoplastic findings (in all rats):
  - No increased incidences; *decreased* mammary gland fibroadenomas in dosed females.

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

Adequate and appropriate: This was a standard 2-year study in Sprague-Dawley rats, using doses approved by the E-CAC (see below), based on MTD in shorter studies. The mean body weights of females at the HD were  $> 10\%$  lower than controls throughout much of the study and might have protected them from some tumor development, so analysis without this (high) dose-group was also conducted for females by Statistician Moh-Jee Ng, M.S.

Evaluation of tumor findings: negative. There were no significant tumor findings for male or female rats. Statistician Moh-Jee Ng, M.S., found a significant increase in hepatocellular adenomas in male rats. However, this was based findings in 2/60 HDM, but in 0/120 control males, 0/60 LDM and 0/60 MDM and does not appear to be biologically relevant, because the incidence is very low and there was no increase in the incidence of carcinomas or the combined incidences of adenomas and carcinomas. Additionally, there were no instances of neoplastic findings in livers of female rats.

**Study no.:** RPT-57596 (2887 pages); TK in RPT-59614 (32 pages).

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

**Date of study initiation:** first dosing on 5/14/03.

**GLP compliance:** yes (see page 2816).

**QA report:** yes (see pages 2818-2821).

**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):

“The Committee concurred with the proposed doses of 30, 100, 300 mg/kg/day for male rats based on the 13-week study results for males (deaths at 1000 and significant decrease in body weight gain at 500 and 1000 mg/kg/day). However, the Committee recommended doses of 50, 150, and 500 mg/kg/day for females since the decrease in body weight gain at 300 mg/kg/day in the 26-week study was minimal and the decrease at 500 mg/kg/day in the 13-week study was acceptable.” However, “The Committee noted that only summaries were received... for the rat (26-week toxicity) [study]. 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: 2 (identical) vehicle control groups (0, 0); males dosed at 30, 100, and 300 mg/kg; females dosed at 50, 150, and 500 mg/kg (calculated as doses of the free base).

Basis of dose selection (MTD, MFD, AUC etc.): MTD.

Species/strain: CD (SD) IGS BR rats ( ~~\_\_\_\_\_~~ )

Number/sex/group (main study): 60/sex/dose group.

Route, formulation, volume: oral gavage in 0.25% polysorbate 80 + 0.5% methylcellulose (4000 cps) in purified water (10 ml/kg); vehicle and drug formulations prepared fresh every 1-2 weeks and stored refrigerated and protected from light.

Frequency of dosing: daily.

Satellite groups used for toxicokinetics or special groups: none.

Age: ~7 weeks old at start of dosing.

Animal housing: 2/cage in plastic solid bottom cages with contact bedding; environmental enrichment.

Restriction paradigm for dietary restriction studies: none.

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 90-107% of the intended concentrations; the pH of the drug formulations was 4.5-4.9, that of the control 5.79-8.4.

Dual controls employed: yes.

Interim sacrifices: no.

Deviations from original study protocol: minor; sporadic misdosings; microscopic exams of testes of rats #295 and 398 were not conducted due to loss identification tags on tissue.

### Observation times

Mortality: generally 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 26, then every 4 weeks.

Food consumption: weekly through week 26, then every 4 weeks.

Histopathology: original analyses by \_\_\_\_\_ DVM, PhD (all male rats) and \_\_\_\_\_, DVM, PhD, DABT (all female rats); 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 at scheduled termination; desvenlafaxine determined by HPLC/UV.

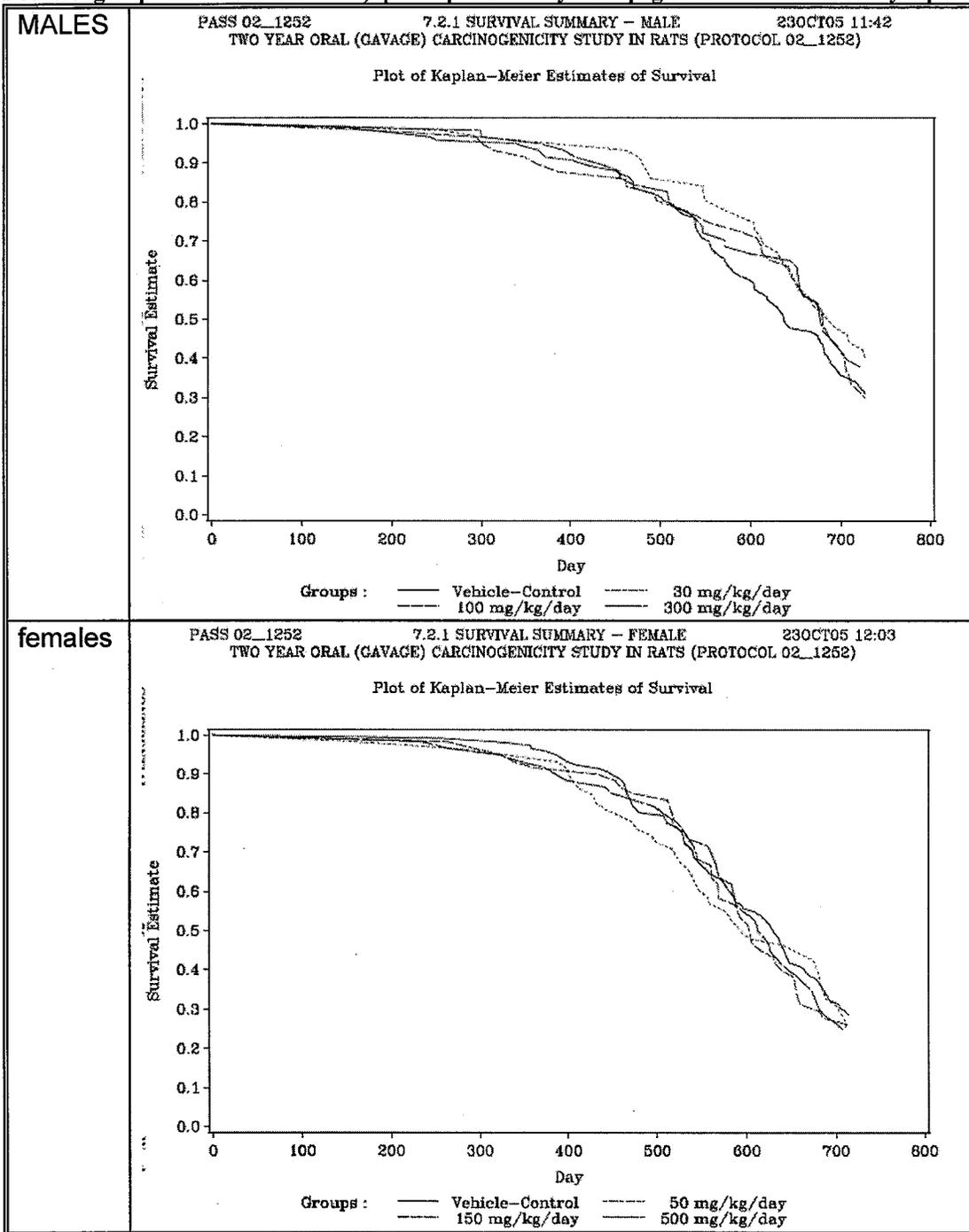
### Results

**Mortality:** There were **no significant drug-related effects on mortality** over the course to the study (see figure, below). At termination (~week 104), survival for HDM was 38% (21/60) compared with 31% (32/120) for controls; survival for HDF was 25% (15/60) compared with 29% (33/120) for controls (see table, below).

For unscheduled deaths of male rats (88/120 controls, 39/60 LDM, 44/60 MDM, 39/60 HDM), the major causes of death in all groups were neoplasia (59% for controls, 44% for LDM, 57% for MDM, 49% for HDM), renal disease (6% for controls, 15% for LDM, 11% for MDM, 13% for HDM), and gavage error (10% for controls, 18% for LDM, 14% for MDM, 10% for HDM). Lower urinary tract disease (6% for controls, 8% for LDM, 9% for MDM, 15% for HDM) and obstructive uropathy (1% for controls, 0% for LDM, 0% for MDM, 5% for HDM) appeared to account for more unscheduled deaths in drug-treated groups (especially HDM) than in controls. More controls and LDM died by undetermined mechanisms (11% for controls, 13% for LDM, 5% for MDM, 0% for HDM).

For unscheduled deaths of female rats (87/120 controls, 47/60 LDF, 45/60 MDF, 45/60 HDF), the major cause of death in all groups was neoplasia (86% for controls, 83% for LDF, 89% for MDF, 84% for HDF). More HDF died by undetermined mechanisms (2% for controls, 2% for LDF, 7% for MDF, 13% for HDF).

Figure 9. Kaplan-Meier estimates of survival in rats treated for 2 years with DVS-233 (data from the 2 control groups have been combined). [Excerpted directly from pages 75 and 76 of the study report.]



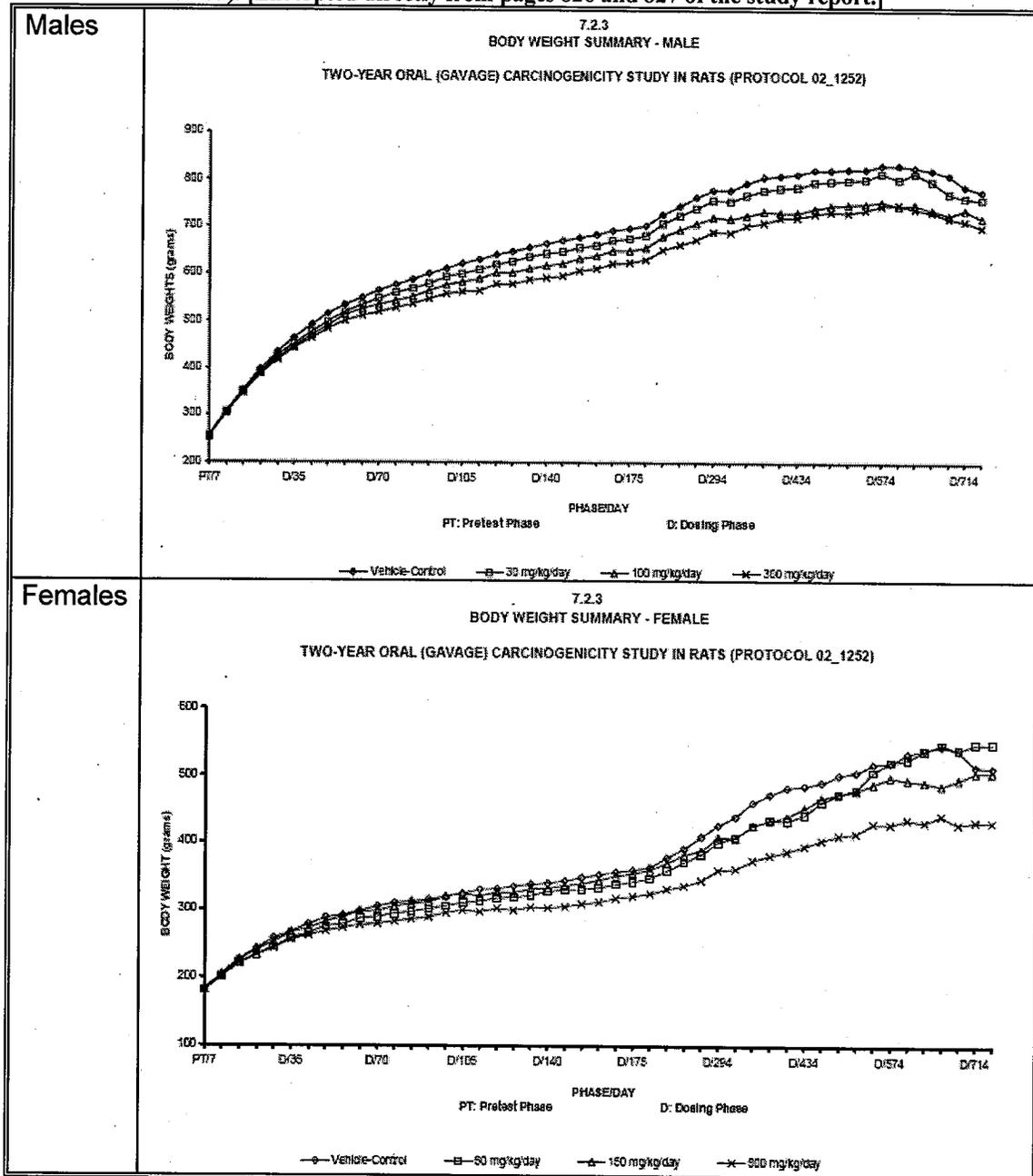
**Table 28. Summary of mortalities in rats treated for 2 years with DVS-233 . [Excerpted directly from page 24 of the study report.]**

	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%	-

**Clinical signs:** The only clinical sign that appeared to be treatment related were salivation and chromodacryorrhea (red pigment around the eyes). Convulsions and tremors were observed sporadically in drug-treated and control rats and were not considered drug-related.

**Body weights:** Body weights were decreased throughout much of the study in MD and HD males ( $\leq 10\%$ ) and HD females ( $>10\%$  for much of the study), compared with controls (see figure, below). In male rats, body weights were significantly decreased compared with controls after 4 weeks of dosing at both the MD ( $\downarrow 3\%$ ) and the HD ( $\downarrow 4\%$ ) and the decreases continued ( $\downarrow 7-9\%$  at MD and  $\sim 10\%$  at HD) to the end of the study; at the LD, weights were only slightly ( $\sim 3\%$ ) decreased (see table, below). In female rats, body weights were significantly decreased compared with controls after 4 weeks of dosing at the HD ( $\downarrow 3\%$ ) and continued to decrease to 16% lower than controls by the end of the study; weights of both LDF and MDF were decreased slightly (compared with controls), but only towards the end of the study (see table, below).

Figure 10. Body weights of rats treated for 2 years with DVS-233 (data from the 2 control groups have been combined). [Excerpted directly from pages 826 and 827 of the study report.]





from 31 studies in 8 laboratories, initiated or published between 1989 and 2002: the incidence for this tumor in male  $\bar{x}$ -CD(SD) male rats ranged from 1.4 to 24.3% in 28 studies).

