no apparent drug effect on the peak response nor on latency to peak response in the auditory startle test in both M and F.

Mating performance and fertility, F1 generation: there was no drug effect on mating index (proportion of mating pairs that mated relative to the number of mating pairs cohabitated; expelled and retained copulatory plugs, vaginal sperm, and pregnancy were used as evidence of mating). In addition, no drug effect was seen on fertility index (proportion of fertile mating pairs relative to the number of mating pairs that mated; pregnancy was used as evidence of fertility). Precoital periods were not different between treated and control animals.

Reproduction parameters, F1 generation: no apparent drug effect on gestation length or litter size.

Progeny measurements, F1 (the progeny will be F2 generation): no drug effect on body wt of progeny or sex ratio. Live birth index (total live born progeny/litter size) and survival index at day 1 (day 1 live progeny/total live born progeny) were not affected by drug treatment.

Progeny observations and examination, F1 generation (the progeny will be F2 generation): some clinical observations that were seen in some of the drug treatment groups and not in the control such as cool to touch [affected litters/total litters were 0/15 in the control, 3/15 at LD, 2/19 at MD, and 1/18 at H (all pups in the litter were affected)], skin pale in color [affected litters/total litters were 0/15 in control, 0/15 at LD, 2/19 (one pup from each litter) at MD, and 1/18 litters at HD (one pup was affected)], and missing tail (seen in only one pup from 1 litter/15 litters) at the LD.

Terminal and necroscopic evaluations:

Dams: animals of the F1 generation were examined grossly (all groups) and histopathologicaly (control and HD only). Grossly, skin nodules (1/19 F at HD) and skin trauma (1/19 F at HD, however, the same animal had two incidences of trauma one in the head and one in the abdomen) while none of these findings were observed in the control or the other treated groups. Histopathologically, the female with skin nodule had "mammary hyperplasia" (this is the same animal that was diagnosed with a mass in the left flank on gestation day 14 that regressed after parturition). The other animal with skin trauma had minimal focal skin inflammation.

Offspring: progeny of F1 generation (this will be F2): progeny that were born dead or died during the lactation period were examined (2 in control, 4 in LD, 9 in MD, and 3 HD) and no significant findings were reported.

Summary of individual study findings: this study consisted of 4 substudies: 1) a fertility study where males treated for 10 weeks prior to mating and throughout two mating trials were mated with females treated with atomoxetine for two weeks prior to mating and throughout one breeding trial (through lactation). 2) Those females, which were designated as F0 females of the delivery component, were allowed to deliver and rear their progeny. 3) A teratology study where females treated with atomoxetine for two weeks prior to mating were mated with males of the fertility study. These F0 females of the teratology component were terminated on gestation day 20 and fetuses were examined for teratological and prenatal drug effects. 4) A postnatal study for behavioral and fertility assessment of the F1 generation. CD rats were used (20/sex/group for all studies except for the postnatal study, 16-19/sex/group). Treated animals received 0, 0.01, 0.03, and 0.06% atomoxetine in their diets which provided a time-weighted average doses of 0, 7, 20, and 40 mg/kg/day for males and 0, 7, 20 and 41 mg/kg/day for females. Body wt and food consumption was measured for all parental animals in F0 and F1 generation. Reproduction and progeny measurements were performed for F0 females of the delivery component. Reproduction and fetal measurements (external, visceral, and skeletal) were performed for the F0 females of the teratology component. Behavioral and fertility assessments were performed for the F1 generation. No mortality was observed in any of the parental animals in F0 or F1 generation. No serious clinical signs were observed but higher incidences of "injury" (no details about their nature were provided) in F0 males were noticed. Decreases in body wt and body wt gain were seen in F0 males and females of both the delivery and teratology component mostly at MD and HD even though were not statistically significant at all times. No decreases in body wt were seen in F1 generation. Decreases in food consumption were seen in F0 generation of both males and females but not in F1 generation. There was no drug effect on mating index, fertility index, or precoital period in both the teratology and delivery components. There was no drug effect on gestation length, litter size, or live birth index in the delivery component. A slightly higher incidence of early resorptions in the teratology study at HD compared to the control, even though the sponsor stated it was within the HC range. Some effects on physical development, or "morphological development" as called by the sponsor, in the progeny of females of the delivery component were seen as delayed incisor eruption and eye opening in the MD and HD animals compared to control (even thought they were not statistically significant). A 7% decrease in female fetal wt at HD was seen in the teratology component. There was no drug effect on visceral or external parameters in fetuses of the teratology component. A hint of incomplete ossification of several bones was noted even though the sponsor stated that they were within the historical control range (not accurate). No drug effect was seen on behavior, fertility or mating indexes, nor on production parameters in F1 generation. No drug effect on body wt of progeny (F2 generation) or sex ratio.

Study title: a segment II study of tomoxetine hydrochloride (LY139603) administered orally to pregnant New Zealand white rabbits

Key study findings: a slight decrease in fetal viability (early resorptions), a slight decrease in female fetal wt, malformations of vascular type (origin of common carotid artery, missing subclavian artery), and some skeletal deviations (incomplete ossification of some bones and extra presacral vertebra)

Study no: B01498
Volume #, and page #: vol 52,toxrpt37
Conducting laboratory and location: Toxicology Research Laboratories
Lilly Research Laboratories
A Division of Eli Lilly and Company
Greenfield, IN 46140
Date of study initiation: July 24 1998
GLP compliance: yes
QA reports: Yes (x) No ()

Drug, lot #, radiolabeled, and % purity: LY 139603, lot#399SB7, 98.5%
Formulation/vehicle: solution/water

Methods:

Species/strain: rabbit/New Zealand White

Doses employed: 0, 10, 30, and 100 mg/kg/day

Route of administration: orally by gavage

Study design: tomoxetine hydrochloride was administered orally by gavage to time-mated female rabbits on day 7 of gestation through day 19.

Number/sex/group: 20/group

Parameters and endpoints evaluated:

Maternal survival and clinical observations: animals were observed daily and at 1 hour postdose during their first 5 days of treatment for survival and clinical signs.

Body wt: measurements were made on Gestation Days 4, 7, 10, 14, 17, 20, 24, and 28.

Food consumption: measurements were collected daily beginning on Gestation Day 4.

Maternal reproductive parameters: cesarean sections were performed on Gestation Day 28. The uterus and ovaries were removed and uterus was weighed. The numbers of corpora lutea, implantations, and preimplantation loss were evaluated.

Fetal parameters: following cesarean section, fetal wt, gender, and morphology were evaluated. Live fetuses were evaluated for external, visceral, and skeletal anomalies. Late resorptions were evaluated for external anomalies only.

Results:

Maternal effects:

Mortality: no deaths or abortions were reported.

Clinical signs: there was a drug-related decrease and sometimes absence of stool where 1/20, 4/20, 5/20, and 15/20 animals in the control, LD, MD, and HD group experienced this sign.

Body weight: slight decreases (~6%) in body wt were seen at HD on days 17 and 20. Body wt gain (g/day) was decreased at MD and HD during gestation days 7-10 (values during that time were –1.8g/day for control, -19g/day for MD and –47.8 g/day for HD).

Food consumption: decreases in food consumption were observed at all doses however, statistically significant changes were seen at MD (only between gestation days 7-10) and HD (gestation days 7-20). The decreases were ~16% at MD and ~50% at HD. Decreases at LD were ~10% but were not statistically significant at any time point.

Toxicokinetics: not performed.

Embryofetal development evaluations:

Maternal parameters: there was no drug effect on the number of corpora lutea/dam, implantations/dam, or preimplantation loss/dam. There was a 6% decrease in the percent of live fetuses/litter at HD compared to that of the control. The percent of early resorptions/litter was dose-dependently increased (0.5% in control, 2.05% at LD, 3.66% at MD and 6.31% at HD). Late resorptions did not show a drug dependent effect. However, total resorptions/litter were increased in drug treated groups compared to control (expressed as %: 1.42 in control, 4.45 at LD, 4.53 at MD, and 7.37 at HD). Litters with resorptions were higher in the treated group compared to control (3/20 in control, 5/18 at LD, 7/20 at MD, and 11/19 at HD).

	Dose (mg/kg)				Historical Control
Parameter	0	10	30	100	Mean (Range)
% Live fetuses/litter	98.6	95.6	95.5	92.6*	94.9
% Early resorptions/litter	0.5	2.05	3.66	6.31*	3.2
% Litters with resorptions	15.0	27.8	35.0	57.9*	26.4

* Significantly different from concomitant control ($p \leq .05$).