There was **no significantly increased incidence of palpable tumors in males or females**. The **incidence of mammary gland fibroadenomas was decreased** in drug-treated females: 57% (68/120) controls, 33% (20/60) LD, 37% (22/60) MD, and 20% (12/60) HD.

Our Statistician found a significant increase in hepatocellular adenomas in male rats. However, this was based findings in 2/60 HDM, but in 0/120 control males, 0/60 LDM and MDM (see table, below) and does not appear to be biologically relevant, because there was no increase in the incidence of carcinomas or the combined incidences of adenomas and carcinomas. It should be noted that in female rats there were no instances of hepatocellular hyperplasia, adenoma, or carcinoma in drug-treated rats, but single incidences of each among control females.

**Table 30. Neoplastic and preneoplastic findings in male rats treated with DVS-233. [Compiled from summary data from the report.]**

FINDING	CONTROLS	LDM	MDM	HDM
Hepatocellular hyperplasia	0/88	1/39	0/44	0/39
Adenoma	0/120	0/60	0/60	2/60
Carcinoma	3/120	0/60	2/60	2/60
Adenoma & carcinoma	3/120	0/60	2/60	4/60

[Because there was some concern about multisystem histiocytic sarcomas in male mice, the incidences of this tumor in this rat study are provided below. There was no drug-related increase in the incidence of this tumor in either male or female rats in this study.

**Table 31. Comparison of incidence of multisystemic histiocytic sarcomas in male and female rats treated with DVS-233. [Compiled from data excerpted directly from pages 1161 and 1167 of the study report.]**

SEX (M/F)	CONTROLS	30/50 mg/kg	100/150 mg/kg	300/500 mg/kg
Male	1/100 (1%)	1/60 (2%)	3/60 (5%)	1/60 (2%)
Female	4/120 (3%)	2/60 (3%)	1/60 (2%)	1/60 (2%)

**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 32. Plasma levels of desvenlafaxine measured 1 hr after final dosing (in 3/sex/group) in the 2-year rat carcinogenicity study. [Excerpted directly from page 35 of study report.]**

Dosage (mg/kg/day)	Day of Study	Gender	Time (hr)	Concentration (ng/mL)
0	729	Male	1	0.00 $\pm$ 0.00 n=6
0	716	Female	1	0.00 $\pm$ 0.00 n=6
30	729	Male	1	3022 $\pm$ 920 n=3
50	716	Female	1	8265 $\pm$ 1856 n=3
100	729	Male	1	15158 $\pm$ 1782 n=3
150	716	Female	1	17754 $\pm$ 4273 n=3
300	729	Male	1	30353 $\pm$ 11162 n=3
500	716	Female	1	38030 $\pm$ 9472 n=3

SD. Standard deviation

However, in their submission dated 10/26/06, the Sponsor provided AUCs from their 4-month rat study. The AUC of 56  $\mu$ g.hr/ml for male rats after 4 months of dosing at 300 mg/kg, would provide a safety margin of ~6-fold for the 10  $\mu$ g.hr/ml AUC at the maximum recommended human daily dose of 200 mg. The HD of 500 mg/kg for female rats in the carcinogenicity study would be expected to produce an AUC of ~130  $\mu$ g.hr/ml, based on AUCs determined for 100 and 300 mg/kg in the 4-month study, which would provide an AUC safety margin of 13-fold for the 10  $\mu$ g.hr/ml AUC at the maximum recommended human daily dose of 200 mg. However, it should be noted that the plasma levels measured in female rats at 500 mg/kg in the carcinogenicity study are only 25% higher than those measured for male rats at 300 mg/kg, suggesting that the systemic exposures in females may not be much higher than those in males.

**2.6.6.5.3 Sponsor's proposed labeling (submitted 4/24/06) for Carcinogenesis:**



/    Page(s) Withheld

       Trade Secret / Confidential

  X   Draft Labeling

       Deliberative Process

## 2.6.6.6 REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

### 2.6.6.6.1 Fertility and early embryonic development:

This section comprises 8 studies in rats: 2 dose-range finding studies, a pivotal study that is a combined fertility and embryo-fetal development study, plus TK, and 4 studies to clarify the effects on fertility. The pivotal study is reviewed here in detail; the results of the other studies are summarized.

#### 2.6.6.6.1.1 Definitive fertility and early embryonic development study:

**Study title:** DVS-233:ORAL (GAVAGE) FERTILITY AND DEVELOPMENTAL TOXICITY STUDY IN RATS (PROTOCOL 02\_0221).

#### Key study findings:

- Doses: 0, 30, 100, and 300 mg/kg by oral gavage for 2 weeks prior to cohabitation (with dosed-males) through GD20 for females, with analysis on GD 21; dosing for 4 weeks prior to and during cohabitation (with dosed females) for males;
- No treatment-related mortalities;
- Dosed males: 5-10% decreased body weights (MTD); decreased prostate weights at all doses, with dose-related increased incidence of (slight) microscopic prostate atrophy at MD and HD (after ~18 weeks of dosing).
- Dosed females: decreased food consumption at all doses during GD 0-5 (pre-implantation) and at HD throughout gestation (GD0-20); decreased body weight gain during gestation at HD (not clearly an MTD).
- Fertility parameters: **disruption of estrus cycles** at all doses; **doubling of time to mate at all doses**, but no effect on mating index; **decreased fertility index** (fraction that became pregnant) at MD (83%) and HD (50%), compared with control (100%); **decreased gravid uterine weights** at HD.
- Maternal parameters: **increased pre-implantation loss** at HD; but no effect on post-implantation loss or number of live fetuses (when normalized to implantation sites).
- Fetal parameters: **fetal weights were slightly decreased** (4% for males and 9% females) at HD; **no teratogenesis**. [NB Due to the pregnancy rate at HD, only half as many fetuses were evaluated at the HD.]
- **NOAEL for fertility is (arguably) the LD of 30 mg/kg** (with only disrupted estrus cycles and doubling of time to mate); based on decreased fertility index at MD (but not LD), and increased pre-implantation loss and decreased gravid uterine weight at HD; no teratogenesis up to HD of 300 mg/kg. The NOAEL dose of 30 mg/kg in rats is 1.5 times the MRHD of 200 mg/day on a mg/m<sup>2</sup> basis (for a 60-kg adult) [30 mg/kg (in rats) x 6/37 = 4.86 mg/kg (in humans) x 60 kg = 290 mg/day = 1.5x 200 mg]. The AUC at 30 mg/kg was 2.8 µg.hr/ml for males (determined after 18 weeks of dosing) and 6.2 µg.hr/ml for pregnant females (on GD 17 after dosing from GD 6).

- [When the dosed males (after ~18 weeks of dosing) were paired with untreated females (~13 weeks after pairing/mating with dosed females), there was no decrease in fertility index compared with controls, but the fertility index in controls was quite low and probably confounded this finding.]
- [Based on supporting studies (reviewed below), it appears that much (if not all) of the decreased fertility seen in the current study, where both males and females were administered drug prior to pairing/mating, is due to maternal (not paternal) effects.]

**Study no.:** RPT-46325.

**Volume #, and page #:** electronic submission, 742 pages.

**Conducting laboratory and location:** Drug Safety, Wyeth Research, Chazy, NY.

**Date of study initiation:** first day of dosing: 4/22/02 for males, 5/6/02 for females).

**GLP compliance:** yes, see page 237.

**QA reports:** yes, see pages 239-240.

**Drug, lot #, and % purity:** DVS-233 (WY-45233 succinate, monohydrate), lot/batch # RB1636, total impurities = \_\_\_\_\_ (revalidation release date 11/12/2001, see page 153 of the report).

## Methods

**Doses:** oral gavage doses of 0, 30, 100, and 300 mg/kg.

**Species/strain:** male and female CD<sup>®</sup> rats, \_\_\_\_\_ CD<sup>®</sup> (SD) IGS BR \_\_\_\_\_, aged 7-9 weeks (males) and 11-13 week (females), weighing 305-360 g (males) and 213-295 g (females), for dosed reproductive assessment; untreated females aged 13-15 weeks at GD0; time-mated females aged 8-10 weeks, weighing 215-250 g.

**Number/sex/group:** 25/sex/dose.

**Housing:** individually in polycarbonate cages with \_\_\_\_\_ bedding, food and water ad lib; except during cohabitation, when pairs were housed in suspended stainless steel cages; assigned to cages by weight-ordered randomization and dose groups were randomly dispersed (one group per column) on each rack.

**Route, formulation, volume, and infusion rate:** oral gavage, as suspension in 0.25% polysorbate 80 and 0.5% methylcellulose (4000 cps) in purified water (10 ml/kg); prepared approximately every 2 weeks and stored refrigerated and protected from light; pH of control was 6.2-9.4, pH of drug formulations was 4.7-5.2; drug formulations were assessed for drug content and found to range from 91.2-103% of nominal concentration; homogeneity was not analyzed, but previous data was referenced.

**Satellite groups used for toxicokinetics:** PK was conducted on GD 17 on a separate group of time-mated (gravid) females treated at 30, 100, or 300 mg/kg, with blood drawn from 3/dose at 0.5 and 4 or 1 and 10 or 2 and 24 hr after dosing; reported under RPT-46989. [PK was also conducted on dosed males following determination of fertility with untreated females (~week 18 of dosing), from blood drawn from 3/dose/timepoint at 0.5, 1, 2, 4, 7, 10, and 24 hr after dosing.]

Study design: female were dosed for 2 weeks prior to cohabitation (with dosed-males) through GD20 and were euthanized on GD 21 for analysis of maternal and fetal parameters; males were dosed for 4 weeks prior to and during cohabitation with dosed females, and due to low pregnancy rate, dosing was continued for 13 more continuous weeks at which time the dosed males were cohabited with untreated females.

Parameters and endpoints evaluated: adult mortality, clinical observations, body weight, food consumption (males and dosed females), estrous cycles (dosed females), fecundity parameters (mating and fertility indices and time to mating), gravid uterine weight, hysterotomy findings on GD 21 (corpora lutea, litter size, embryo/fetal mortality), postmortem observations, and macroscopic, microscopic, and organ weight evaluations in males (testes, epididymides, seminal vesicles, and prostate); placental appearance; fetal sex, weight, external and palatal anomalies; and fetal skeletal and visceral anomalies (offspring from dosed females only).

## Results

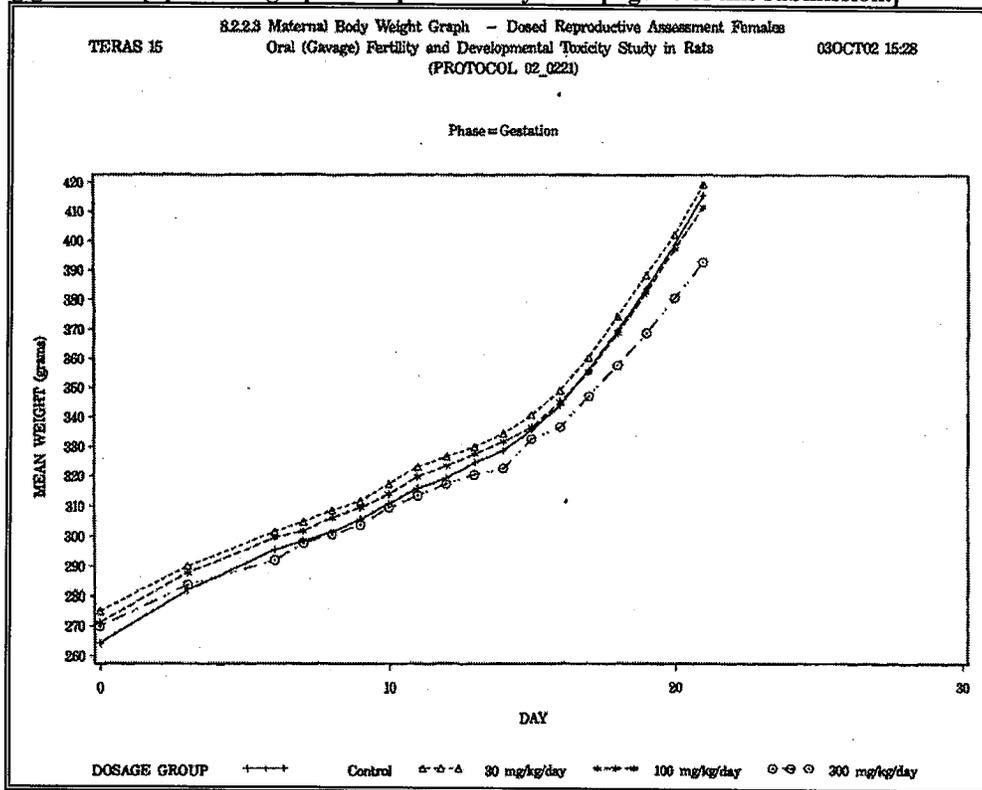
Mortality: None of the premature deaths was attributable (directly) to drug treatment. Two HD males died prior to cohabitation with dosed females: 1 due to gavage trauma (esophageal perforation at necropsy), 1 with changes that were assumed to be spontaneous (hydronephrosis, enlarged kidneys, distended ureter and urinary bladder, and thickened wall of urinary bladder), because similar findings were not seen after 18 weeks of treatment in the current study, nor were they seen at 3-times the dose (1000 mg/kg) in a 13-week study. The 2 reproductive assessment females paired with these males were electively euthanized prior to mating. Additionally, 1 MD female in the TK group died after blood collection; this death was considered accidental.

Clinical signs: CNS signs, including: salivation at  $\geq 30$  mg/kg reciprocal forepaw treading (proserotonergic) at  $\geq 100$  mg/kg; other signs included red pigment around nose/mouth and/or eyes and yellow discoloration of fur, especially in perineal area.

Body weight and food consumption: In males: decreased body weight gain in HDM ( $\downarrow 15\%$  vs controls at week 4, with slightly decreased food consumption); after 18 weeks of dosing in males, there was dose-related decreased body weight gain at  $\geq 30$  mg/kg (76-91% of controls) and **decreased body weight** (89-96% of controls). In females: no effects on body weight prior to mating (decreased food consumption in MDF ( $\downarrow 10\%$ ) and HDF ( $\downarrow 19\%$ ) during week 1), although food consumption was decreased in MDF (90% of controls) and HDF (81% of controls). After 2 weeks of dosing (at the time of pairing) and at the beginning of gestation, the mean weights of all treated groups tended to be higher than controls. During gestation HDF gained less body weight than other groups (81% of control value; see figure, below) and had decreased gravid uterus weights (86% of controls); adjusted (for gravid uterine weight) gestation body weight gain was decreased in MDF (81% of control) and HDF (73% of control); food consumption was decreased in

all female dose-groups during GD 0-5 (preimplantation; dose-related 81-94% of controls) and in HDF throughout gestation (GD0-20; 88% of controls).

**Figure 11. Desvenlafaxine treatment at HD of 300 mg/kg decreased body weight gain of female rats during gestation. [Sponsor's graph excerpted directly from page 76 of this submission.]**



**Toxicokinetics:**

Table 33. Systemic exposures to desvenlafaxine in male rats (after 18 weeks of daily dosing; the same rats used for mating) and pregnant female rats (after daily dosing from GD 6-17; not the same rats used for mating). [Sponsor's tables excerpted directly from page 25 (males) and page 30 (females) of the study report.]

MALES	Dosage	C <sub>max</sub>	t <sub>max</sub>	AUC <sub>0-24</sub>	t <sub>1/2</sub> <sup>a</sup>	AUC/Dose
	(mg/kg/day)	(ng/mL)	(hr)	(ng·hr/mL)	(hr)	
	30	1016 ± 168	1.0	2882 ± 254	4.1	96.1 ± 8.5
	100	2634 ± 568	1.0	14456 ± 1175	3.1	145 ± 12 <sup>b</sup>
	300	5601 ± 1526	0.5	52610 ± 3654	2.9	175 ± 12 <sup>b</sup>

a: Determined from the mean concentration - time profiles  
 b: Significantly different than the corresponding value at the lowest dosage (30 mg/kg/day)

PREGNANT FEMALES	Dosage	C <sub>max</sub>	t <sub>max</sub>	AUC <sub>0-24</sub>	t <sub>1/2</sub> <sup>a</sup>	AUC/Dose
	(mg/kg/day)	(ng/mL)	(hr)	(ng-hr/mL)	(hr)	
	30	1465 ± 295	1.0	6195 ± 467	5.7	207 ± 16
	100	2623 ± 408	1.0	22960 ± 1759	4.4	230 ± 18
	300	7129 ± 1708	4.0	95437 ± 16088	ND	318 ± 54 <sup>b</sup>
a: Determined from the mean concentration - time profiles b: Significantly different than the corresponding value at the lowest dosage (30 mg/kg/day) ND: Not Determined due to insufficient data in the terminal phase						

**Necropsy:** In males (after ~18 weeks of dosing): **Prostate weights** (absolute and relative to body weight) were decreased (dose-relatedly) at all doses, with dose-related increased incidence of (slight) microscopic **prostate atrophy** at MD (28%) and HD (61%), compared with controls (4%) and LD (4%).

**Fertility parameters for pairings of dosed females and dosed males (see tables, below):** Essentially all pairs of rats mated (mating index ranged from 92-96%), however, the **time to mate was doubled in dosed groups** compared with control (see table, below). The fertility index was dose-dependently decreased: 100% of controls, 96% at LD, 83% at MD and 50% at HD became pregnant (see table, below).

**Table 34. Mating and fertility indices (upper panel) and time to mating (lower panel) for male and female rats administered desvenlafaxine by oral gavage. [Sponsor's tables excerpted directly pages 95 and 93 of the study report.]**

PARAMETER		GROUP	N	TOTAL NUMBER	MEAN	PERCENT REFERENCE	STANDARD DEVIATION	TREND P-VALUE	OVERALL P-VALUE	PAIRWISE P-VALUE
8.2.2.6 Mating and Fertility Indices Summary and Analysis - Dosed Females Teras 15 Oral (Gavage) Fertility and Developmental Toxicity Study in Rats (PROTOCOL 02_0221) 02JAN04 11:26										
MATING INDEX	Control		24	22	0.92	100	0.28		0.885	
	30 mg/kg/day		25	24	0.96	105	0.20	F		F
	100 mg/kg/day		25	23	0.92	100	0.28	F		F
	300 mg/kg/day		23	22	0.96	104	0.21	0.633-		F
FERTILITY INDEX	Control		22	22	1.00	100	0.00		0.001	
	30 mg/kg/day		24	23	0.96	96	0.20	0.169-		0.674
	100 mg/kg/day		23	19	0.83	83	0.39	0.012-		0.085
	300 mg/kg/day		22	11	0.50	50	0.51	0.001-		0.001
Sign(positive, negative) of Trend P-value indicates direction of trend test. No sign indicates a two tailed test was performed. F denotes follow up test not appropriate.										
8.2.2.7 Time to Mate Summary and Analysis - Dosed Females Teras 15 Oral (Gavage) Fertility and Developmental Toxicity Study in Rats (PROTOCOL 02_0221) 03OCT02 14:43										
TIME TO MATE (Days)	Control		22	2.23	100	1.15			0.007	
	30 mg/kg/day		24	4.38	198	3.15	0.002+			0.002
	100 mg/kg/day		23	4.13	185	3.36	0.014+			0.026
	300 mg/kg/day		22	5.55	227	3.58	0.002+			0.002

In dosed females: Disrupted estrus cycles (such as variable cycle lengths, 3 consecutive days in estrus, no identified estrus, only 1 completed cycle in the 14-day period) occurred with higher incidence in all dosed groups: 2/25 controls, 11/25 LDF, 9/25 MDF, and 15/23 HDF. However, for estrus cycles that were fully completed, mean length was similar between groups. The Sponsor considered the decreased fertility in rats (changes in estrus cycling and time to mating) due to SSRI action (to stimulate prolactin production/release, which can/may alter estrus cycles and induce pseudo pregnancy).

Maternal reproduction parameters for dosed females (see table, below): There were no treatment effects on number of corpora lutea, however, **pre-implantation loss was increased at HD**, with implantation sites for only 73% of the corpora lutea, compared with 96% in controls. There was no treatment effect on post-implantation loss. However, there was a 14% decrease in the number of live fetuses (per litter) at the HD, compared with controls, presumably reflecting the increased pre-implantation loss (17% at HD, compared with only 4% for controls). When I calculated the ratio of live fetuses:corpora lutea and live fetuses:implantation sites for each dam in each treatment group, this assumption was confirmed: there was no difference among groups when the number of live fetuses was normalized to implantation sites (88.6, 90.7, 92.1, and 90.1% for controls, LD, MD, and HD, respectively); however, when the number of live fetuses was normalized to corpora lutea, the number at the HD was less than for the other groups (75.1% for HD, compared with 85.8, 81.8, and 88.3 for controls, LD, and MD, respectively). Thus, **the slight decrease in live fetuses/litter at the HD was due to pre-implantation loss (and contributed to the decreased fertility index).**

**Table 35. Maternal variables from study of 0, 30, 100, and 300 mg/kg oral (gavage) doses of desvenlafaxine in rats (females dosed from 2 weeks prior to mating through GD 20, with analysis on GD 21; males dosed for 4 weeks prior to and through mating). [Compiled from values from summary tables on pages 97-99 of study report.]**

PARAMETER	DOSE, mg/kg/d (through GD21)			
	0	30	100	300
Paired females	24	25	25	23
Mated females	22	24	23	22
<b>Pregnant Females at termination</b>	<b>22</b>	<b>23</b>	<b>19</b>	<b>11</b>
Mean corpora lutea	17.1	17.6	16.8	16.7
Mean implantation sites	16.5	15.9	16.1	13.9
<b>Pre-implantation loss, %, per dam</b>	<b>4%</b>	<b>10%</b>	<b>4%</b>	<b>17%</b>
<b>Mean live fetuses</b>	<b>14.6</b>	<b>14.4</b>	<b>14.8</b>	<b>12.6</b>
Mean dead fetuses	0.0	0.05	0.0	0.0
Mean early resorptions	1.86	1.41	1.26	1.27
Mean late resorptions	0.00	0.05	0.00	0.09
Post-implantation loss, %, per dam	11%	9%	8%	10%

***Fetal parameters (from matings of dosed dams and dosed sires):***

Fetal weights and sex ratios (see table, below): Fetal weights were slightly decreased (4% for males and 9% females) at HD, compared with controls. There was no effect of treatment on sex distribution.

Fetal terminal and necroscopic evaluations: Treatment did not affect external morphology; and there were not treatment-related changes in visceral or skeletal findings. For comparison, the incidences of overall decreased skeletal ossification are presented in the table, below.

**Table 36. Embryo/fetal variables from study of 0, 30, 100, and 300 mg/kg oral (gavage) doses of desvenlafaxine in rats (females dosed from 2 weeks prior to mating through GD 20, with analysis on GD 21; males dosed for 4 weeks prior to and through mating). [Compiled from values from summary tables on pages 103-104 (for fetal weights) and pages 109-123 (for morphological abnormalities) of study report.]**

PARAMETER	DOSE, mg/kg/d (gestational D6-17)			
	0	30	100	300
Mean live fetuses/litter	14.6	14.4	14.8	12.6
Males per litter	6.9	5.9	9.1	6.0
Mean % males	52	46	45	55
Mean fetus weights, g				
males	5.11	5.17	4.96	4.92*
females	4.85	4.89	4.77	4.43*
Total litters examined	22	22	19	11
Total fetuses examined for external abnormalities	322	317	281	138
Total fetuses examined for visceral abnormalities	162	158	141	71
Total fetuses examined for skeletal abnormalities	160	159	140	67
Vascular variations	4/162 2/22	11/159 7/22	6/141 4/19	1/71 1/11
Decreased skeletal ossification	65/160 20/22	52/159 17/22	62/140 17/19	21/67 9/11

Placental morphology was not altered by treatment. The finding of fused placentas in 2 HD does and 1 control was considered spontaneous, as it is a commonly observed at the test facility.

Treated males mated with untreated females: There was no decrease in mating index due to treatment of males; essentially all pairs mated with mean times to mating of 2-3 days (see table, below). Although the fertility index was not decreased for any dose-group compared with controls (see table, below), the fertility index for controls (83%) appeared to be low (lower than that for the LD); this may have confounded the interpretation. The mating of the dosed males with untreated females revealed no treatment effects on female body weights or weight gains, gravid uterine weights, fetal sex ratios, or fetal weights; fetal external morphology was not altered (with only a single misshapen tail at MD); and placental morphology was un affected (with only fused placentas seen in control and HD groups).

**Table 37. Mating and fertility indices (upper panel) and time to mating (lower panel) for dosed male rats (administered desvenlafaxine by oral gavage for ~18 weeks) paired with untreated cohort female rats (~13 weeks after pairing/mating with dosed females). [Sponsor's tables excerpted directly pages 139 and 137 of the study report.]**

8.3.1.6 Mating and Fertility Indices Summary and Analysis - Cohort Females										
TERAS 15		Oral (Gavage) Fertility and Developmental Toxicity Study in Rats (PROTOCOL 02_0221)						02JAN04 11:41		
PARAMETER	GROUP	N	TOTAL NUMBER	MEAN	PERCENT REFERENCE	STANDARD DEVIATION	TREND P-VALUE	OVERALL P-VALUE	PAIRWISE P-VALUE	
MATING INDEX	Control	24	23	0.96	100	0.20		0.390		
	30 mg/kg/day	25	25	1.00	104	0.00	F			
	100 mg/kg/day	25	25	1.00	104	0.00	F		F	
	300 mg/kg/day	23	23	1.00	104	0.00	0.911-		F	
FERTILITY INDEX	Control	23	19	0.83	100	0.39		0.667		
	30 mg/kg/day	25	23	0.92	111	0.28	F			F
	100 mg/kg/day	25	20	0.80	97	0.41	F			F
	300 mg/kg/day	22	18	0.82	99	0.39	0.325-			F
Sign(positive, negative) of Trend P-value indicates direction of trend test. No sign indicates a two tailed test was performed. F denotes follow up test not appropriate.										
8.3.1.5 Time to Mate Summary and Analysis - Cohort Females										
TERAS 15		Oral (Gavage) Fertility and Developmental Toxicity Study in Rats (PROTOCOL 02_0221)						03OCT02 14:43		
PARAMETER	GROUP	N	MEAN	PERCENT REFERENCE	STANDARD DEVIATION	TREND P-VALUE	OVERALL P-VALUE	PAIRWISE P-VALUE		
TIME TO MATE (Days)	Control	23	3.09	100	1.76		0.188			
	30 mg/kg/day	25	2.36	76	1.08	F			F	
	100 mg/kg/day	25	2.60	84	1.47	F			F	
	300 mg/kg/day	23	2.09	68	1.12	0.973+			F	

**2.6.6.6.1.2 Clarification studies**

The Sponsor has provided several additional studies aimed at clarifying the effects DVS on fertility in rats seen in the study above. One study, where the previous HD (300 mg/kg) was administered to male and female rats prior to pairing/mating (as was done in the earlier study), confirmed the decrease in live embryo/fetuses per litter and increased post-implantation loss, but not the increased time to mating, or decreased fertility index, seen in the previous study. Based on the reversibility part of this study, the decreased live embryos and increased post-implantation loss were reversible after discontinuation of the drug (discontinuation for 2 weeks in females and 10 weeks in males). This study also determined that 10-week dosing of male rats at 300 mg/kg DVS did not alter sperm parameters (number or motility) and did not alter sex hormones (testosterone, prolactin, DHT) when measured near the time of mating; however, the lack of effect on time to mating or fertility index in this study makes the negative findings on these hormonal parameters less useful.

In another study, designed to separate the effects of DVS on males and females, rats were treated with 100 or 300 mg/kg DVS (from 4 weeks prior to pairing/mating for males, from 2 weeks prior to pairing/mating for females), then paired/mated with untreated rats of the opposite sex (dosed males to virgin females, dosed females to male breeders). When only males were treated with DVS, there were no deficits in fertility. When only females were treated with DVS, there were alterations in their estrus cycles and the time to mating was increased. This study suggests that much (if not all) of the decreased fertility seen when both males and females were dosed with DVS in the earlier study was due to effects on the dosed females.

A final study attempted to further examine the effects of DVS (at 300 mg/kg) on estrus cycles of female rats and to investigate the reversibility of those effects. However, that study did not provide any useful information, because there were no clear effects on estrus cycles during the 4 weeks of dosing with DVS.