Fetal parameters:

Fetal gender was not affected by the treatment. Female fetal weight at HD was decreased by 5% compared to control group. The number of fetuses with malformations/litter was increased at MD (38%) and HD (46%) compared to control even though these increases were not statistically significant. The number of male fetuses with malformations/litter was increased at MD (60%) and HD (152% compared to control) even though these increases were not statistically significant. The number of affected implants (combination of resorptions, dead, and malformed fetuses)/litter were higher at MD (69%) and HD (110%) compared to control. The number of litters with affected implants was increased at MD and HD compared to the control group (8/20 in control, 12/20 at MD and 13/19 at HD).

The "malformations" that were observed were mainly cardiovascular where "atypical origin of the common carotid artery" was seen in 9 conceptuses in 4 litters at HD compared to 4 conceptuses in 2 litters in the control group. Also absent subclavian artery was reported in 4 conceptuses in 2 litters at HD while none were reported in the control group. Other cardiovascular anomalies that were observed in treated animals but not in control included: enlarged heart (1 fetus at HD), small ventricle (1 fetus at HD), and fused aorta/pulmonary artery (1 fetus at MD and 1 fetus at HD) (the fetuses in the HD were 3 different fetuses but 2 were from the same litter). Other anomalies (absent heart papillary muscle and heart ventricle thinning) were seen in the same fetus in the control but in different fetuses of the treated groups (1 fetus at HD had absent heart papillary muscle and 1 fetus at HD had ventricle thinning). One fetus at the HD dose had a combination of these anomalies (absent heart papillary muscle and small ventricle). See the following table for the incidence of these anomalies.

	Dose (mg/kg)				
	0	10	30	100	Total HC[a]
Visceral Findings Fetuses (Litters)	172 (20)	173 (18)	176 (20)	160 (19)	4111 (569)
Heart enlarged	0	0	0	1(1)[b]	1(1)
Heart misshapen	1(1)[c]	0	1(1)	0	1(1)
Heart papillary muscle absent	1(1)[c]	0	0	1(1)[b]	0
Heart ventricle small	0	0	0	1(1)[b]	0
Heart ventricle focal thinning	1(1)[c]	0	0	1(1)[b]	2(2)
Aorta enlarged	0	0	1(1)	0	2(2)
Aorta/pulmonary artery fused	0	0	1(1)	1(1)	3(3)
Left carotid artery atypical origin	4(2)	1(1)	1(1)	9(4)	1(1)
Innominate artery absent	0	0	1(1)	0	0
Subclavian artery absent	0	0	0	4(2)	2(2)

[a] Historical control data, Lilly Research Laboratories 1989-1998.

[b] A total of 3 fetuses from 3 different litters (16203, 16813, and 16943) had one or more of these findings.

[c] Findings were from 1 fetus in Litter 16780.

There were other malformations reported at the LD and MD only such as displaced liver lobe (4 fetuses from 3 litters at MD and 1 fetus from 1 litter at LD), displaced stomach (3 fetuses from 2 litters at MD and 1 fetus from 1litter at LD) and none in the control or HD group. There were also 8 fetuses of 1 litter at MD that had fused metacarpals; however, this might not be drug related since it occurred in fetuses of one litter and only at MD. Skeletal deviations (incomplete ossification of the forepaw medial phalanx) were seen at HD (15 fetuses from 5 litters) while 1 was seen in the control. Extra presacral vertebra was seen in all groups (8 fetuses from 2 litters in control, 8 fetuses from 4 litters at LD, 17 fetuses from 4 litters at MD, and 9 fetuses from 4 litters at HD). The fact that this observation was seen in all groups including the control might suggest that it might be drug unrelated.

Table D3: **Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603**

Study B01498

	TREATMENT GROUP			
	00	01	02	03
EXAMINATION TYPE	CONCEPTUSES(LITTERS) EXAMINED			
EXTERNAL	174(20)	178(18)	178(20)	162(19)
VISCERAL	172(20)	173(18)	176(20)	160(19)
SKELETAL	172(20)	173(18)	176(20)	160(19)

NOTE: LIVE AND DEAD FETUSES AND LATE RESORPTIONS WERE GIVEN EXTERNAL EXAMS.
LIVE AND DEAD FETUSES WERE GIVEN SKELETAL EXAMS;
ONLY LIVE FETUSES WERE GIVEN VISCERAL EXAMS.

Table D3: **(Continued) Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603, Study B01498**

	TREATMENT GROUP			
	00	01	02	03
MALFORMATIONS	CONCEPTUSES (LITTERS) AFFECTED			
EXTERNAL				
ABDOMEN-UMBILICUS-TORSION	1(1)a	1(1)a	2(2)a	2(2)a
VISCERAL				
CARDIOVASCULAR SYS-AORTA-PULMONARY ARTERY-FUSED	0(0)	0(0)	1(1)b	1(1)b
CARDIOVASCULAR SYS-AORTA-ENLARGED	0(0)	0(0)	1(1)b	0(0)
CARDIOVASCULAR SYS-COMMON CAROTID -ATYPICAL ORIGIN	4(2)b	1(1)b	1(1)b	9(4)b
CARDIOVASCULAR SYS-HEART-VENTRICLE -PAPILLARY MUSCLE-ABSENT	1(1)c	0(0)	0(0)	1(1)c
CARDIOVASCULAR SYS-HEART-VENTRICLE -FOCAL THINNING	1(1)c	0(0)	0(0)	1(1)c
CARDIOVASCULAR SYS-HEART-VENTRICLE-SMALL	0(0)	0(0)	0(0)	1(1)c
CARDIOVASCULAR SYS-HEART-ENLARGED	0(0)	0(0)	0(0)	1(1)c
CARDIOVASCULAR SYS-HEART-MISSHAPEN	1(1)c	0(0)	1(1)c	0(0)
CARDIOVASCULAR SYS-INNOMINATE ARTERY-ABSENT	0(0)	0(0)	1(1)b	0(0)
CARDIOVASCULAR SYS-SUBCLAVIAN ARTERY-ABSENT	0(0)	0(0)	0(0)	4(2)b
CENTRAL NERVOUS SYS-BRAIN-LATERAL VENTRICLE -DILATED	0(0)	0(0)	0(0)	1(1)
DIGESTIVE SYSTEM-GALL BLADDER-RUDIMENTARY	2(2)	0(0)	3(3)	0(0)
DIGESTIVE SYSTEM-LIVER-LOBE-DISPLACED	0(0)	1(1)	4(3)	0(0)
DIGESTIVE SYSTEM-STOMACH-DISPLACED	0(0)	1(1)	3(2)	0(0)
RESPIRATORY SYSTEM-DIAPHRAGM-HERNIA	0(0)	1(1)	4(3)	0(0)
RESPIRATORY SYSTEM-LUNG-LOWER LOBE-ABSENT	0(0)	0(0)	1(1)	0(0)
RESPIRATORY SYSTEM-LUNG-UPPER LOBE-SMALL	0(0)	0(0)	1(1)	0(0)
SPECIAL SENSE SYSTEM-EYE-SMALL	0(0)	0(0)	1(1)	0(0)

Table D3: **(Continued) Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603, Study B01498**

	TREATMENT GROUP			
	00	01	02	03
MALFORMATIONS	CONCEPTUSES (LITTERS) AFFECTED			
SKELETAL				
APPENDAGES-FOREPAW-METACARPAL-FUSED	0(0)	0(0)	8(1)	0(0)
APPENDAGES-FOREPAW-PROXIMAL PHALANX-ABSENT	3(2)	0(0)	1(1)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN-LUMBAR VERTEBRA -ARCH-ABSENT	1(1)	0(0)	0(0)	1(1)
AXIAL SKELETON-VERTEBRAL COLUMN -THORACIC VERTEBRA-ARCH-ABSENT	1(1)	1(1)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -THORACIC VERTEBRA-ARCH-SMALL	0(0)	1(1)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -THORACIC VERTEBRA-CENTRUM-DISPLACED	1(1)	0(0)	0(0)	0(0)
SKULL-HYOID BONE-BODY-ABSENT	1(1)	0(0)	0(0)	0(0)

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Table D3: (Continued) Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603, Study B01498

DEVIATIONS	TREATMENT GROUP 00	01	02	03
	CONCEPTUSES (LITTERS) AFFECTED			
VISCERAL				
CARDIOVASCULAR SYS-AORTA-ARCH-ARTERY-EXTRA	5(4)	2(2)	2(2)	0(0)
DIGESTIVE SYSTEM-LIVER-LOBE-EXTRA	5(3)	1(1)	3(3)	3(2)
RESPIRATORY SYSTEM-LUNG-POSTCAVAL LOBE-ABSENT	11(7)	1(1)	6(5)	3(3)
RESPIRATORY SYSTEM-LUNG-POSTCAVAL LOBE-SMALL	1(1)	3(3)	1(1)	1(1)
SKELETAL				
APPENDAGES-FOREPAW-MEDIAL PHALANX -INCOMPLETE OSSIFICATION	1(1)	4(3)	2(1)	15(5)
APPENDAGES-FOREPAW-METACARPAL -INCOMPLETE OSSIFICATION	12(2)	0(0)	0(0)	1(1)
APPENDAGES-FOREPAW-PROXIMAL PHALANX -INCOMPLETE OSSIFICATION	0(0)	0(0)	1(1)	0(0)
APPENDAGES-HINDPAW-MEDIAL PHALANX-BIPARTITE	1(1)	0(0)	0(0)	0(0)
APPENDAGES-HINDPAW-MEDIAL PHALANX -INCOMPLETE OSSIFICATION	2(2)	0(0)	9(2)	0(0)
AXIAL SKELETON-RIB CAGE-RIB-FUSED	1(1)	1(1)	0(0)	2(2)
AXIAL SKELETON-RIB CAGE-RIB-SPADE	1(1)	0(0)	1(1)	1(1)
AXIAL SKELETON-RIB CAGE-RIB-THICK	2(2)	1(1)	0(0)	0(0)
AXIAL SKELETON-RIB CAGE-STERNEBRA-BIPARTITE	0(0)	0(0)	1(1)	0(0)
AXIAL SKELETON-RIB CAGE-STERNEBRA-FUSED	1(1)	3(2)	1(1)	2(2)
AXIAL SKELETON-RIB CAGE-STERNEBRA-MISALIGNED	1(1)	0(0)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -CERVICAL VERTEBRA-ARCH-INCOMPLETE OSSIFICATION	0(0)	0(0)	2(1)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -CERVICAL VERTEBRA-CENTRUM-BIPARTITE	0(0)	0(0)	1(1)	0(0)

Table D3: (Continued) Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603, Study B01498

DEVIATIONS	TREATMENT GROUP 00	01	02	03
	CONCEPTUSES (LITTERS) AFFECTED			
AXIAL SKELETON-VERTEBRAL COLUMN -CERVICAL VERTEBRA-CENTRUM -INCOMPLETE OSSIFICATION	1(1)	0(0)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -CERVICAL VERTEBRA-CENTRUM-MISSHAPEN	0(0)	0(0)	1(1)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN-LUMBAR VERTEBRA -CENTRUM-BIPARTITE	0(0)	1(1)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN-LUMBAR VERTEBRA -CENTRUM-HEMI	1(1)	0(0)	0(0)	1(1)
AXIAL SKELETON-VERTEBRAL COLUMN -PRESACRAL VERTEBRA-EXTRA	8(2)	8(4)	17(4)	9(4)
AXIAL SKELETON-VERTEBRAL COLUMN -THORACIC VERTEBRA-CENTRUM-BIPARTITE	0(0)	2(2)	0(0)	0(0)
AXIAL SKELETON-VERTEBRAL COLUMN -THORACIC VERTEBRA-CENTRUM-HEMI	1(1)	1(1)	0(0)	0(0)
PELVIC GIRDLE-PUBIS-INCOMPLETE OSSIFICATION	7(4)	1(1)	1(1)	7(2)
SKULL-CALVARIA-FRONTAL BONE -INCOMPLETE OSSIFICATION	1(1)	0(0)	1(1)	1(1)
SKULL-CALVARIA-PARIETAL BONE -INCOMPLETE OSSIFICATION	0(0)	0(0)	1(1)	0(0)
SKULL-CALVARIA-ACCESSORY BONE	2(2)	2(2)	2(2)	5(2)
SKULL-HYOID BONE-ARCH-BENT	2(2)	11(6)	5(4)	3(2)
SKULL-HYOID BONE-BODY-INCOMPLETE OSSIFICATION	28(12)	10(7)	32(14)	24(10)

Table D3: **(Continued) Developmental Anomalies in Fetuses of Female Rabbits Given Gavage Doses of 139603, Study B01498**

	TREATMENT GROUP			
	00	01	02	03
VARIATIONS	CONCEPTUSES(LITTERS) AFFECTED			
SKELETAL				
AXIAL SKELETON-RIB CAGE-RIB-EXTRA	82(18)	68(17)	73(17)	50(13)
AXIAL SKELETON-RIB CAGE-RIB-RUDIMENTARY	42(17)	57(17)	49(16)	50(16)
AXIAL SKELETON-RIB CAGE-STERNEBRA -INCOMPLETE OSSIFICATION	24(10)	26(11)	36(15)	11(8)

a: Conceptus classified as a late resorption.

b: Great vessel anomalies occurred in 2, 1, 3, and 6 litters in the 0, 10, 30, and 100-mg/kg groups, respectively.

c: Heart anomalies occurred in 1, 0, 1, and 3 litters in the 0, 10, 30, and 100-mg/kg groups, respectively.

Summary of individual study findings: New Zealand White time-mated female rabbits (20/group) were treated with 0, 10, 30, and 100 mg/kg/day atomoxetine orally by gavage on gestation day 7 through 19. Animals were observed 1-h postdose during the first 5 days for survival and clinical signs. Body wt was measured at certain days and food consumption was measured daily. The uterus and ovaries were weighed and the number of corpora lutea, implantations, and preimplantation loss were evaluated. Fetal wt, gender, and morphology were evaluated. Live fetuses were evaluated for external, visceral, and skeletal anomalies. There was no mortality or abortions reported. The most prominent clinical sign in treated animals was decreases/absent stool. Slight decreases (6%) in body wt at HD. Statistically significant decreases in food consumption at MD (16%) and HD (50%). A slight increase in early resorptions was seen in females treated with HD. A slight decrease (6%) in percent of live fetuses was seen at HD. Female fetal weight at HD was slightly decreased (5%). Even though not statistically significant, the number of fetuses with malformations/litter at MD and HD was increased. These were mainly male fetuses. The malformations observed were mainly cardiovascular and mostly an increase in the incidence of "atypical origin of the common carotid artery" and absence of subclavian artery at HD. Other cardiovascular anomalies which were also observed in fetuses of treated animals included enlarged heart (1 at HD), small heart ventricle (1 at HD), absent heart papillary muscle (1 at HD), focal thinning of the heart ventricle (1 at HD), and fused aorta/pulmonary artery (1 at MD and 1 at HD). Some of these anomalies (absent heart papillary muscle and focal thinning of ventricle) were seen in the same fetus of the control group while the other anomalies (enlarged heart, small ventricle and fused aorta/pulmonary artery) were not seen in control. Some skeletal deviations that were observed included incomplete ossification of the forepaw (HD).

Remarks: in the discussion the sponsor acknowledged that growth retardation, malformations and death at HD are indicators of development toxicity, however, they stated that "these findings are not conclusive because affected parameters were generally within in-house historical control (HC) ranges..". Generally, most of these values were within the HC range. However, the concurrent control value failed to follow a pattern similar to the treated group in the study indicating that the change in the treated group might be drug related even though it is within the HC range. For example, HC range for fetal female wt was 35.9-39.8 g and the value for HD group was 36.78 g, which was closer to the lower end of the HC range. When the concurrent control value was examined, it was found to be in the upper end of the range (38.8g), opposite to what one might predict based on the general trend in the study (i.e. a decrease at HD). So it should be considered that the change in the HD group in this example was not a common factor seen in all groups in the study but rather a specific effect that reflected on the treated group which is probably due to drug. Another example is when the sponsor indicated that statistical significance seen for the decrease (6%) in fetal viability at HD was due to the unusually low percentage (0.5%) of early resorptions/litter in the concurrent control compared to the HC range of 0%-11.9%. As in the previous example, this unusually low percentage in the concurrent control was not seen as a general trend in the study since animals at HD were within the historical control range but somewhere in the middle of the range and not at the lower end of the range like the concurrent control value. Therefore, if there was no drug effect one will expect this value to be at the lower end also just like the control group. So even though this 6% decrease was within the HC range, the fact that the concurrent control value was at the lower end of the range means that the drug is probably responsible for the increase in early resorptions.

The sponsor has indicated that the previously discussed decrease in female fetal wt was not associated with a delay in development (such as delayed ossification). However, the sponsor failed to acknowledge that even though skeletal malformations were not seen, there was an increase in skeletal deviations such as incomplete ossification of the forepaw medial phalanx at HD (15 fetuses from 5 litters) in comparison to control (1 fetus).

The sponsor stated that a relationship between the occurrence of structural anomalies in the heart and large vessels was unlikely since the affected vessels and the heart have different embryonic origins. However, the fact that the heart and blood vessels have different embryonic origins does not prevent the drug from affecting both these embryonic tissues causing anomalies to both sites.