These 3 studies are summarized below.

DVS-233: MULTIPLE DOSE ORAL (GAVAGE) INVESTIGATIVE REPRODUCTION STUDY IN RATS (PROTOCOL 04\_1812): Study rpt-57867 (Wyeth, Chazy, NY; GLP (see page 262); QAed (see pages 264-265); electronic submission, 262 pages; first day of dosing: 10/18/04 for males, 12/13/04 for females non-reversibility phase, 2/7/05 for females reversibility phase).

Objective: effects on male reproductive hormones and epididymal sperm counts, epididymal motility and reversibility of effects on estrus cyclicity and fertility.

Methods: 0 or 300 mg/kg (DVS, lot/batch RB1636) to male (for at least 10 wks prior to and during pairing for non-reversibility phase and 10 weeks of dosing followed by 10 weeks drug-free prior to pairing) and female (for at least 2 weeks prior to and during pairing and gestation (to GD 7) for non-reversibility phase and 2 weeks of dosing followed by at least 2 weeks drug-free prior to pairing) rats — CD (SD) IGS BR, 15/sex/dose for each phase, non-reversibility and reversibility).

Endpoints evaluated: mortality, clinical observations, body weight, food consumption, estrous cycles, fecundity parameters (mating behavior [non-reversibility phase], mating and fertility indices, time to mating), gravid uterine weight, hysterotomy findings on GD 12 (corpora lutea, litter size, embryo mortality), male hormone levels, weights of testes, epididymides, and prostate, epididymal sperm count and motility, and postmortem observations.

Results: salivation in M and F, yellow discoloration of peltage and red pigment around nose/mouth in F; slight transient decreased in body weight gain and food consumption. **No effects on estrous cyclicity** measured for 2 weeks prior to and 2 week during pairing/mating (*which was altered in earlier study*); **no effects on mating performance** (mating index was 100% in both groups of non-reversibility rats and 93% in both groups of reversibility rats; **no differences in time to mate, which was increased in earlier study**); **no effects on fertility** (fertility index was 100% for all groups, dosed or control, non-reversibility or reversibility; *which was decreased in earlier study*); **decreased**

**number of live embryos** (when pairing occurred during dosing period) **that reflected increased post-implantation loss** (due to dead embryos) and possibly (non-significant) decrease in corpora lutea and increase in pre-implantation loss; no effects on these parameters when mating occurred after 10 and 2 weeks drug discontinuation in M and F, respectively (see table, below); for males, no effects on sperm parameters (counts or motility), concentrations of prolactin, testosterone, or DHT or reproductive organ weights in males in either non-reversibility or reversibility groups.

**Table 38. Maternal variables from study of 0 and 300 mg/kg oral (gavage) doses of desvenlafaxine administered to rats prior to and during mating and gestation (females dosed from 2 weeks prior to mating through GD 7, with analysis on GD 12; males dosed for 4 weeks prior to and through mating), compared with rats mated after discontinuation of dosing (2 weeks and 10 weeks after discontinuation in females and males respectively). [Compiled from values from summary tables on pages 93-96 of study report.]**

PARAMETER	DURING DOSING (IRREVERSIBILITY)		AFTER DISCONTINUATION (REVERSIBILITY)	
	Control	300 mg/kg	Control	300 mg/kg
Paired females	14	15	15	14
Mated females	14	15	14	13
Pregnant Females at GD 12	14	15	14	13
Mean corpora lutea	16.4	15.1	16.2	16.6
Mean implantation sites	15.9	13.7	15.8	16.0
Pre-implantation loss, %, per dam	3%	9%	3%	4%
Mean live embryos	15.3	<b>12.7*</b>	14.9	15.2
Mean dead embryos	0.14	0.40	0.14	0.00
Mean resorptions	0.43	0.67	0.71	0.82
Post-implantation loss, %, per dam	4%	<b>8%*</b>	6%	5%

**Conclusions:** This study confirms the decrease in live embryo/fetuses per litter and increased post-implantation loss in pregnancies resulting from mating male and female rats that have been dosed with DVS-233 at 300 mg/kg (from 10 week prior to and through mating for males and from 2 weeks prior to and through at least GD 7 for females). In this study, fertility was determined at GD 12 (compared with GD 21 in the earlier study), so the increased post-implantation loss was due to dead embryos, rather than resorptions. Based on the reversibility part of this study, the decreased live embryos and increased post-implantation loss were reversible after discontinuation of the drug (discontinuation for 2 weeks in females and 10 weeks in males). This study also determined that 10-week dosing of male rats at 300 mg/kg DVS did not alter sperm parameters (number or motility) and did not alter sex hormones (testosterone, prolactin, DHT) when measured near the time of mating; however, there was also no effect of this treatment on mating index, time to mating, or fertility index in this study. This study did not confirm the prolonged time to mating or the decreased fertility index seen in the earlier study.

DVS-233: ORAL (GAVAGE) FERTILITY STUDY IN RATS (PROTOCOL 03\_1705): Study rpt-52502 (Wyeth, Chazy, NY; GLP (see page 229); QAed (see page 231); electronic submission, 248 pages; first day of dosing: 11/24/03 for males, 1/5/04 for females).

Objective: investigating gender sensitivity of impaired fertility (seen in study above).

Methods: doses of 0, 100, 300 mg/kg (DVS-233, lot/batch number RB2691) to male and female rats (15/sex/dose;  $\bar{X}$  CD (SD) IGS BR rats, pairing/mating was conducted for dosed males with untreated (cohort) females (15/dose), and for dosed females with breeder males (15/dose); at GD14, histopathological assessment of fertility. Dosed males were dosed for 4 weeks prior to pairing/mating and through ~GD 14 (for untreated females). Dosed females were dosed from 2 weeks prior to pairing/mating through GD 7.

Results: dosed males, salivation at both doses, decreased body weight, weight gain, and food consumption at HD, no effects on ability to mate, time to mate, or fertility (paired with untreated females); cohort females, no deaths, no effects on clinical observations, body weights or weight gains, gravid uterine weights, food consumption, estrous cycles, mating performance and fertility (1 from each group was not pregnant), with increased pre-implantation losses at HD, but largely confined to 1 female.

dosed females, clinical obs of salivation at MD, HD, red pigment around nose/mouth and yellow discoloration of peltage at HD, decreased body weight gain at both doses in first week of gestation, decreased food consumption at HD during first week of treatment and first week of gestation, **no effects on gravid uterine weights; altered estrus cycles at HD** (9/15 entered prolonged diestrus and stopped having regular cycles); **all dosed females mated, but mean time to mate was increased by approximately 1 day at both doses** (3.4 days at 100 mg/kg, 3.0 days at 300 mg/kg, compared with 2.1 days for controls) at both doses, but **no reduction in mating index (100% for all 3 groups) or pregnancy rates (fertility index was 93% for controls and 100 mg/kg group, 100% for 300 mg/kg group)**, no effect on number of corpora lutea, no clear increase in pre-implantation loss (mean values of 2% for controls, 9% for 100 mg/kg group and 5% for 300 mg/kg group), no effect on post-implantation loss, number of live embryos, number of implantations (all parameters determined at GD 14 with dosing through GD 7).

Conclusions: The decrease in fertility seen in the previous study where both males and female rats were dosed prior to pairing/mating was not seen in this study where dosed males and dosed females were paired/mated with untreated virgin females and male breeders, respectively. No decrements in fertility were seen for dosed males paired/mated with untreated females. For dosed females, estrus cycles were altered at HD (prolonged diestrus) and the time to mate was increased (without a decrease in mating index); however, the other parameters that were altered in the earlier study (fertility index, gravid uterine weights, pre-implantation loss) were not affected in this study where only females were treated (and assessment was made at GD 14, vs GD 21 in the earlier study).

**DESVENLAFAXINE SUCCINATE: ORAL (GAVAGE) ESTROUS CYCLE EVALUATION STUDY OF DESVENLAFAXINE SUCCINATE IN FEMALE RATS (WYETH PROTOCOL 05\_1726) Study rpt-60456**

, GLP (see pages 11-12); QAed (see pages 13-15); electronic submission, 149 pages; first day of dosing: 8/2/05).

**Objective:** disturbance of cyclicity and reversability of effect.

**Methods:** 0 or 300 mg/kg (DVS-233, lot/batch RB1636) administered (by oral gavage as a suspension in 0.25% polysorbate 80; 0.5% methylcellulose (4000 cps); 10 ml/kg) to female rats (virgin female CD(SD) rats, 30/dose; ~83 days old (~12 weeks) at start of dosing) for 28 days, followed by 4-week recovery period; estrus cycling also monitored for 2 weeks prior to dosing. Endpoints: mortality, clinical observations, body weight, food consumption, estrus cycles, and postmortem observations following a four-week recovery period.

**Results:** no mortalities; salivation; slightly (8%) decreased food consumption, but no effect on body weight or gain; post mortem unremarkable. The study report claims 1) DVS-233 dosing resulted in increased incidence of rats with increased cycle length and resulting decreased number of cycles during the 28-day dosing period; and 2) perturbations in cycling persisted for ~2 weeks after discontinuation of dosing, but during the second week of recovery, the average number of cycles, the number of rats with 3 cycles (per 14 days), and the number of rats with 6 or more consecutive days of diestrus were comparable between groups. However, inspection of the data (see table, below) does not support these claims: 1) although the average number of cycles per 14 days was increased in the DVS group (compared with controls) during the first week of dosing, this was not the case during the second week of dosing or the overall value for the 4 weeks of dosing; and 2) although the average number of cycles per 14 days was increased in the DVS group (compared with controls) during the first week following cessation of dosing, this cannot really be considered a persistence, since it was not seen during the week of dosing just prior to cessation of dosing; similarly the lack of effects in the DVS group during dosing cessation (the second week or whole 4 weeks) cannot be considered a reversal, since there was no (persistent) effect during dosing.

**Table 39. Effects on estrus cycles prior to, during, and after discontinuation of 300 mg/kg DVS-233 administered by oral gavage to female rats (30/dose) for 2 weeks. [Compiled from values from summary tables from pages 36-42 of study report.]**

DOSING PHASE		CYCLES/14 DAYS		% RATS WITH 3 CYCLES/14 DAYS		% RATS WITH >6 DAYS DIESTRUS	
		control	DVS	control	DVS	control	DVS
Pre-dosing	D-13-0	3.0	3.1	83.3%	<b>56.7%*</b>	0%	0%
Dosing	D2-16	3.7	<b>3.2*</b>	23.3%	36.7%	0%	3.3%
	D17-29	2.9	2.7	70.2%	46.7%	6.7%	13%
	D2-29	3.3	3.0	6.7% <sup>1</sup>	6.7% <sup>1</sup>		
Recovery	D30-43	3.5	<b>2.8*</b>	33.3%	43.3%	3.3%	23%
	D44-57	2.5	2.7	63.3%	60.0%	20%	17%
	D30-57	3.0	2.8	10% <sup>2</sup>	16.7% <sup>2</sup>	20%	37%

<sup>1</sup>: most rats in both groups had 7 cycles/4 weeks: 80% of controls and 60% of DVS group.

<sup>2</sup>: most rats in both groups had 7 cycles/4 weeks: 60% of controls and 33% of DVS group.

**Conclusions:** This study did not provide useful information about DVS effects on estrus cycling in rats and their reversal, because there were no clear effects during the 4 weeks of dosing.

#### 2.6.6.6.1.3 Dose-range finding studies

REPRODUCTIVE EVALUATION OF WY-45,233 IN THE ADULT MALE AND FEMALE RAT: (study report gtr-15791; 1988; Wyeth-Ayerst; 6-page report): male and female S-D rats (CD®) were administered desvenlafaxine (females: Wy-45,233 E (base), corrected for 66.26 % active moiety; males: Wy-45,233 D (acid)) at 50 mg/kg by oral gavage as suspension in water; 1) female rats dosed on day of proestrus and euthanized 1 day later at estrus: no decrease in number of rats ovulating or in number of ova shed; 2) females caged with males on evening of proestrus and dosed GD 1-7 (claudogen: pre-implantation) or GD7-12 (interceptive: post implantation): no change in number of implantation sites or inhibition of pregnancy (at least 1 live fetus); 3) male rats dosed daily for 14 days, with necropsy at day 15: no obvious effects on body weights, or weights of prostate, seminal vesicles, epididymides, testes, levator ani, adrenal, thyroid, anterior pituitary.

DVS: ORAL (GAVAGE) FERTILITY AND DEVELOPMENTAL TOXICITY DOSE RANGING STUDY IN RATS: (Study rpt-45574; 2002; Wyeth, Chazy, NY; 212-page report): oral gavage doses of 0, 75, 225, and 675/450 mg/kg to male (for 4 weeks prior to cohabitation) and female (for 2 weeks prior to cohabitation through GD 20; HD lowered on day 9, due to 6% body weight loss) S-D rats (CD VAF; 10/sex/dose), females were euthanized on GD21.

**Results:** CNS signs; decreased body weight gain; no effects on mating performance or estrous cycles; decreased fertility rates esp at HD (↓30%); dose-related decreased fetal weights at MD (↓7%) and HD (↓12%) and decreased placental weights; no effects on mean numbers of implantations per litter, live fetuses per litter, pre- and post-implantation loss, fetal gross morphology, fetal sex distribution, or placental appearance; NO(A)EL for general reproductive performance (estrous cycles, mating, and fertility) = 225 mg/kg; NO(A)EL for prenatal offspring development = 75 mg/kg.

DVS-233: MULTIPLE DOSE ORAL (GAVAGE) INVESTIGATIVE REPRODUCTION STUDY IN FEMALE RATS (PROTOCOL 04\_1661): Study rpt-56476: (Wyeth, Chazy, NY; not GLP (see page 81); not QAed; electronic submission, 102 pages; first day of dosing: 9/20/04).

**Objective:** investigating estrus cycling and repro hormones in female rats.

**Methods:** 0 or 300 mg/kg for at least 2 weeks (15 female rats/dose).

**Results:** alopecia and salivation, slight decreased in body weight gain and food consumption during first week of dosing, slight increase in rats not cycling or cycling irregularly, associated with decreased prolactin and estrogen during diestrus, which changes are considered the cause of the alterations of cyclicity.