The sponsor's statement "Although the heart anomalies in the 100-mg/kg group occurred in 3 fetuses from three different litters…., 1 fetus had an enlarged heart, another had a small ventricle, and a third had an absent papillary muscle and ventricular focal thinning, similar to 1 control fetus" was not exactly correct since the one fetus that had two anomalies had absent papillary muscle and a small ventricle which is not similar to the control fetus that had absent papillary muscle and focal thinning of the heart ventricle. However, regardless of this minor error, the sponsor implied that these findings are insignificant on the basis that "there was no consistency in the type of findings". The reviewer does not agree with the sponsor that these changes are insignificant because there was not consistency in their type but rather because the number of the affected fetuses was low (1 at HD for each of these incidences). In addition, these findings were not observed in the another study conducted with similar treatments (see the next reviewed study).

As for the occurrence of large vessel anomalies, the sponsor indicated that the occurrence of these anomalies has increased in this species in studies conducted in their laboratories. Studies "in preparation" were cited in which the absence of subclavian

artery and aorta/pulmonary fusion have each been observed "at least once in 2 out of 3 recent studies" while the HC data contained 2 fetuses with absent subclavian artery and 3 fetuses with fused aorta/pulmonary out of 4,111 evaluated fetuses. The exact number of affected fetuses in these studies "in preparation" was not clear. Similar argument was used for the incidence of atypical origin of the left common carotid artery where the number of affected fetuses in the concurrent control and HD group (4 and 9 fetuses, respectively), exceeded the cumulative historical control occurrence (1 out of 4,111fetuses).
The absence of the right subclavian artery was described as "unusual" and the sponsor has indicated that this finding, which was not seen in the concurrent control, has been seen only in 2 control fetuses historically. The fact that all the animals with this finding had normal right anterior appendages (since this artery is the blood supply for these parts) led the sponsor to conclude that adequate blood supply to these parts was available. In spite of this suggestion by the sponsor, this anomaly should be taken into consideration when the drug is going to be given to pregnant women or women of child bearing age.

Study title: a study of the effects of LY139603 on embryo/fetal development in rabbits

Key study findings: variations in the origin of the left carotid artery (originating from the brachicephalic trunk)

Study no: 353002
Volume #, and page #: vol 53, toxrpt 42
Conducting laboratory and location:

Date of study initiation: November 9, 1998
GLP compliance: yes
QA reports: Yes (x) No ()
Drug, lot #, radiolabeled, and % purity: LY139603, lot #399SB7, 98.5%
Formulation/vehicle: solution/water

Methods:

Species/strain: rabbit/New Zealand White

Doses employed: 0, 10, 30, 100, and 150 mg/kg/day

Route of administration: orally by gavage

Study design: artificially inseminated New Zealand White rabbits were treated with the indicated doses of atomoxetine hydrochloride daily from gestation day 7 through 19

Number/sex/group: 22/sex/group for the main study and 5/treatment group for the toxicokinetic study

Parameters and endpoints evaluated:

Survival and clinical observation: animals were observed daily for mortality and morbidity. Individual detailed clinical observations were recorded daily from gestation days (GD) 0-29 (prior to test article administration and approximately 1 hour following dosing).

Body wt: body wts for all females were recorded on gestation days 0, 3, 7, 10, 14, 17, 20, 23, 26, and 29.

Food consumption: maternal food consumption was recorded on a daily basis throughout gestation.

Maternal parameters: the branching of the great vessel of the dams was examined. The uterus and ovaries were excised. The number of the corpora lutea, the number and location of all fetuses, early and late resorptions, and the total number of implantation sites were recorded. Maternal tissues were preserved in 10% neutral buffered formalin for possible future histopathological examination.

Fetal parameters: fetuses were weighed and a detailed external examination was performed which included examination of the eyes, palate, and external orifices. Crown-rump measurements were recorded for late resorptions. The sex was determined internally. Visceral and skeletal examinations were also performed. External, visceral, and skeletal findings were recorded either as malformations (structural anomalies that alter general body conformity, disrupt, or interfere with body function, or may be incompatible with life) or developmental variations (alterations in anatomic structure that are considered to have no significant biological effect on animal health or body conformity, representing slight deviations from normal).

Results:

Mortality: 1 animal in the 30 mg/kg group died on GD 17, one animal in the 100 mg/kg died on GD 16, and 3 animals from the 150 mg/kg group died on GDs 9, 10, and 15. According to the sponsor, an additional animal from the 150 mg/kg group was euthanized for humane reasons on GD 21. This group was terminated early and was not further evaluated. One animal from the 100 mg/kg aborted on gestation day 23 and was euthanized on that day. According to the sponsor, the animal from the 30 mg/kg group that died on GD 17 died immediately following dosing did not show a decrease in body wt but at necropsy foamy contents in all the lobes of the lungs were described in the histopath section. Accordingly, the sponsor considered this death as drug unrelated (considered gavage related). The death of the animal in the 100 mg/kg group was considered drug related since the animal exhibited clinical signs that were similar to those seen in animals treated with 150 mg/kg that were euthanized. These signs included wt loss and pulmonary congestion (rales). This animal was nongravid and at necropsy red areas were described in the stomach.

Clinical signs: the most prominent clinical signs observed in the daily examinations were decreased urination (2/22 in the 100 mg/kg group, 8/22 in the 150 mg/kg group, and none in the other groups) and defecation (2/22 animals in control, 2/22 in the 10 mg/kg group, 1/22 in the 30 mg/kg group, 10/22 in the 100 mg/kg group, and 17/22 in the 150 mg/kg group). Some of the signs observed only at 150 mg/kg were whole body tremors, hypoactivity, mydriasis, and rales.

The following signs were observed both at the 100 and 150 mg/kg treated groups 1-h after dosing: whole body tremors (11/22 in the 100 mg/kg treated group and 12/22 in the 150 mg/kg group), labored respiration (1/22 in the 100 mg/kg group and 2/22 in the 150 mg/kg group), rapid respiration (2/22 in the 100 mg/kg group and 1/22 in the 150 mg/kg group), mydriasis (6/22 in the 100 mg/kg group and 7/22 in the 150 mg/kg group), and nasal congestion (6/22 in the 100 mg/kg group and 5/22 in the 150 mg/kg group). Two hours post dosing, these signs were only observed in the 150 mg/kg group.

Body weight: a 7% decrease in body wt was seen in the 100 mg/kg treated group starting on GD 14. At the 150 mg/kg dose a decrease (7%) was first seen on GD 10 and on GD 20 the decrease was 16% compared to the control. On GD 23 the decrease in body wt in the 100 mg/kg treated group was ~3% and the decrease at the 150 mg/kg treated group was ~9% and both were statistically significant.

Food consumption: food consumption was decreased by 44% compared to control in the 100 mg/kg treated group, which was first observed between GDs 7-10 and continued until GD 20. In the 150 mg/kg treated group the decrease in food consumption was more pronounced (53-70% compared to control between GDs 7-20).

Gross findings: at the scheduled necropsy on GD 29 the number of cystic oviducts seen in the treated animals (dams) were higher than the control group (2, 2, 7, and 8 in the control, 10, 30, and 100 mg/kg treated groups). Other gross findings that were seen in the treated animals but not the control included accessory spleen (2, 1, and 2 in the 10, 30, and 100 mg/kg groups) and variation in the origin of the carotid artery, i.e. originating from the brachicephalic trunk (1, 3, and 1 in the 10, 30, and 100 mg/kg treated group).

Toxicokinetics: treatment of pregnant New Zealand rabbits (5/group) with atomoxetine hydrochloride (10, 30, and 100 mg/kg) orally by gavage from GD 7-19 resulted in a dose-related increase in atomoxetine and its metabolites N-desmethyltomoxetine and 4-hydroxytomoxetine. Data from the 150 mg/kg group were not reported since the group was terminated early. In addition data from animals that were found to be non gravid were not included. There was no control group to compare changes in body wt, food consumption, and clinical signs. However, the changes seen were not drastically different from what was seen in the main study.

Increased levels of atomoxetine and its metabolites were seen with increasing dose. There was an increase in the levels of atomoxetine and its metabolites with treatment since plasma levels on GD 19 were higher than those on GD 7 (especially at 100 mg/kg). The sponsor stated that these changes are likely to be due to changes in clearance and/or volume of distribution. The levels of the 4-hydroxy metabolite were lower than those of the N-desmethyl metabolite. The sponsor indicated that run-to-run variability was seen. According to the sponsor this variability did not appear to be due to either analyte degradation or deconjugation resulting in the formation of analyte (i.e. glucuronide conjugate). No other explanation for this observation was proposed.

Table 9: Plasma Pharmacokinetic Summary in Gravid Female New Zealand White Rabbits Following Oral Administration of Atomoxetine Hydrochloride for up to 13 Days (ADME Report 35)

Parameter	Dose of LY139603[a]	Study Day of Sample Collection Day 0 (Gestational Day 7)	Day 12 (Gestational Day 19)
Atomoxetine			
AUC (ng•hr/mL)	10 mg/kg	138	178
C_{max} (ng/mL)		40.7	70.7
AUC (ng•hr/mL)	30 mg/kg	522	630
C_{max} (ng/mL)		170	203
AUC (ng•hr/mL)	100 mg/kg	2162	3228
C_{max} (ng/mL)		430	1114
AUC (ng•hr/mL)	150 mg/kg	NC	NC
C_{max} (ng/mL)		NC	NC
4-Hydroxyatomoxetine			
AUC (ng•hr/mL)	10 mg/kg	15.3	19.6
C_{max} (ng/mL)		3.5	6.8
AUC (ng•hr/mL)	30 mg/kg	63.7	83.1
C_{max} (ng/mL)		12.6	24.6
AUC (ng•hr/mL)	100 mg/kg	232	280
C_{max} (ng/mL)		37.6	55.2
AUC (ng•hr/mL)	150 mg/kg	NC	NC
C_{max} (ng/mL)		NC	NC
***N*-Desmethylatomoxetine**			
AUC (ng•hr/mL)	10 mg/kg	170	185
C_{max} (ng/mL)		35.4	48.8
AUC (ng•hr/mL)	30 mg/kg	488	638
C_{max} (ng/mL)		115	182
AUC (ng•hr/mL)	100 mg/kg	1933	3586
C_{max} (ng/mL)		354	876
AUC (ng•hr/mL)	150 mg/kg	NC	NC
C_{max} (ng/mL)		NC	NC

Abbreviations: AUC = total systemic exposure (for Day 0 = area under the plasma concentration-time curve from 0 to ∞ and for Day 12 = area under the plasma concentration-time curve from 0 to last observation above the quantitative limit); C_{max} = maximal observed plasma concentration; NC = Not calculated due to animal death and early treatment group termination.

[a] Dose of LY139603 is 8.8 (10), 26.3 (30), 87.5 (100), or 131.5 (150) mg/kg/day of tomoxetine as the free base.

Note: Values are reported as mean (n = 5 for 10 mg/kg/day, 4 for 30 mg/kg/day, 3 for 100 mg/kg/day).

For embryofetal development evaluations:

In-life observations:

Terminal and necropsic evaluations:

Dams: no differences were observed between control and treated animals in the following parameters: viable fetuses, early resorptions, late resorptions, pre- and post implantation loss, corpora lutea, fetal sex ratios, and fetal wt.

Offspring: external malformations (spina bifida and short tail) were observed in only 1 fetus in the 10 mg/kg treated group. No other malformations or variations of the external type were observed.

Visceral malformations and variations: soft tissue malformations were observed in two fetuses in the 10 mg/kg group where one animal experienced lobular lung agenesis and one had left testis and epididymis agenesis. No other visceral malformations were reported. Other soft tissue variations were reported such as major blood vessel variation (left carotid artery arising from the brachicephalic trunk: 6(5), 5(2), 3(3), and 11(9) fetuses (litter) in the control, 10, 30, and 100 mg/kg (when they were expressed as "%per litter" the values were 6.9, 7.8, 9.6, and 10.9 in the cont, 10, 30, and 100 mg/kg). Other variations of the soft tissue origin were accessory spleen seen in 7(3), 16(7), 6(5), 15(7) in the control, 10, 30, and 100 mg/kg, which when expressed as "%per litter" were 8.8, 22.9, 6.9, and 14 in the control, 10, 30, and 100 mg/kg groups, respectively.

Skeletal malformations and variations: vertebral anomaly with or without associated rib anomaly was seen in 1(1), 1(1), and 2(1) in the control, 30, and 100 mg/kg groups. All of these cases of malformations were extra and/or forked ribs and arches. One case of sternebra malalignment was seen in 1 fetus of the 100 mg/kg and none in the other groups. Several skeletal variations were observed such as those in the 27 presacral vertebrae (#of observations expressed as "% per litter" were 18.5, 17.1, 20.3, and 23.8 in control, 10, 30, and 100 mg/kg group), 7th sternebra (observations expressed as "%per litter" were 3.7 at 100 mg/kg and 0 in all other groups), sternebrae #5 and/or #6 unossified (observations expressed as %per litter were 3, 6.3, 6.3, and 6.8 in control, 10, 30, and 100 mg/kg, respectively), and 25 presacral vertebrae (expressed as %per litter 1, and 2.7 at 30 and 100 mg/kg, respectively and 0 in control and 10 mg/kg groups).

Table 14: Number Of Fetuses And Litters With Variations - Summary

PROJECT NO.: 353002 A STUDY OF LY139603 ON EMBRYO/FETAL DEVELOPMENT IN RABBITS PAGE 1
SPONSOR:LILLY RESEARCH
DAY 29

	FETUSES					LITTERS				
DOSE GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	80	92	87	97	0	16	17	14	18	0
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	80	92	87	97	0	16	17	14	18	0
ACCESSORY SPLEEN	7	16	6	15	0	3	7	5	7	0
MAJOR BLOOD VESSEL VARIATION	6	5	3	11	0	5	2	3	9	0
RETROCAVAL URETER	1	6	2	1	0	1	3	2	1	0
GALLBLADDER ABSENT OR SMALL	1	2	0	1	0	1	2	0	1	0
NUMBER EXAMINED SKELETALLY	80	92	87	97	0	16	17	14	18	0
13TH FULL RIB(S)	42	46	39	53	0	12	14	12	15	0
27 PRESACRAL VERTEBRAE	16	15	20	24	0	6	9	8	9	0
13TH RUDIMENTARY RIB(S)	12	15	22	13	0	10	10	10	9	0
STERNEBRAE WITH THREAD-LIKE ATTACHMENT	1	0	0	1	0	1	0	0	1	0
7TH STERNEBRA	0	0	0	2	0	0	0	0	1	0
HYOID ARCH(ES) BENT	6	7	0	1	0	4	4	0	1	0
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	2	6	6	7	0	2	4	3	6	0
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	1	0	2	1	0	1	0	2	1	0
EXTRA SITE OF OSSIFICATION ANTERIOR TO STERNEBRA #1	0	0	0	1	0	0	0	0	1	0
25 PRESACRAL VERTEBRAE	0	0	1	3	0	0	0	1	2	0
REDUCED OSSIFICATION OF THE 12TH RIB(S)	0	0	0	2	0	0	0	0	2	0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 150 MG/KG/DAY

Summary of individual study findings: 22/sex/group artificially inseminated New Zealand White rabbits were treated orally by gavage with 0, 10, 30, and 100 mg/kg atomoxetine from gestational day (GD) 7-19. Survival, clinical observation, food consumption, and body wt were evaluated. Maternal parameters including: the number of corpora lutea, the number of implantations, the number and location of all fetuses, and early and late resorptions were evaluated in the dams. In addition, the branching of the great vessels was evaluated in the dams. Fetal examination included external, visceral, and skeletal parameters. There was one death at 30, one death at 100, and 3 deaths at 150 mg/kg groups. The death at the 30 mg/kg dose was considered drug unrelated. The animals at the 150 mg/kg dose were terminated early due to toxicity. A slight decrease (7%) in body wt at 100 mg/kg and a larger decrease at 150 mg/kg (16%) was observed. A 44% decrease in food consumption was seen in the 100 mg/kg treated group compared to the control. An even larger decrease (50-70%) in food consumption was seen at the 150 mg/kg. Gross finding in the dams showed a slight increase in cystic oviducts in the treated animals compared to the control. Some variations in the origin of the carotid artery were seen in the treated group (dams) compared to the control. External malformation (spina bifida and short tail) was observed in one fetus in the 10 mg/kg group. Visceral malformations (agenesis) were observed in 1 fetus in the lung and another fetus in the testis and epididymis in the 10 mg/kg treated group. The most prominent visceral variation observed was the origin of carotid artery. Left carotid artery was originating from the brachicephalic trunk in 6(5), 5(2), 3(3), and 11(9) fetuses (litter) in the control, 10, 30, and 100 mg/kg group. The sponsor indicated that it was within the historical control data. However, looking at the historical control data, the values presented (0-31.5%) were for the category "major blood vessel variation" and not specifically for this type of variation (origin of carotid artery). Other visceral variations included accessory spleen. Some skeletal anomalies were reported but they did not seem to be drug related (extra and/or forked ribs). Other skeletal variations (vertebrae or sternebrae) did not reflect a drug effect.