### 2.6.6.6.2 Embryofetal development

The effects of desvenlafaxine were determined on embryo-fetal development in both rats and rabbits. The embryo-fetal effects in rats were assessed in the same study that was used to assess effects on fertility (and reviewed, above), so only the results on embryo-fetal development were presented in this section. The study report for the rabbit study is reviewed in full here (below).

#### 2.6.6.6.2.1 In rats

**Study title:** DVS-233: ORAL (GAVAGE) FERTILITY AND DEVELOPMENTAL TOXICITY STUDY IN RATS (PROTOCOL 02\_0221).

This study also served as a fertility study and was reviewed in detail under that section (above). Only the key study findings are presented here.

#### Key study findings:

- Doses: 0, 30, 100, and 300 mg/kg by oral gavage for 2 weeks prior to cohabitation (with dosed-males) through GD20 for females, with analysis on GD 21; dosing for 4 weeks prior to and during cohabitation (with dosed females) for males;
- No treatment-related mortalities;
- Dosed males: 5-10% decreased body weights (MTD); decreased prostate weights at all doses, with dose-related increased incidence of (slight) microscopic prostate atrophy at MD and HD (after ~18 weeks of dosing).
- Dosed females: decreased food consumption at all doses during GD 0-5 (pre-implantation) and at HD throughout gestation (GD0-20); decreased body weight gain during gestation at HD (not clearly an MTD).
- Fertility parameters: disruption of estrus cycles at all doses; doubling of time to mate at all doses, but no effect on mating index; **decreased fertility index** (fraction that became pregnant) at MD (83%) and HD (50%), compared with control (100%); **decreased gravid uterine weights** at HD.
- Maternal parameters: **increased pre-implantation loss** at HD; but no effect on post-implantation loss or number of live fetuses (when normalized to implantation sites).
- Fetal parameters: **fetal weights were slightly decreased** (4% for males and 9% females) at HD; **no teratogenesis**. [NB Due to the pregnancy rate at HD, only half as many fetuses were evaluated at the HD.]
- NOAEL for fertility is (arguably) the LD of 30 mg/kg (with only disrupted estrus cycles and doubling of time to mate); based on decreased fertility index at MD (but not LD), and increased pre-implantation loss and decreased gravid uterine weight at HD; no teratogenesis up to HD of 300 mg/kg. The NOAEL dose of 30 mg/kg in rats is 1.5 times the MRHD of 200 mg/day on a mg/m<sup>2</sup> basis (for a 60-kg adult) [30 mg/kg (in rats) x 6/37 = 4.86 mg/kg (in humans) x 60 kg = 290

mg/day = 1.5 x 200 mg]. The AUC at 30 mg/kg was 2.8 µg.hr/ml for males (determined after 18 weeks of dosing) and 6.2 µg.hr/ml for pregnant females (on GD 17 after dosing from GD 6).

- **NOAEL for teratogenicity is presumed to be >300 mg/kg. (However, the number of fetuses evaluated at that dose was only half that for other groups, because of the low pregnancy rate and wasn't an adequate test of teratogenicity at that dose).** The (presumed) NOAEL dose of 300 mg/kg in rats is 15 times the MRHD of 200 mg/day on a mg/m<sup>2</sup> basis (for a 60-kg adult) [300 mg/kg (in rats) x 6/37 = 48.6 mg/kg (in humans) x 60 kg = 2916 mg/day = 15 x 200 mg]. **It seems more appropriate to consider the NOAEL for teratogenicity to be 100 mg/kg, the highest dose that had adequate numbers of fetuses for analysis; 100 mg/kg is 5 times the MRHD on a mg/m<sup>2</sup> basis.** The AUC at 300 mg/kg was 95 µg.hr/ml and that at 100 mg/kg was 23 µg.hr/ml for pregnant females (on GD 17 after dosing from GD 6).

#### 2.6.6.6.2.2 In rabbits

**Study title:** DVS-233: ORAL (GAVAGE) DEVELOPMENTAL TOXICITY STUDY IN MATED FEMALE RABBITS (PROTOCOL 02\_0177).

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

- Doses: 0, 7.5, 25, 75 mg/kg GD 6-18, with analysis on GD 29;
- 2 deaths due to gavage trauma (1 LD, 1 HD);
- 2 abortions (1 L, 1 HD)
- **Maternal toxicity:** slight (3%) decrease in food consumption at HD, without change in body weight gain [in a DRF study, this dose resulted in reduced body weight gain (to 81% of controls) and decreased food consumption (to 92% of controls) and was within ~10-fold of a lethal dose.];
- **Embryo/fetal toxicity:** no effects on embryo/fetal mortality, fetal weight, fetal morphology (including sex distribution), or placental appearance; **no teratogenicity;**
- **The NOEL for both maternal and developmental effects, including teratogenicity, was the HD of 75 mg/kg.** [Although an MTD for maternal toxicity was not demonstrated in this study, the HD could be considered acceptable based on mortality at less than 10-fold that dose in a supporting study.] The NOAEL dose of 75 mg/kg in rabbits is 7.3 times the MRHD of 200 mg/day on a mg/m<sup>2</sup> basis (for a 60-kg adult) [75 mg/kg (in rabbits) x 12/37 = 24.3 mg/kg (in humans) x 60 kg = 1460 mg/day = 7.3 x 200 mg]. The AUC at this dose of 75 mg/kg on GD 18 was 2.5 µg.hr/ml.

**Study no.:** RPT-46439.

**Volume #, and page #:** electronic submission (249 pages).

**Conducting laboratory and location:** Drug Safety, Wyeth Research, Chazy, NY.

**Date of study initiation:** first day of dosing (for first mated females): 4/20/02;  
euthanasia of last female: 5/22/02.

**GLP compliance:** yes, see page 119.

**QA reports:** yes, see page 121.

**Drug, lot #, and % purity:** DVS-233 (WY-45233 succinate, monohydrate), lot/batch no. RB1636, total impurities = \_\_\_\_\_ (revalidation release date 11/12/01; see page 80).

### Methods

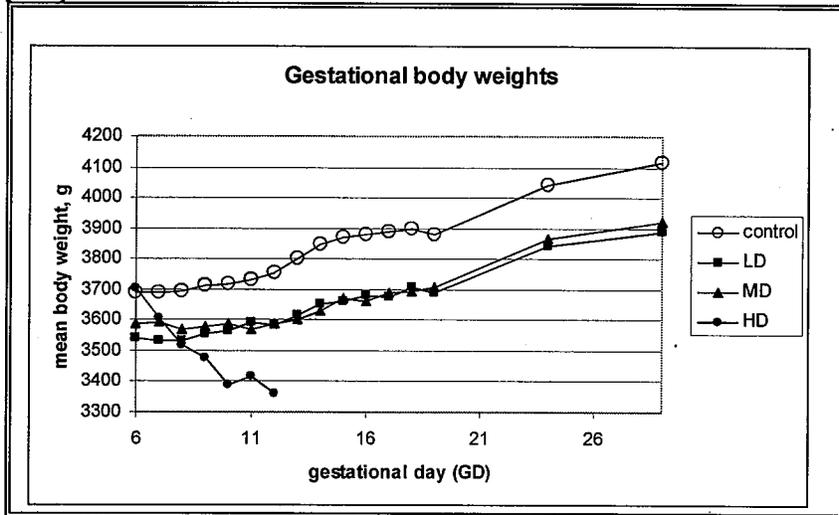
**Doses:** 0, 7.5, 25, 75 mg/kg/day (of active moiety) by oral gavage (2 ml/kg, catheter flushed with additional 2 ml water).

[Doses were based on dose-range finding study (RPT-45134) at doses of 0, 75, 225, 675 mg/kg/day from GD 6-18 (time-mated NZ-white rabbits, from \_\_\_\_\_ 8/dose). MTD < 675 mg/kg, based on body weight loss (decreased 9% from GD 6-11), near cessation of food consumption, and poor prognosis for recovery: all were cool to touch; 1 was found dead on GD 11, another was euthanized on GD 12 due to ataxia and 17% loss of body weight (vs GD 6); group terminated early at GD 12/13.

Body weights are presented in the figure, below. Clearly the HD is above an MTD. At lower doses, body weight gains were reduced: 64% of controls at MD and 81% of controls at LD, with parallel decreases in food consumption (77 and 92% of controls for MD and LD, respectively); the only developmental effect was a slight increase in embryo-fetal mortality at 225 mg/kg. The LD of 75 mg/kg is  $\sim 1/10^{\text{th}}$  the clearly toxic dose of 675 mg/kg; the MD of 225 mg/kg is  $\sim 1/3^{\text{rd}}$  of that dose. It could be argued that the MD of 225 mg/kg is too close to the dose that resulted in such dramatic body weight loss and poor condition (with some mortality). Consequently, the LD of 75 mg/kg could be considered appropriate for the definitive study, as was chosen by the Sponsor.

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**Figure 12. Decreased body weights in a DRF study in pregnant rabbits treated from GD 6 with desvenlafaxine (by oral gavage) at the HD of 675 mg/kg (but only decreased body weight gain at lower doses of 225 and 75 mg/kg). [Graphed from data presented in summary tables, pages 28-30 of the study report.]**



Toxicokinetic analysis determined AUCs of 2.7  $\mu\text{g}\cdot\text{hr}/\text{ml}$  at LD of 75 mg/kg and 24  $\mu\text{g}\cdot\text{hr}/\text{ml}$  at the MD of 225 mg/kg; TK was not conducted at HD of 675 mg/kg.]

**Species/strain:** time-mated (to breeder males) female New Zealand White (SPF) rabbits, ~5-6 weeks old and weighing 3091-3987 g at start of dosing; acclimated 5 days prior to treatment.  
**Number/sex/group:** 20/group; assigned to cages by weight-ordered randomization, dosage groups randomly dispersed (one group per column) on each rack.

**Housing:** individually in stainless steel wire bar cages with plastic-molded tray compartments; 180 g/day food (GD 6-28) and water ad lib.

**Route, formulation, volume, and infusion rate:** oral gavage, as suspension in 0.25% polysorbate 80 and 0.5% methylcellulose (4000 cps) in purified water (10 ml/kg); prepared twice (presumably weekly) and stored refrigerated and protected from light; for both preparation days, pH of controls were 6.4 & 7.5, pH of drug formulations was 4.6-4.6; for both preparation days, drug formulations were assessed for drug content and found to range from 97.2-98.4% of nominal concentration; stability and homogeneity were not analyzed, but previous data was referenced.

**Toxicokinetics:** conducted on main study rabbits after dosing on GD 18: blood samples collected (ear artery or saphenous vein) from 4/dose at 0 (pre-dose), 2, 6, and 10 hr and from 4 (others)/dose at 1, 4, 8, and 24 hr.

**Study design:** time-mated females were dosed by oral gavage from GD 6-18, with laparotomy at GD 29 (or after abortion or death).

Parameters and endpoints evaluated: mortality, clinical signs, body weights (on GD 6-19, 24, 29), food consumption (determined daily, calculated for GD 6-8, 9-11, 12-15, 16-18, 19-23, 24-28) for dams in-life; after laparotomy on GD 29: gross examination of abdominal and thoracic viscera; weight of gravid uterus with ovaries, number of corpora lutea; number, type, position of implantation sites.

Fetal examinations included: gross external examination; weights for live fetuses; sex determination; gross and visceral exam on ~ half each litter; skeletal exam on the other half of each litter.

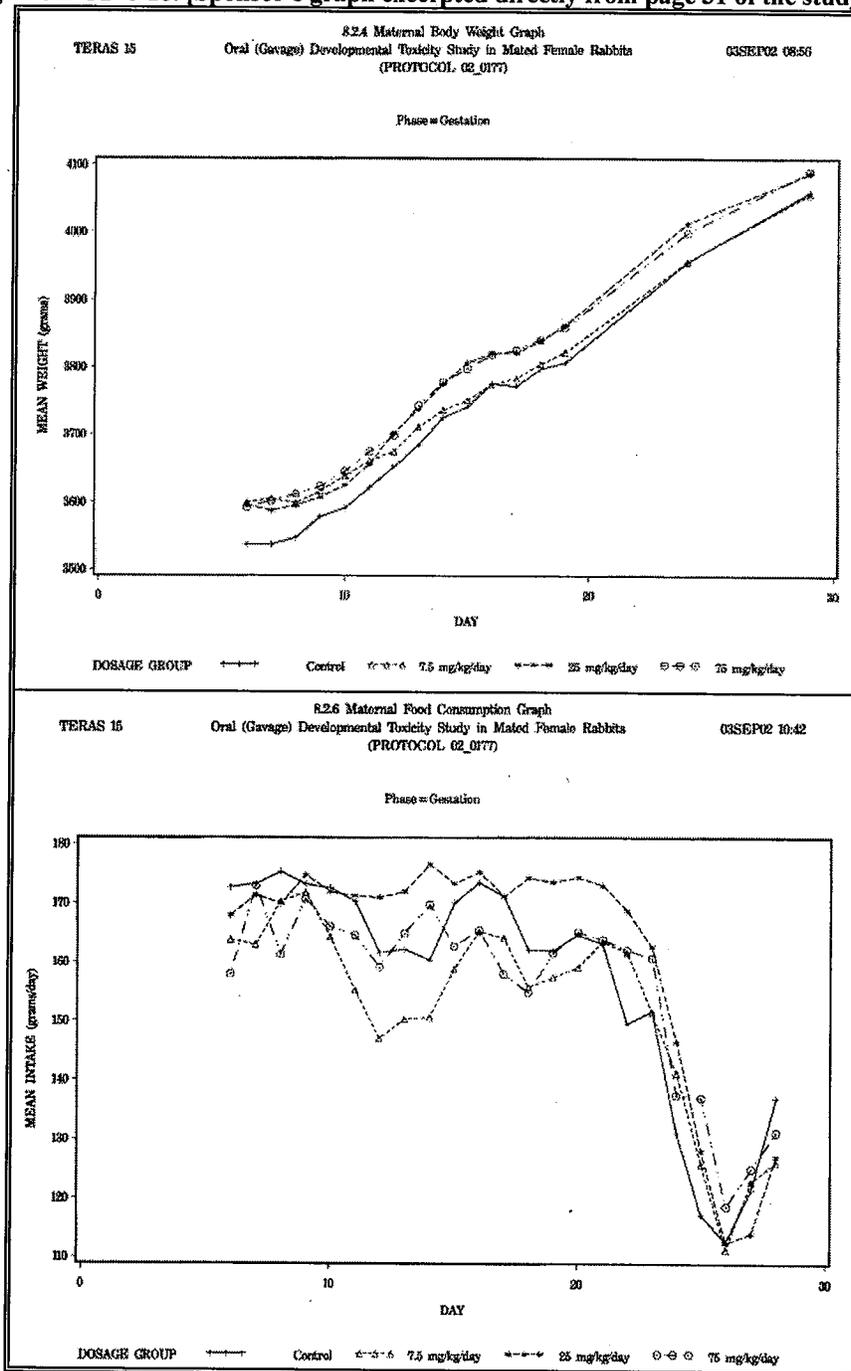
## Results

Mortality and clinical signs (dams): There were no compound-related deaths, clinical observations, or postmortem observations. The 2 premature deaths were attributed to gavage trauma (LD #26, found dead on GD 11, with tracheal perforation (and abnormal content in thoracic cavity, entrance to lungs, trachea) noted at necropsy (this doe was replaced with a spare doe, which was given the same number, LH #26); HD #65 died shortly after dosing on GD 17, with signs of respiratory distress, and distended and red-discolored lungs and red fluid in thoracic cavity noted at necropsy). Additionally, 2 dams aborted (LD #29 at GD 26, with no maternal pathology findings reported; and HD #78 at GD 27, with only accessory spleen (very common in this study) reported at necropsy).

Based on starting group sizes of 20 mated does and 1) loss to death by gavage error of 1 LD, which was replaced; 2) loss to death by gavage error of 1 HD; 3) loss due to abortion of 1 LD; 4) loss due to abortion of 1 HD; then the group size at necropsy on GD 20 should have been: 20 for controls, 19 for LD, 20 for MD, and 18 for HD. However, summary tables only give data for 19 controls, 18 LD, 20 MD, and 17 HD; thus 1 control, 1 LD, and 1 HD are unaccounted for. Examination of the hysterectomy records indicated that the following does were missing: control #3, LD #29 (abortion), #35, HD #65 (gavage error), #70, #78 (abortion); therefore, it appears that control #3, LD #35 and HD #70 were not pregnant. These 3 does that (apparently) were not pregnant and the 2 does that aborted were not included in the tables provided in the study report. The Sponsor did not consider the abortions drug-related, since the incidence was not dose-related.

Body weight and food consumption (dams): There were no effects of treatment on body weights or weight gains; the mean body weight curves are essentially super imposable (see figure below). Food consumption was slightly decreased at HD (to 97% of controls) throughout the dosing period (but only statistically significant at the beginning (GD 6-8) and end (16-18) of dosing). Food consumption was also slightly decreased throughout the dosing period at LD (averaging 94% of controls), which may be reflected in the slightly lower body weight gain in that group. There were no effects on food consumption at MD.

Figure 13. Lack of effect on desvenlafaxine treatment on body weights (upper panel) and possible effect on food intake (lower panel) in mated female rabbits treated at doses of 7.5, 25, or 75 mg/kg by oral gavage from GD 6-18. [Sponsor's graph excerpted directly from page 31 of the study report.]



Toxicokinetics: Desvenlafaxine was essentially not detectable in the LD group, but systemic exposures could be calculated at the MD and HD (see table, below). Both C<sub>max</sub> and AUC increased more than dose-proportionately from 25 to 75 mg/kg; C<sub>max</sub>

increased 12-fold and AUC increased 13-fold for the 3-fold increase in dose. The AUC exposure was 0.2 µg.hr/ml at the MD of 25 mg/kg and 2.5 µg.hr/ml at the HD of 75 mg/kg.

**Table 40. Systemic exposures to desvenlafaxine on GD 18 in pregnant rabbits after daily dosing from GD 6-18. [Sponsor's tables excerpted directly from page 19 of the study report.]**

PHARMACOKINETIC PARAMETERS FOR ODV (MEAN ± STANDARD ERROR OF MEAN)					
Dosage (mg/kg/day)	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
7.5	ND	ND	ND	ND	ND
25	108 ± 70	1.0	196 ± 87	1.6	7.86 ± 3.49
75	1283 ± 562	1.0	2493 ± 745	1.3	33.2 ± 9.9 <sup>b</sup>
a: Determined from the mean concentration – time profiles					
b: Significantly different than the corresponding values at other dosages					
AUC/Dose: dose-normalized AUC; ND = Not Determined (see text below)					

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.):

Maternal reproduction parameters: Desvenlafaxine treatment did not appear to adversely affect maternal parameters, in spite of the decreased gravid uterine weight, increased pre-implantation loss, and decreased number of live fetuses at HD (see table, below). It should be noted that there were slightly fewer implantation sites at MD and HD, an effect that should not be related to drug treatment, as implantation occurs prior to GD 6, when dosing was initiated; the Sponsor concluded that this variability was random. Consequently, the numbers of fetuses in the HD litters would be limited by the lower numbers of implantation sites. [This was confirmed when I calculated the number of live fetuses as a fraction of the implantation sites for each litter, because there was no difference among the groups (mean values were 95.9% for controls, 94.2% for LD, 96.6% for MD, and 93.9% for HD.)]

**Table 41. Maternal variables for embryo-fetal (Segment II) study of 0, 7.5, 25, and 75 mg/kg oral (gavage) doses of desvenlafaxine in rabbits from GD 6-18 (based on hysterectomy on GD 29). [Sponsor's values.]**

PARAMETER	DOSE, mg/kg/d (gestational D6-18)			
	0	7.5	25	75
Time-mated females at start (or by replacement)	20	21	20	20
Mortalities (not drug-related)	0	1	0	1
Abortions	0	1	0	1
Non-pregnant at necropsy	1	1	0	1
Gravid rabbits completing study	19	18	20	17
Mean gravid uterine weight, g	543	528	528	481
Mean corpora lutea/dam	10.7	9.9	10.0	9.8
Mean implantation sites/dam	9.3	9.1	8.4	8.1
Pre-implantation loss, %, per dam	12%	8%	16%	26%
Mean live fetuses/litter	9.0	8.6	8.1	7.5

PARAMETER	DOSE, mg/kg/d (gestational D6-18)			
	0	7.5	25	75
Mean dead fetuses	0	0	0	0
Mean early resorptions	0.26	0.33	0.20	0.35
<b>Mean late resorptions</b>	<b>0.11</b>	<b>0.17</b>	<b>0.05</b>	<b>0.24</b>
Mean total resorptions	0.37	0.50	0.25	0.59
<b>Post-implantation loss, % per dam</b>	<b>4%</b>	<b>6%</b>	<b>3%</b>	<b>6%</b>

Offspring (malformations, variations, etc.):

*Fetal parameters:*

Fetal weights and sex ratio: There was no effect of desvenlafaxine treatment on the sex ratio of fetuses or in fetal weights, in either males or females (see table, below.)

Fetal terminal and necroscopic evaluations: Although the Sponsor provided summaries of the incidence (by litter and across all litters) of each of the external, visceral and skeletal findings for each dose-group; they did not group the findings as malformations, deviations, and variations. However, inspection of the (summary) data suggested that this Reviewer could adequately assess the teratogenic effects of desvenlafaxine in this study based on this analysis.

There were no treatment-related external findings.

There were no significant treatment-related increases in incidences of any visceral malformations. The findings of increased vascular variations appear to be of arguable importance. The incidence of absent innominate (or brachiocephalic) artery, a common variation, was increased at MD and HD and incidence of overall vascular variations was increased at HD. The incidence of absent innominate artery was slightly increased (see table, below) at MD (in 28% of fetuses, 46/162, from 15/20 litters) and HD (in 30% of fetuses, 38/127, from 12/17 litters) compared with controls (in 14% of fetuses, 24/170, from 13/19 litters) or LD (in 21% of fetuses, 32/155, from 11/18 litters), but the fraction of litters affected was similar across the groups, so this finding was not considered significant. The incidence of overall vascular variations (i.e., absent innominate artery and thoracic vascular variations) was slightly increased (see table, below) at HD (in 39% of fetuses, 50/127, from 14/17 litters) compared with controls (in 20% of fetuses, 34/170, from 15/19 litters), LD (in 25% of fetuses, 39/155, from 12/18 litters), MD (in 31% of fetuses, 51/162, from 16/20 litters), but the Sponsor argues that this reflects the increased incidence of absent innominate artery.

Treatment-related changes in incidences of skeletal findings appeared to be limited to several variations related to state of maturation (see table, below). The incidence of reduced number of ossified front phalanges was increased at HD (in 9% of fetuses, 11/127, from 4/17 litters), compared with controls (in 2% of fetuses, 3/170, from 3/19 litters), LD (in 3% of fetuses, 5/155, from 3/18 litters), and MD (in 5% of fetuses, 8/160,

from 4/20 litters); the Sponsor argues that this was not significant because. The incidence of intercranial bone ossification (largely between nasal bones) was increased at HD (in 4% of fetuses, 5/127, from 3/17 litters) compared with controls (0 incidence) or LD (in 1% of fetuses, 2/155, from 2/18 litters) or MD (in 1% of fetuses, 2/160, from 2/20 litters). The incidence of overall reduced skeletal ossification was not altered (dose-relatedly), with approximately half of the litters from each group affected: controls (in 12% of fetuses, 20/170, from 10/19 litters), LD (in 20% of fetuses, 31/155, from 12/18 litters), and MD (in 16% of fetuses, 25/160, from 9/20 litters), and HD (in 25% of fetuses, 32/127, from 10/17 litters).

Although not mentioned by the Sponsor, the incidence of bipartite sternebrae appeared to be slightly increased at MD (in 3% fetuses, 5/160, from 5/20 litters) and HD (in 3% fetuses, 4/127, from 4/17 litters), compared with controls (in 1% fetuses, 2/170, from 2/19 litters) and LD (in 0.6% fetuses, 1/155, from 1/18 litters); however, this finding did not reach statistical significance (p=0.059 for fetuses, p=0.065 for litters affected). Additionally, it seems likely that this finding reflects slightly delayed maturation, as it occurred at low incidence in controls as well as dosed rabbits and in only 1 fetus in each affected litter. However, this could not be further investigated because the specific fetuses with findings were not identified in the data provided in the study report; consequently, it could not be determined whether the specific fetuses with bipartite sternebrae also had lower body weights or other indications of delayed maturation.

**Table 42. Embryo/fetal variables for embryo-fetal (Segment II) study of 0, 7.5, 25, and 75 mg/kg oral (gavage) doses of desvenlafaxine in rabbits rabbits from GD 6-18 (based on hysterectomy on GD 29). For incidences of variations and malformations, the upper ratio is for total fetuses, the lower ratio is for litters. [Extracted from Sponsor's summary tables of visceral findings (pages 56-61) and skeletal findings (pages 62-76 of study report).]**

PARAMETER	DOSE, mg/kg/d (gestational D6-18)			
	0	7.5	25	75
Total litters with live fetuses	19	18	20	17
Mean live fetuses/litter	8.9	8.6	8.1	7.5
Fraction males	48%	49%	46%	51%
Mean fetus weights, g				
males	46.6	43.8	46.4	46.2
females	42.2	41.6	46.1	44.3
Total fetuses examined for external & visceral abn	170	155	162	127
Total fetuses examined for skeletal abn	170	155	160	127
Visceral variations:				
Absent innominate artery	24/170 13/19	32/155 11/18	46/162* 15/20	38/127* 12/17
Thoracic vascular variations	11/170 5/19	10/155 7/18	7/162 6/20	18/127 8/17
Vascular variations	35/170 15/19	39/155 12/18	51/162 16/20	50/127* 14/17
Skeletal variations:				
Reduced number of ossified front phalanges	3/170 3/19	5/155 3/18	8/160 4/20	11/127 4/17
Intercranial bone ossification	0/170 0/19	2/155 2/18	2/160 2/20	5/127 3/17
Reduced skeletal ossification	20/170	31/155	25/160	32/127

PARAMETER	DOSE, mg/kg/d (gestational D6-18)			
	0	7.5	25	75
	10/19	12/18	9/20	10/17

Placental morphology was not altered.

### 2.6.6.6.3 Prenatal and postnatal development

**Study title:** DVS-233: ORAL PERINATAL AND POSTNATAL TOXICITY STUDY WITH BEHAVIORAL AND REPRODUCTIVE ASSESSMENTS OF OFFSPRING IN RATS (PROTOCOL 03\_2348).

#### Key study findings:

- Doses: 0, 30, 100, or 300 mg/kg/day, orally by gavage, for ~37 days, to pregnant rats from implantation (GD6) through lactation and weaning (PND 21).
- Maternal (F0) toxicity: transient weight loss at HD from GD 6-7, which resulted in 18% decreased weight gain (compared with controls) during gestation (GD 6-21); accompanied by decreased food consumption. Gestation duration was slightly increased at HD.
- F1 pup toxicity: **decreased birth weights and decreased viability at PND 4 at HD**; no effects on sensory (acoustic startle, pupillary closure, visual placing responses) or anatomic (age at vaginal opening, preputial separation) development; no effects on behavior (locomotor activity, learning and memory assessed for passive avoidance or performance in "E" water maze); no effects on reproductive variables (mating or fertility index or F2 fetal parameters).
- The NOAEL for F0 maternal toxicity could be considered to be the MD of 100 mg/kg, based on decreased maternal weights, decreased food consumption during gestation, and slightly increased gestational duration at the HD.
- 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 the HD.

**Study no.:** RPT-56483.

**Volume #, and page #:** electronic submission, 1224 pages.

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

**Date of study initiation:** \_\_\_\_\_

**GLP compliance:** yes, see page 6.

**QA reports:** yes, see page 7-11.

**Drug, lot #, and % purity:** DVS-233 \_\_\_\_\_ (WY-45233 succinate monohydrate), lot # RB2691, total impurities = \_\_\_\_\_ (released 10/9/03).

**Methods:**

Doses: 0, 30, 100, or 300 mg/kg/day, orally by gavage, for ~37 days, from implantation (GD6) through lactation and weaning (PND 21). [Doses were based on decreased fetal body weights at  $\geq 225$  mg/kg (but not at 75 mg/kg) in a dose range finding (fertility and development) study and increased pre-implantation loss at  $\geq 100$  mg/kg and decreased fetal weights at 300 mg/kg in the definitive fertility and developmental study.]