Reproductive and developmental toxicology summary:
See separate summaries for individual studies reviewed previously.
The following summaries will be described for additional studies that which were pertained.
Study R07581 (tox rept 09, volume 51) entitled "an eighteen week basic fertility study in Wistar rats given compound LY139603 in the diet": in this study 10 rats/sex/group were treated with 0, 0.02, 0.04, or 0.08% tomoxetine (lot 866-83F-212) in the diet. The diets provided a time weighted average daily doses of approximately 15, 29, or 57 mg/kg for males and 12, 23, or 46 mg/kg for females from two weeks premating through gestation (the levels were higher during lactation due to increased food consumption, values were approximately 24, 48, 83 mg/kg/day). Males were treated for 10 weeks prior to mating while females were treated for two weeks prior to mating, throughout mating, gestation, and lactation. A decrease in body wt and food consumption was observed in both males and females. Males had a decrease (12% compared control) in body wt at HD at treatment day 71 and a 9% at study termination (treatment day 118). Females had a 10% decrease in body wt at MD between premating day 0-6 and a 14% decrease between gestation day 0-6 and 9% between gestation day 7-13. At HD, females had a decrease of

16% from control between premating day 0-6, 19% between gestation day 0-6, 9% decrease between gestation day 7-13, 12% between gestation day 14-20, and 16% between lactation day 0-13. No drug effect on fertility, mean gestation length, or gestational survival. There was a decrease in the survival of the progeny of females treated with MD and HD (% survival was 96, 92, 63, and 42% in the control, LD, MD, and HD respectively). Most of the progeny mortality was seen prior to postpartum day seven. The mean body weights of the HD progeny were lower than the control group on post natal days 1 and 7 (on postpartum day 1 the decrease was 16% and on postpartum day 7 the decrease was 22% compared to control). A slight decrease (5%) was still seen on postpartum days 14 and 21 but it was not statistically significant. According to the sponsor "no noteworthy necropsy findings in the 31 progeny that died prior to postpartum day 21".

Study R11881 (tox rept 11, volume 52) entitled "a teratology study of compound LY139603 administered orally to Wistar rats": 25 females/group were treated with 0, 25, 60, and 150 mg/kg/day tomoxetine (lot #866-83F-212) orally by gavage from gestation day 6 to 15. One female at HD died and decreases in body wt and food consumption were seen at HD. There was no effect for the drug on reproduction parameters (# of corpora lutea, implantations, and live fetuses), however, a slightly higher incidence of resorptions was seen at MD and HD compared to control even though the sponsor did not consider it as significant. The mean values for resorptions were 0.4, 0.6, 1, and 1 in control, LD, MD, and HD groups, respectively. No anomalies (external, visceral, and skeletal) were increased with drug treatment.

Study B7191 (tox rept 10, volume 52) entitled "a teratology study of compound LY139603 administered orally to Dutch Belted rabbits": artificially inseminated female rabbits (15/group) were treated with 0, 25, 50, and 100 mg/kg/day tomoxetine (lot# 866-83F-212) orally by gavage from gestation day 6 to 18. One rabbit from the control group died on gestation day 24. One rabbit from the MD died on gestation day 17. One rabbit at LD aborted on gestation day 26. One rabbit from HD appeared thin most of the time and was found not to be pregnant at the end of the study. Body wt did not appear to be affected while food consumption was decreased (18-41% at HD, from gestation day 6-27, compared to control). No effects on the following reproduction parameters: corpora lutea, implantations, and live fetuses. However, there appeared to be an increase in resorptions at HD compared to the control group (mean value was 0.3, 0.4, 0.4, and 0.6 for control, LD, MD, and HD groups, respectively). The sponsor did not consider this as drug related. There was no effect for the drug on fetal wt. External, visceral, and skeletal examinations did not indicate a drug effect.

Reproductive and developmental toxicology conclusions: an MTD can be considered met in the rat studies based on the decreases in body wt and body wt gain seen in treated males and females and in rabbits based on the deaths that were observed at the HD (150 mg/kg in one study when the dose was dropped to 100 mg/kg). From fertility studies conducted in rats, it appears that the drug does not affect fertility. However, a slightly higher incidences of early resorptions were observed in both rabbits (both Dutch Belted and White New Zealand) and rats (CD and Wistar), even though this observation was not acknowledged by the sponsor. The drug had the following effects on fetuses and progeny: decreased live fetuses (New Zealand rabbits) and progeny survival (Wistar rats), decreased female fetal wt (CD rats and New Zealand rabbits) and female weight in the progeny of Wistar rats from days 1-7, and a delay in physical landmarks or "developmental landmarks" as called by the sponsor (incisor eruption and eye opening) in CD rats. In addition, fetal "malformations" and specifically the origin of the carotid artery in New Zealand rabbits (these "malformations" were called "deviations" in another study) and missing subclavian artery were observed. The malformations (or deviations) in the origin of the carotid artery were seen in two separate studies in New Zealand white rabbits, however the sponsor attributed these findings to the higher incidence of background levels of this anomaly in these rabbits. Incomplete ossification in various bones in both CD rats and New Zealand rabbits (called "malformations" in rats and "deviations" in rabbits) were seen.

Some of the effects of the drug on fetal wt and fetal development could be attributed to the general effect of the drug on body wt and food consumption (both decreased) in the dams. If these were the only effects of the drug it is probably considered cautiously safe to give it to pregnant women. However, due to the other effects seen (decreased progeny survival and malformations in major blood vessels) it is recommended that the drug not be used in women of childbearing potential.

Labeling recommendations:

In rabbits treated with up to 100 mg/kg/day [2.6 times the maximum recommended human dose (MRHD) in EM and 0.3 times the MRHD in PM based on AUC values, and 18 times the MRHD based on mg/m^2], a decrease in female fetal weight and a decrease in live fetuses was observed in addition to an increase in incomplete ossification of forepaw medial phalanx. An increase in resorptions was observed in treated dams. Major blood vessel abnormalities such as atypical origin of the carotid artery were higher in fetuses of treated females compared to fetuses of control animals while missing subclavian artery was seen in fetuses of treated females only.

In female rats treated with dietary atomoxetine time-weighted average dose of approximately 40 mg/kg/day (3 times MRHD based on mg/m^2 value) two weeks prior to mating and throughout organogenesis, female fetal weight was decreased and an increase in the incidence of incomplete ossification of bones was observed in both fetal sexes. The dams in this study demonstrated a higher incidence of early resorptions. When female rats were treated with atomoxetine in a similar dietary method with a dose of approximately 20 mg/kg/day two weeks prior to mating throughout lactation, a decrease in progeny survival and weight during the first week postpartum and a delay in physical development of the progeny were observed. From fertility studies conducted in rats treated with up to 50 mg/kg/day, atomoxetine does not appear to affect fertility.

VIII. SPECIAL TOXICOLOGY STUDIES: JUVENILE STUDIES

Study title: a 75-day repeated dose toxicity study in young Fischer 344 rats administered tomoxetine hydrochloride (LY139603) orally by gavage and companion blood level study.

Key study findings: decreases in body wt and food consumption at HD in both M and F. Delayed onset of puberty in both M and F. Decreased cauda epididymal wt at MD and HD and decreased number of sperms in this structure at HD. For the toxicokinetic study, there was a decrease of plasma levels of both atomoxetine and the 4-hydroxymetabolite with maturation.

Study no: study R01799 & R01899 (toxicokinetic study)
Volume#, and page #: tox rept 45, volume 43, page 1
Conducting laboratory and location: Eli Lilly and Company
Date of study initiation: 07 Feb 1999-23 Apr 1999
GLP compliance: yes
QA reports: yes (x) no ():
Drug, lot#, radiolabel, and % purity: LY 139603, lot# 399SB7, purity 98.5%
Formulation/vehicle: solution/water

Methods:
Dosing

Species/strain: rats, Fischer 344

Doses employed: 0, 1, 10, and 50 mg/kg/day

Route of administration: orally/gavage (administered in a volume of 10 ml/kg)

Study design: 10-day old animals were treated with atomoxetine hydrochloride from postnatal day 10 to 84 (Test Days 0-74).
Number/sex/group: 10/sex/group for main study and 36/sex/group for toxicokinetic study

Observations and times:
Survival and Clinical Observations: rats assigned for the main study were examined daily for survival, general physical condition and behavior. Daily observations evaluated muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, locomotion, and presence of external lesions or growth. Rats were observed at approximately 2 and 6 hours postdose on Test Days 0 through 4 for clinical signs of toxicity. Rats for the toxicokinetic study were examined daily for survival and general physical condition.

Body weight: for the main study rats were weighed on Test Days 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, and 74. Body wt for animals in the toxicokinetic study were not included and were collected for the purpose of dose calculation according to the sponsor.

Food consumption: for the main study food was measured on Test Days 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, and 74. Food consumption was not collected for the toxicokinetic study.

Developmental landmarks:
Vaginal patency: females were examined daily for vaginal patency beginning on Postnatal Day 28 (Test Day 18) until all animals were observed positive.