Species/strain: time-mated female Sprague-Dawley rats CD<sup>®</sup> [SD]IGS BR, 77-84 days old and 234-288 g at start of treatment.

Number/sex/group: 25/dose-group; following weighing on GD 3, F0 females were assigned to dose-groups randomly, stratified for body weight.

Route, formulation, volume: oral gavage, as suspension in 0.25% polysorbate 80, NF and 0.5% methylcellulose (4000 cps) in purified (deionized) water (10 ml/kg); prepared weekly and stored refrigerated and protected from light; pH of control was 5.5-7.98, pH of drug formulations was 4.36-4.82; drug formulations were assessed for homogeneity and drug content and found to be homogeneous (sample from top, middle and bottom) and ranged from 94-110% of nominal concentration. Satellite groups used for toxicokinetics: not done.

Housing: F0 females were housed individually in stainless steel, mesh-bottomed cages until GD 18, when they were transferred to solid-bottomed cages, with corn-cob bedding; pelleted commercial lab diet and purified tap water ad lib; it was not clear how F1 pups were housed after weaning.

Study design: F0 time-mated female rats were dosed with 0, 30, 100, or 300 mg/kg desvenlafaxine from GD 6 through PND 21; on PND 4, litters were culled to 4 F1 pups/sex; on PND 21 (at weaning), 1/sex/litter were chosen for subsequent adult testing (see below), the remaining F1 pups and F0 dams were sacrificed and complete gross pathology examinations were conducted.

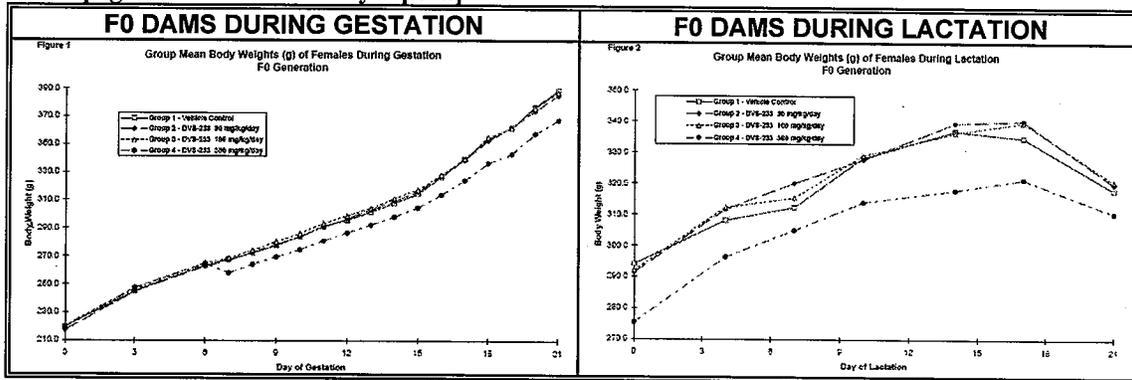
Parameters and endpoints evaluated: F1 pups: acoustic startle (PND 12), papillary closure reflex, visual placing responses, vaginal opening, preputial separation, learning and memory (passive avoidance and "E" water maze), and motor activity; reproductive parameters: estrus cycles in females (1/sex/dose-group) for 14 days prior to mating and during mating, mating (non-siblings) at ~85 days of age (with pairing for up to 14 days), fertility assessment in females at GD 21 (gross exam, corpora lutea counted, gravid uterus weighed, uterine contents examined, the number and position of live fetuses, dead fetuses and early, middle and late resorptions and/or empty implantation sites recorded, each fetus weighed, given a detailed external examination), full gross necropsy on F1 males 2-3 weeks after mating.

**Results:**

F<sub>0</sub> in-life: no premature mortality [1 LDF was euthanized early on GD 20, due to early littering]; salivation post-dosing at HD throughout dosing period; **transient weight loss**

at HD from GD 6-7 (see figure, below), which resulted in 18% decreased weight gain (compared with controls) during gestation (GD 6-21); accompanied by decreased food consumption (HD decreased 24% vs controls) from GD 6-9; decreased maternal weights at HD at GD 21 (decreased 6% vs controls). No effects at lower doses (LD or MD).

Figure 14. Treatment of F0 dams with HD of 300 mg/kg desvenlafaxine from GD 6 –PND 21 decreased body weights during gestation and during lactation. [Sponsor’s graphs, excerpted directly from pages 50 & 52 of the study report.]



F0 necropsy: No gross pathology findings at any dose. There were no effects of treatment on pregnancy rate, gestation index, pup sex ratio, or live-born pups. Gestation duration was slightly increased at HD (increased 0.5 day). There were no effects on live birth index or numbers of dead or malformed pups.

Table 43. Treatment of F0 dams with HD of 300 mg/kg desvenlafaxine from GD 6 –PND 21 slightly increased duration of gestation (and possibly of parturition), but did not alter other maternal reproductive parameters. [Sponsor’s table, excerpted directly from pages 81 & 82 of the study report.]

Table 8		Group Mean (S.D.) Maternal Performance F0 Generation					
		No. of Mated Females	No. of Pregnant Females	Pregnancy Rate (%)	Gestation Index (%)	Length of Gestation (Days)	Duration of Parturition (h)
Group 1 - Vehicle Control	Mean S.D. N	25	25	100.0	100.0	21.4 (0.50) 25	2.32 (0.826) [N=14]
Group 2 - DVS-233 30 mg/kg/day	Mean S.D. N	25	24	96.0	100.0	21.3 (0.46) 24	2.14 (0.725) [N=7]
Group 3 - DVS-233 100 mg/kg/day	Mean S.D. N	25	24	96.0	100.0	21.7 (0.48) 24	2.01 (0.869) [N=12]
Group 4 - DVS-233 300 mg/kg/day	Mean S.D. N	25	24	96.0	100.0	21.9 b (0.45) 24	2.66 (1.031) [N=3]

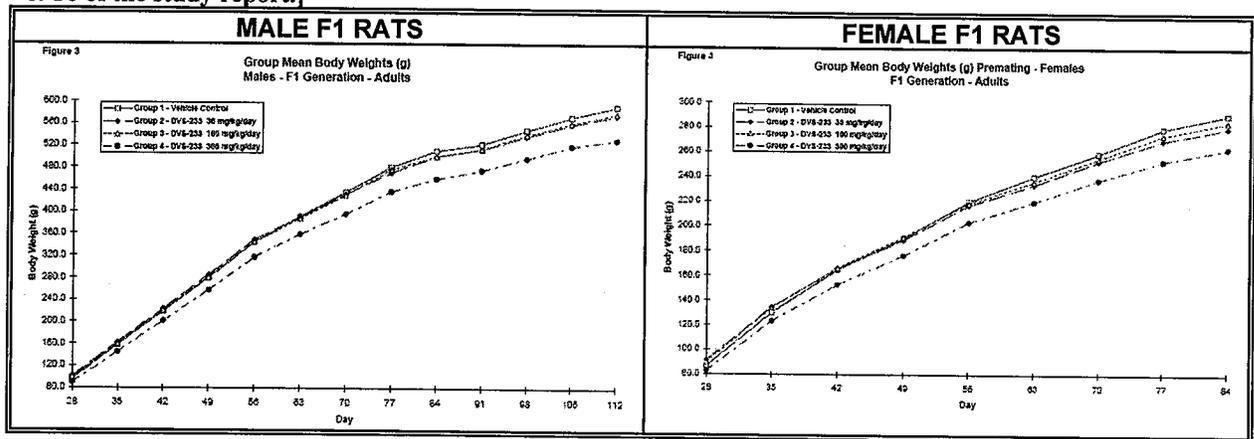
Significantly different from control group (group 1) value: a - P<=0.05 b - P<=0.01 c - P<=0.001 (Wilcoxon)  
 Significantly different from control (group 1) value: \* P<=0.05 \*\* P<=0.01 \*\*\* P<=0.001 Fisher's

Table 9		Group Mean (S.D.) Maternal Performance F0 Generation					
		Sex Ratio (%) Males	No. of Pups at Birth			No. of Implant Scars	Live Birth Index (%)
			Live	Dead	Malformed		
Group 1 - Vehicle Control	Mean	50.1	13.2	0.3	0.00	14.4	92.2
	S.D.	(12.15)	(2.17)	(0.61)	(0.000)	(2.27)	(8.54)
	N	25	25	25		25	25
Group 2 - DVS-233 30 mg/kg/day	Mean	49.3	12.6	0.5	0.00	14.0	88.7
	S.D.	(14.32)	(2.72)	(1.32)	(0.000)	(1.78)	(15.59)
	N	24	24	24		24	24
Group 3 - DVS-233 100 mg/kg/day	Mean	49.0	13.2	0.4	0.00	14.5	91.2
	S.D.	(11.39)	(1.83)	(1.01)	(0.000)	(1.28)	(10.66)
	N	24	24	24		24	24
Group 4 - DVS-233 300 mg/kg/day	Mean	49.4	13.0	0.5	0.00	14.6	89.2
	S.D.	(15.01)	1.94	(0.66)	(0.000)	(1.76)	(8.49)
	N	24	24	24		24	24

Significantly different from control group (group 1) value: a - P<=0.05 b - P<=0.01 c - P<=0.001 (Wilcoxon)  
Significantly different from control (group 1) value: \* P<=0.05 \*\* P<=0.01 \*\*\* P<=0.001 Fisher's

**F<sub>1</sub> physical development:** F1 pups from F0 dams treated with HD of 300 mg/kg had lower birth weights (decreased 12.5% for males and 10% for females, vs controls) and this decrease in weight (up to 10% compared with controls) persisted on in development (PND 28-112 in figure, below). [It should be noted that litters were culled to 4 /sex on PND 4 and at weaning only 1/sex/litter was continued for subsequent testing.]

**Figure 15. Decreased body weights in F1 pups (from PND 28-122) from F0 dams treated with HD of 300 mg/kg desvenlafaxine from GD 6 –PND21. [Sponsor’s graphs, excerpted directly from pages 54 & 56 of the study report.]**



**A higher fraction of F1 pups from the HD group died between birth and PND 4,** compared with controls (see table, below). The viability index at PND 4 was 92.0% in the HD group, compared with 98.5% in controls. This decrease in viability index was attributable to multiple deaths in 3/24 litters (9/16, 3/14, and 4/12). The viability index for the HD group was not different from controls at subsequent time points (PND 7-21); there was no effect on the viability index (at any time) for the LD and MD groups. [It should be noted that 1/24 HDMs was euthanized on PND 116 due to poor and/or deteriorating condition, with respiratory abnormalities. At necropsy, macroscopic findings in lungs (uncollapsed, with dark foci) and trachea (pale, clear fluid) were

considered by the Pathologist to be “major contributory factors” in the rat’s deterioration, but the origin of the findings was unclear and considered “likely unrelated to the administration of the test article.”]

**Table 44. Decreased viability index for F1 pups (males and females combined) from F0 dams treated with HD of 300 mg/kg desvenlafaxine from GD 6 –PND21. [Sponsor’s table, excerpted directly from page 84 of the study report.]**

		Group Mean (S.D.) Viability Data (%)			
		F1 Generation - Pups			
		Day Post Partum			
		Day 4	Day 7	Day 14	Day 21
		Viability	Survival	Survival	Lactation
		Index	Index	Index	Index
		(%)	(%)	(%)	(%)
Group 1 - Vehicle Control	Mean	98.5	100.0	100.0	100.0
	S.D.	3.15	0.00	0.00	0.00
	N	25	25	25	25
Group 2 - DVS-233 30 mg/kg/day	Mean	98.7	100.0	100.0	100.0
	S.D.	3.81	0.00	0.00	0.00
	N	24	24	24	24
Group 3 - DVS-233 100 mg/kg/day	Mean	98.6	100.0	100.0	100.0
	S.D.	4.11	0.00	0.00	0.00
	N	24	24	24	24
Group 4 - DVS-233 300 mg/kg/day	Mean	92.0 a	99.5	99.5	99.5
	S.D.	13.35	2.55	2.55	2.55
	N	24	24	24	24

Significantly different from control group (group 1) value: a - P<=0.05 b - P<=0.01 c - P<=0.001 (Wilcoxon)

There was no effect of treatment on the age at which pups exhibited an acoustic startle reflex, measured from PND 12 in all (4/sex/litter) F1 pups; mean day of development ranged from 12.0-12.3 in males and 12.1-12.2 in females. Pupillary closure and visual placing responses on PND 21 were not different among groups (average of 100% for each function in each group). The age at vaginal opening in females, monitored from PND 26, were no different among the groups, with group averages ranged from PND 31.2-31.3 for controls, LD, and MD groups to PND 30.3 for HD group. The age at preputial separation in males, monitored from PND 35, was not different among groups (average values were PND 44.2, 42.6, 43.1, and 44.7 for controls, LD, MD, and HD, respectively; LD was significantly lower than control, but this seems unlikely to have biological significance).

F1 behavioral evaluation:

Passive avoidance, with single conditioning trial (of unspecified maximum duration: time to cross from bright to dark side, with crossing followed by a foot shock a 1mA for 2 sec) and step-through latency (maximum of 2 min) determined 1 hr later on ~PND 49 and step-through latency determined again 24 hr later: there was no dose-related decrement in performance in initial conditioning trial (all rats crossed, i.e., failed to avoid) or performance at either 1 or 24 after training, where the number of rats crossing/erring decreased compared with the training session (indicating that learning occurred), and more rats erred at 24 hr than at 1 hr after training (there was some extinction of the learning), regardless of group or sex.

Locomotor activity was measured for 1 hr (and analyzed in 6 x 10-min intervals) in figure 8 mazes on ~PND 60. There were no differences among groups regarding activity measured in any interval or in total activity counts for the entire hour. In all groups, activity decreased over the hour session (indicating habituation) and females tended to be more active than males (both in the initial interval and overall, which is a typical sex difference in rodents).

“E” water maze behavior/learning were tested between PND 60-70, time to exit the maze and number of errors were recorded for 5 tests (each ≤ 1 min, with 15 min intervening) on the first day of testing, with 2 additional tests ~24 hr later. There were no differences among groups regarding latency to exit the maze on the first trial or subsequent training trials; all groups learned and average latencies after the 5<sup>th</sup> training trial were ~1/2 those after the 1<sup>st</sup>. All groups also retained this learning: latencies determined in the 2 trials 24 hr after training were similar to those at the end of training.

F<sub>1</sub> reproduction: At 87-92 days of age, opposite-sex pairs of F1 rats (from the same treatment-group, but avoiding sibling matings) were allowed to cohabit for 14 days; females were examined for mating daily (vaginal lavage for spermatozoa); mated females were sacrificed on GD 21 and assessed for pregnancy parameters (and gross pathology); mated males were necropsied (gross pathology only) 2-3 weeks after mating.

Estrous cycles (measured for 14 days prior to pairing and until mating) were unaffected by treatment: number of days in estrus, number of cycles seen, and average length of observed cycles were not different among the groups.

Parental performance, reflected in mating index, fertility index, and conception rate, was not affected by treatment (see table, below). It should be noted that in general, rats from the control group tended to perform slightly poorer than rats from the drug-groups, particularly with respect to the mating index.

**Table 45. Desvenlafaxine treatment of F0 dams (GD 6 – PND 21) did not alter reproductive performance of F1 generation rats. [Sponsor’s table excerpted directly from page 163 of this submission.]**

	No. Placed for Mating Males	No. Placed for Mating Females	No. Mating	Mean (S.D.) Day to Mating	No. Females Pregnant	Mating Index (%)	Fertility Index (%)	Conception Rate (%)
Group 1 - Vehicle Control	25	25	22	Mean 3.5 S.D. (1.93) N 20	21	88.0	84.0	95.5
Group 2 - DVS-233 30 mg/kg/day	24	24	23	Mean 3.7 S.D. (2.61) N 23	21	95.8	87.5	91.3
Group 3 - DVS-233 100 mg/kg/day	24	24	22	Mean 3.4 S.D. (3.11) N 21	21	91.7	87.5	95.5
Group 4 - DVS-233 300 mg/kg/day	24	24	22	Mean 3.0 S.D. (1.99) N 22	22	91.7	91.7	100.0

Significantly different from control group (group 1) value: a - P<=0.05 b - P<=0.01 c - P<=0.001 (Wilcoxon)  
Significantly different from control (group 1) value: \* P<=0.05 \*\* P<=0.01 \*\*\* P<=0.001 Fisher's

Gross pathology on F1 males and females did not reveal any treatment-related findings.

Uterine findings (see table, below): There were no treatment-related changes in number of corpora lutea, number of implantation sites, number of live fetuses (no dead in any group), sex ratio of fetuses, pre-implantation losses (which were essentially all early resorptions), post-implantation losses or gravid uterus weights. [It should be noted that although F1 females from the HD group had lower body weights at mating, their weight gain during gestation paralleled that of the other groups.]

**Table 46. Desvenlafaxine treatment of F0 dams (GD 6 – PND 21) did not alter uterine findings in mated F1 generation rats. [Sponsor's table excerpted directly from pages 159-61 of this submission.]**

Table 34 Group Mean (S.D.) Uterine Findings						
F1 Generation - Adults						
		Total No. of Corpora Lutea	Total Implan- tation Sites	Male Fetuses	Female Fetuses	Sex Ratio (% Males)
Group 1 - Vehicle Control	Mean	17.3	15.1	6.6	7.9	45.1
	S.D.	4.42	5.04	3.04	3.21	12.03
	N	19	19	19	19	18
Group 2 - DVS-233 30 mg/kg/day	Mean	18.6	16.7	7.9	7.9	50.9
	S.D.	2.74	2.08	2.46	3.08	16.72
	N	20	20	20	20	20
Group 3 - DVS-233 100 mg/kg/day	Mean	18.8	16.0	7.6	7.5	50.6
	S.D.	2.76	2.29	1.98	2.26	11.94
	N	20	20	20	20	20
Group 4 - DVS-233 300 mg/kg/day	Mean	18.8	17.0	8.0	8.1	49.6
	S.D.	2.31	1.50	2.23	2.10	12.37
	N	22	22	22	22	22
Significantly different from control group (group 1) value: a - P ≤ 0.05 b - P ≤ 0.01 c - P ≤ 0.001 (Wilcoxon)						
		Live Fetuses	Dead Fetuses	Early Resorp- tions	Middle Resorp- tions	Late Resorp- tions
Group 1 - Vehicle Control	Mean	14.5	0.0	.4	.1	.1
	S.D.	5.12	0.00	.60	.23	.23
	N	19	19	19	19	19
Group 2 - DVS-233 30 mg/kg/day	Mean	15.7	0.0	1.0	0.0	0.0
	S.D.	2.43	0.00	1.03	0.00	0.00
	N	20	20	20	20	20
Group 3 - DVS-233 100 mg/kg/day	Mean	15.1	0.0	.9	0.0	0.0
	S.D.	2.23	0.00	1.14	0.00	0.00
	N	20	20	20	20	20
Group 4 - DVS-233 300 mg/kg/day	Mean	16.1	0.0	.8	0.0	0.0
	S.D.	1.91	0.00	1.22	0.00	0.00
	N	22	22	22	22	22
Significantly different from control group (group 1) value: a - P ≤ 0.05 b - P ≤ 0.01 c - P ≤ 0.001 (Wilcoxon)						

		Sum of Resorp- tions	Pre- Implan- tation Loss (%)	Post Implan- tation Loss (%)	Gravid Uterus Weight (g)
-----					
Group 1 - Vehicle Control	Mean	.5	15.6	8.4	104.6
	S.D.	.61	20.68	22.53	22.66
	N	19	19	19	18
Group 2 - DVS-233 30 mg/kg/day	Mean	1.0	9.7	6.2	110.1
	S.D.	1.03	6.89	6.74	16.89
	N	20	20	20	20
Group 3 - DVS-233 100 mg/kg/day	Mean	.9	13.5	5.1	105.6
	S.D.	1.14	15.10	6.77	14.60
	N	20	20	20	20
Group 4 - DVS-233 300 mg/kg/day	Mean	.8	9.2	4.9	110.6
	S.D.	1.22	6.55	7.43	12.76
	N	22	22	22	22
-----					
Significantly different from control group (group 1) value: a - P ≤ 0.05 b - P ≤ 0.01 c - P ≤ 0.001 (Wilcoxon)					

**F<sub>2</sub> findings:** The weights, sex and external observations of the F<sub>2</sub> generation were unaffected by treatment. Fetal weights (for males, females, or combined) were not different among the treatment groups.

Fetuses examined at GD 21 did not show any treatment-related increase in external major malformations or minor anomalies: major malformations were limited to 1) intestines protruding at umbilicus in 1 control fetus and 2) tail shortened in another control fetus, from a different litter; minor anomalies were limited to domed skull in 1 LD fetus. Only external abnormalities were assessed; the number of litters and fetuses examined were: 18/276 for controls, 21/330 for LD, 20/303 for MD, and 22/355 for HD.

**Conclusions:** The Sponsor considered the NOAEL for F<sub>0</sub> rats to be the MD of 100 mg/kg, based on decreased maternal weights, decreased food consumption during gestation, and slightly increased gestational duration at the HD. 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 the HD.

**2.6.6.6.4 Sponsor's proposed labeling (submitted 4/24/06) for Impairment of Fertility and for Pregnancy:**

/      Page(s) Withheld

     Trade Secret / Confidential

  X   Draft Labeling

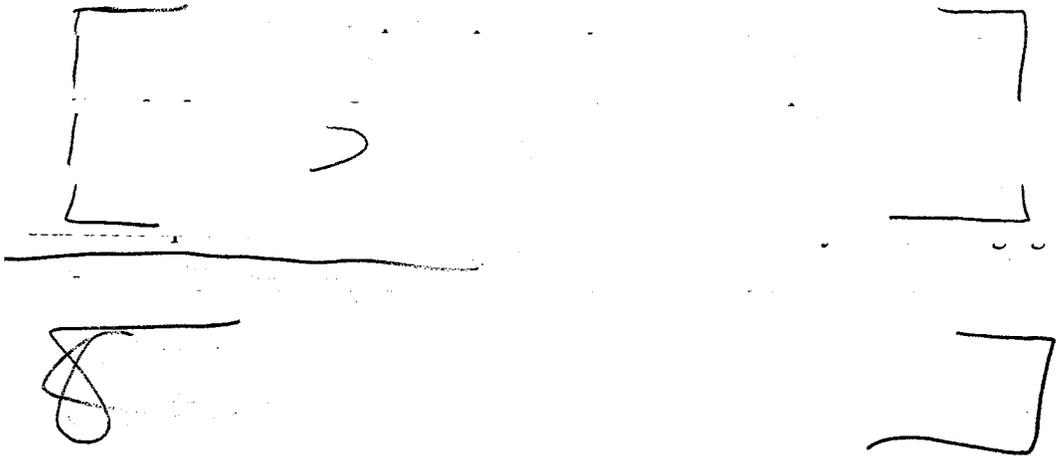
     Deliberative Process

**2.6.6.6.5 Approved labeling for venlafaxine:**

Venlafaxine labeling:

**Teratogenic Effects—Pregnancy Category C**

Venlafaxine did not cause malformations in offspring of rats or rabbits given doses up to 11 times (rat) or 12 times (rabbit) the maximum recommended human daily dose on a mg/kg basis, or 2.5 times (rat) and 4 times (rabbit) the human daily dose on a mg/m<sup>2</sup> basis. However, in rats, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation, when dosing began during pregnancy and continued until weaning. The cause of these deaths is not known. These effects occurred at 10 times (mg/kg) or 2.5 times (mg/m<sup>2</sup>) the maximum human daily dose. The no effect dose for rat pup mortality was 1.4 times the human dose on a mg/kg basis or 0.25 times the human dose on a mg/m<sup>2</sup> basis. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.



**2.6.6.6.6 Labeling for reproductive effects proposed by this Reviewer:**



2 Page(s) Withheld

       Trade Secret / Confidential

  X   Draft Labeling

       Deliberative Process

Withheld Track Number: Pharm/Tox-4

#### 2.6.6.7 Local tolerance

All pivotal toxicity studies were conducted using the clinical route of administration, namely oral; consequently, local tolerance would have been assessed (to some extent) in those studies.

The Sponsor also conducted a 14-day gastrointestinal tolerability study in dogs (3/sex/treatment) using oral extended-release tablets, the clinical formulation (RPT-45841): desvenlafaxine at 600 mg/day, as 2 x 200-mg tablets (i.e., 3 times the MRHD of 200 mg on a mg/day basis) did not produce any effects on macro- or microscopic findings in the gastrointestinal tract (cecum, colon, duodenum, esophagus, GALT, ileum, jejunum, mandibular or mesenteric lymph nodes, stomach, or tongue), compared with same-formulation placebo tablets. Assuming a 10 kg-dog and 60-kg human, this gives a safety margin of 18 for the MRHD, based on mg/kg doses (which reflect oral gastrointestinal exposure better than mg/m<sup>2</sup> doses, which better reflect systemic exposure).

#### 2.6.6.8 Special toxicology studies

DVS-233 (as desvenlafaxine succinate monohydrate) was tested in vitro for compatibility with rabbit and human blood (RPT-51017); the results indicated that “would not be expected to significantly damage erythrocytes or precipitate plasma proteins when administered in vivo.”

#### 2.6.6.9 Discussion and Conclusions:

Brief overview of nonclinical findings (excerpted from the Executive Summary, above):

Desvenlafaxine is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI), with no MAOI activity, and no apparent affinity (>10uM) for muscarinic cholinergic, H1 histaminergic, alpha1- adrenergic receptors or ion channels including calcium, potassium and sodium.

Desvenlafaxine was adequately assessed in non-clinical studies to support its approval for chronic treatment of 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.

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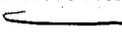
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**2.6.7 TOXICOLOGY TABULATED SUMMARY**

Only the toxicology studies that are considered pivotal for review of this NDA at presented in the table, below. These and additional studies have been reviewed and/or discussed in more detail in earlier sections of this review.

STUDY TYPE		GENERAL RESULTS
General toxicity	6-mo in rats	No remarkable findings.
	9-mo in dogs	No remarkable findings.
Genotoxicity	Ames test(s)	Negative.
	In vitro chr ab	Negative.
	In vivo chr ab tests (2)	Negative.
Carcinogenicity	2-year in mice	Negative.
	2-year in rats	Negative.
Reproductive toxicity	Fertility/embryo-fetal dev in rats	Decrease fertility and decreased fetal weights.
	Embryo-fetal dev in rabbits	No remarkable findings.
	Pre- and post-natal dev in rats	Decreased birth weights and decreased viability at PND 4.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

**Conclusions:** Conclusions have been presented above (in the Executive Summary and in section 2.6.6.9).

**Unresolved toxicology issues:** 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 PND 6, 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  $\sim 1/10^{\text{th}}$  the dose (1000 mg/kg) that was lethal in a dose-range finding study.

Additionally, we have determined that desvenlafaxine was not positive for clastogenicity in the in vivo chromosome aberration assay in rats. This assay had been previously considered positive and was included in Effexor (venlafaxine) labeling as such. Consequently, the labeling for both Effexor IR and Effexor XR should be changed to reflect this decision.

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**Recommendations:** The Sponsor should be asked to commit to conducting a standard embryo-fetal toxicity study in rats; this may be done after approval. The labeling should be revised to lower the NOAEL for teratogenicity to 100 mg/kg, the highest dose that had adequate numbers of fetuses for analysis; 100 mg/kg is 5 times the MRHD on a  $\text{mg}/\text{m}^2$  basis.

Labeling should be revised to reflect the decision that desvenlafaxine was negative for clastogenicity in the in vivo rat chromosomal aberration assay. [The labeling for both Effexor IR and Effexor XR should also be changed to reflect this decision.]

**Information to be communicated to the Sponsor:**

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.

Additionally, we have revised labeling to lower the NOAEL for teratogenicity to 100 mg/kg, the highest dose that had adequate numbers of fetuses for analysis in the currently available study; 100 mg/kg is 5 times the MRHD on a  $\text{mg}/\text{m}^2$  basis.

Finally, we have determined that desvenlafaxine was not positive for clastogenicity in the in vivo chromosome aberration assay in rats and indicated this in our revisions to labeling. The labeling for both Effexor IR and Effexor XR will also need to be changed to reflect this decision.

**Suggested 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.

**Signatures:**

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

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