Preputial separation: males were examined daily for preputial separation beginning on Postnatal Day 35 (Test Day 25) until all animals were observed positive.
Vaginal Lavage: was performed daily on Postnatal Day 71 through 84 (Test Days 61-74). The resulting wash was examined microscopically to evaluate vaginal cytology.
Cauda epididymal sperm collection: the cauda portion of the right epididymis was collected from all males after 74 days of treatment. Sperm samples were analyzed for motility, progressive motility, straightness, path velocity, progressive velocity, and sperm number.

Hematology and clinical chemistry:
Blood samples were obtained from the orbital plexus immediately prior to necropsy from rats fasted overnight. The following hematological parameters were determined: erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, blood cell morphology, total leukocyte count, leukocyte differential, and platelet count. For the determination of the following coagulation parameters, blood samples were obtained from the abdominal aorta: activated partial thromboplastin time and prothrombin time. The following clinical chemistry parameters were determined: glucose, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, alanine transaminase, aspartate transaminase, gama glutamyltransferase, creatinine phosphokinase, calcium, inorganic phosphorus, sodium, potassium, chloride, cholesterol, triglycerides, total protein, albumin, globulin, and albumin/globulin ratio.

Morphologic pathology: necropsies included examinations of all external body surfaces and orifices, the thoracic, abdominal, pelvic, and cranial cavities and their viscera, cervical tissues and organs, and external surfaces of muscle, nerve, and spinal cord. The length of the left femur was also measured.

Organ weights: the following organs were weighed: kidneys, liver, heart, spleen, uterus, ovaries, testes, prostate, adrenals, seminal vesicles, thyroids and parathyroids, pituitary, brain, and epididymis.

Histopathology: the following tissues were examined microscopically from each control and HD group rats:
Kidneys, ileum, parathyroid, liver, ovary, pituitary, heart, testis, cerebrum, lung, prostate, cerebellum, spleen, brain stem, tongue, thymus, adrenal, uterus, stomach, thyroid, epididymis, lymph node, salivary gland, pancreas, duodenum, jejunum, cecum, colon, rectum, cervix, vagina, seminal vesicle, skin, mammary gland, skeletal muscle, urinary bladder, bone (femur), eye, bone marrow (sternum), harderian gland, esophagus, trachea, aorta, sciatic nerve, and spinal cord.
In addition, testes, prostate, epididymides, seminal vesicles, ovaries, uterus, cervix, and vagina from the 1- and 10-mg/kg group rats were examined.

Hepatic microsomal enzyme evaluation: liver samples from 6 control animals/sex were collected at necropsy on Test Day 0, samples from 6 animals/sex/treatment group were collected at necropsy on Test Days 37 and 74. Microsomal preparations were prepared and used to determine the total cytochrome P450 content.

Toxicokinetics: animals (36/sex/group) were treated from PND 10 to PND 84 with 0, 1, 10, or 50 mg/kg tomoxetine hydrochloride. Plasma concentrations of tomoxetine and its metabolites (4-hydroxytomoxetine or LY-424478 and N-desmethyltomoxetine or LY-137877) were determined on Test Days 0, 37, and 74 (PND 10, 47, and 84). Six animals per sex per dose group were bled after dosing on Test Day 0, while three animals per sex per dose group were bled after dosing on Test Days 37 and 74.

Results:
Survival: one M in the control group died during tattooing, and one M in HD in the toxicokinetic study was euthanized in moribund condition on Test Day 32.

Clinical observations: one M in HD experienced whole body intermittent tremors on Test Day 2 and 2 F at HD experienced the same signs one on day 1 and one on day 3.

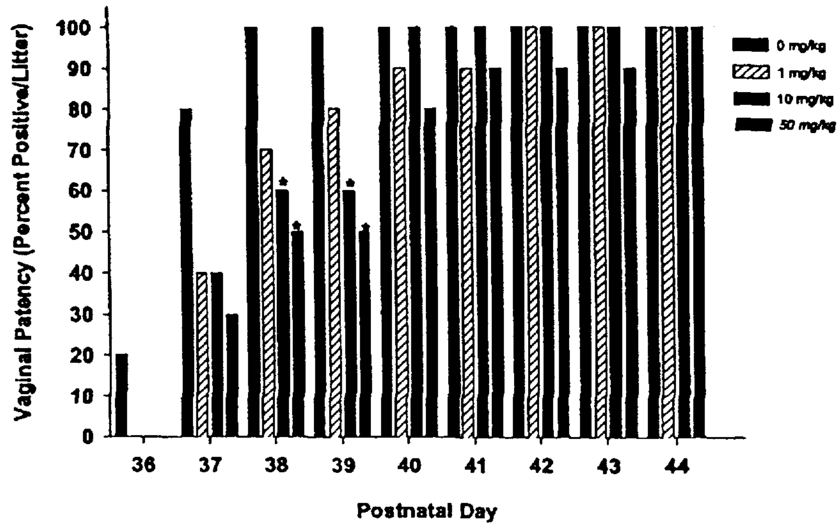
Body wt: decreases in body wt were seen in M at HD. A 3% decrease (compared to control) was initially seen on day 4 of treatment which continued to be seen throughout the study period (the decrease was about 7% in some cases) even though was not statistically significant at various time points. This kind of a decrease was also seen at HD in females, and was first observed on day 2 (a 1% decrease in comparison to control, statistically significant) and it reached 5% decrease at later time points in the study. Occasional decreases (~3%) that were statistically significant were seen at MD and LD also.

Food consumption: decreases in food consumption were observed in M at HD. The decrease reached statistical significance by day 36 (a decrease of 8% from control), even though it was seen from day 25. The decrease continued to the end of the study (at certain times it was decreased by 12% compared to control) even though it was not statistically significant at all times. Similar findings were observed in females.

Developmental landmarks:
Vaginal patency: there appeared to be a drug related decrease in vaginal patency that was seen in all treated groups in comparison to control. The average age (postnatal day) of vaginal patency was 37, 38.3, 38.4, and 39.2 for control, LD, MD, and HD groups, respectively. See the following figure for the drug effect.

APPEARS THIS WAY
ON ORIGINAL

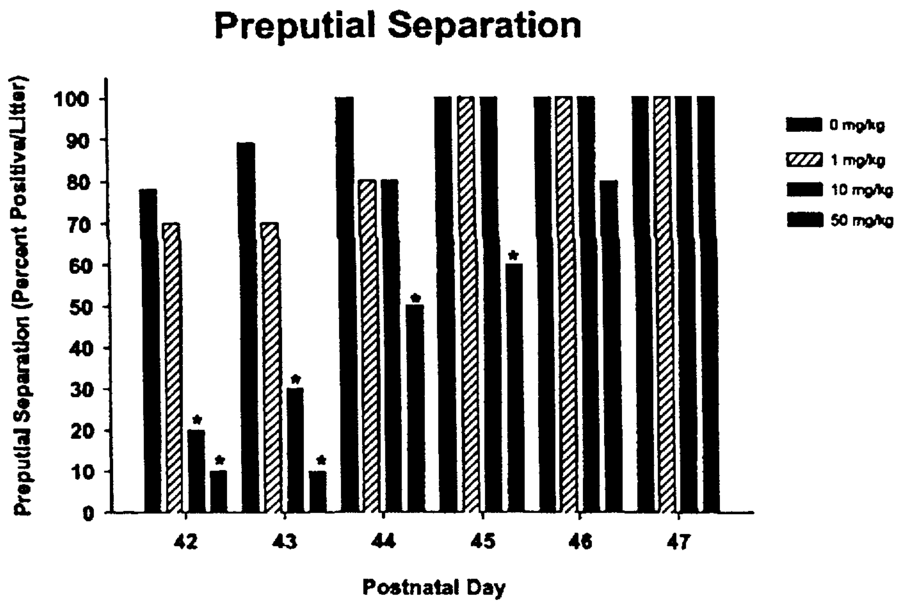
Vaginal Patency



* = p≤.05

By postnatal day 40, there were no significant treatment-related differences between groups and by day 44 vaginal patency was observed in all females.

Preputial separation: significant delays in the onset of preputial separation in the treated M at the MD and HD. The average postnatal days of preputial separation were 42.3, 42.8, 43.7, and 44.9 for the control, LD, MD, and HD respectively. The percent of animals that reached preputial separation on postnatal day 43 was 78%, 70%, 20%, and 10% in the control, LD, MD, and HD, respectively. By day 46, preputial separation was observed in all M in the control, LD and MD groups and in 80% of HD group. See the following figure.



* = p≤.05

Vaginal lavage and estrous cycle length: there was no apparent drug effect on estrous cycle length nor on the number of estrous cycles/female.

Sperm motion: there was no drug effect on sperm motion (%motile, %progressive, and %straightness).
Epididymal sperm concentration: it was apparent that the cauda epididymal wt was decreased with treatment and it was statistically significant at the MD and HD. The decrease in wt was 14% and 25% compared to control at the MD and HD, respectively. The number of sperm/cauda were decreased at MD by 13%, even though it was not statistically significant, and it was significantly decreased by 24% in the HD group. When sperm concentration was expressed per gram of tissue, there was no apparent drug effect.

Hematology: a decrease (~25%) in activated prothrombin time in M at all doses that was statistically significant. A slight but not statistically significant increase (~5%) in platelets in M at all doses.

Clinical chemistry: triglycerides were decreased (27%) in M at HD.

Organ wts: the absolute wt of the following organs in M treated with HD were decreased when compared to the control: heart (12%), spleen (16%), prostate (18%), and adrenals (13%). These decreases were also reflected on the ratio of wt/body wt as following: heart (6%), spleen (10%), prostate (13%), and adrenals (7%). Slight decreases were seen in the absolute wt of other organs in M at HD (liver, seminal vesicles, thyroid, and epididymis, decreases were less than 10%) but these decreases were not seen in the ratio of wt/body wt. There was a 6% increase in the ratio of the brain wt/body wt in M at HD.

In females treated with HD there were decreases in the absolute wt of spleen (14%), ovaries (14%), and pituitary (19%). These decreases were also seen in the ratio of wt/body wt as following: spleen (11%), ovaries (11%), and pituitary (17%). Slight decrease in the absolute wt of other organs were seen at HD (kidneys, liver, heart, and adrenals, decreases were less than 10%). Decreases (<10%) were also reflected on the ratio of wt/body wt for these organs.

Gross and histopathology: there were no drug related gross or histopathological changes.

Femoral length: there were no differences in femoral length between control and treated groups in either males or females.

Toxicokinetic study: plasma concentrations were increased with increasing dose. No differences were observed between males and females. Plasma levels were decreasing with maturation since the levels were highest on Test Day 0 in comparison to Days 37 and 74. See the following table for values.

Table 1: Mean Plasma Pharmacokinetic Data Summary for Tomoxetine Free Base (404363) in Young Fischer 344 Rats Following Daily Oral Dosing of 1, 10, or 50 mg/kg/day of Tomoxetine HCl for up to 75 days

Parameter	Administered Dose (mg/kg/day) 1[a]			10[a]			50[a]		
Sex	M	F	M+F	M	F	M+F	M	F	M+F
Day 0 (PND 10)									
$AUC_{0.25-t}$ (ng•hr/mL)	31.7	34.1	32.6	354.2	398.8	376.5	2625.2	2485.7	2569.4
C_{max} (ng/mL)	3.78	5.81	4.89	41.70	57.80	49.76	449.61	368.34	408.97
T_{max} (hour)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Day 37 (PND 47)									
$AUC_{0.25-t}$ (ng•hr/mL)	NC	NC	NC	44.6	71.3	84.3	335.7	1084.2	710.0
C_{max} (ng/mL)	NC	2.0	NC	15.50	6.44	10.97	24.76	293.44	159.10
T_{max} (hour)	NC	0.25	NC	0.25	0.25	0.25	0.25	0.25	0.25
Day 74 (PND 84)									
$AUC_{0.25-t}$ (ng•hr/mL)	NC	NC	NC	48.6	63.2	55.9	435.8	709.8	572.8
C_{max} (ng/mL)	NC	NC	NC	3.82	9.61	6.71	29.88	91.60	59.87
T_{max} (hour)	NC	NC	NC	0.25	0.25	0.25	6.00	0.25	0.25

Abbreviations: M = male; F = female; t = 24 hour or the last time point above the limit of quantitation; NC = not calculated, due to the number of sample results that were BQL (<1 ng/mL) a value could not be calculated on this study day; PND = Postnatal day; AUC = Area under the plasma concentration curve; C_{max} = Maximal plasma concentration; T_{max} = Time of maximal plasma concentration; [a] = 0.86, 8.6 or 43.2 mg/kg/day tomoxetine free base.

Although data for the 4-hydroxymetabolite were not available for all time points due to the limitation of the detection level, from the available data it was clear that like the parent compound there were lower plasma levels as the animals matured. As for the other metabolite, the limitation of the detection level for this metabolite did not allow for conclusions to be made about its fate with maturation.

Hepatic enzyme induction:
Cyt P450 content was increased with treatment on test day 74 at all doses in both M and F, however, only the HD dose group was statistically significant (136% in M and 57% in F relative to the control group). This increase was not seen on day 37. There appears to be a decrease in Cyt P450 with age in control F since the levels on day 37 were decreased by 12% and by 21% on day 74 from those on day 0.
The decrease in plasma tomoxetine levels with age as was seen in the toxicokinetic study could not be explained by the increase in Cyt P450 with treatment since the decrease in plasma drug levels was obvious on test day 37 as well as 74 while enzyme induction was not seen until day 74.

Summary of individual study findings: 10-day old rats were treated with 0, 1, 10, and 50 mg/kg/day tomoxetine from PND 10 to PND 84 (Test Days 0-74). A companion blood level study was conducted. One M at HD in the toxicokinetic study was euthanized in moribund condition on test day 32. Slight decreases (~7%) in body wt were seen in M and F at HD. Slight decreases (~8%) in food consumption were seen in M and F at HD. Decreases in vaginal patency were observed in F with treatment (1.3, 1.4, and 2.2 days delay in the vaginal patency in the LD, MD, and HD groups in comparison to the control). In M there was a delay in the onset of preputial separation with treatment, the average postnatal days for preputial separation were 42.3, 42.8, 43.7, and 44.9 in control, LD, MD, and HD group respectively (not statistically significant at LD). The cauda epididymal wt was decreased with treatment at the MD and HD (14, and 25% respectively). The number of sperms/cauda were decreased at MD (13% not statistically significant) and HD (24%), however, when expressed per gram of tissue, there was no apparent drug effect. Slight decreases in the absolute wt of some organs in M (heart, spleen, prostate, and adrenals) and F (spleen, ovaries, and pituitary) at HD. No drug effect on histopathology or femoral length. In the toxicokinetic study it was apparent that there was decreased plasma levels in matured animals in comparison to the young. Hepatic Cyt P450 content was increased significantly only at HD in both M and F and only on day 74.

Conclusions:
There was a delayed sexual maturation in both males (preputial separation, MD and HD) and females (vaginal patency, all doses) treated with atomoxetine. However, these changes were not accompanied with histopathological changes in the sex organs or changes in the estrous cycle length or number/female. Sexual maturation was eventually reached in these animals. This delay in the onset of maturity might not be of a major concern since maturity was eventually reached in both sexes.
In addition to the delayed sexual maturation in M, a decrease in the cauda epididymal wt was seen at MD and HD which was also associated with a decrease in the total

sperm/cauda epididymis at HD. The sponsor in their discussion proposed that this decrease in the number of sperm might not be of a concern since it was only about 25% and a decrease of 90% or more is needed to affect fertility in rat. However, it is not known what will be the effect on humans and how big of a decrease will be seen. However, this decrease in the number of sperms was not associated with changes in motility or straightness of their movement. No histopathological findings have indicated abnormalities in the testes when microscopical examinations were performed (the sponsor indicated that normal spermatogenesis was found as determined by microscopic examination of the testes). The decrease in the total number of sperm was attributed to "possible" changes in epididymal sperm transport. The sponsor referred to findings in the literature where abolition of peripheral noradrenergic nerves decreased epididymal contractility and caused slow sperm transit time in the epididymis thus increasing cauda epididymal wt and increased sperm number. Since atomoxetine is a norepinephrine reuptake inhibitor, the sponsor theorized that atomoxetine could be increasing the contractility of the ductules in the epididymis and thus increasing the transport of sperms through the epididymis. This might be a possibility however further studies might be needed to prove this hypothesis. The sponsor also has referred to studies where increased epididymal sperm transport with normal spermatogenesis would not be accompanied with infertility. Fertility in rats was assessed in a separate study (below), and no drug effect was seen.

Study title: a reproduction and fertility assessment study in Fischer 344 rats administered tomoxetine hydrochloride (LY139603) orally by gavage from postnatal day 10 through mating and implantation

Key study findings: decreases in body wt and food consumption at HD. No effect on time to mating, mating index in both M and F, or fertility index in both M and F. A decrease in corpora lutea in F at HD. There was no drug effect on pregnancy, implantaions, preimplantation loss or postimplantation loss.

Study no: R07799
Volume#, and page #: toxicology report 49, volume 44, page 1
Conducting laboratory and location: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Date of study initiation: 30 Aug 1999- 12 Dec 1999
GLP compliance: yes
QA reports: yes (x) no ():
Drug, lot#, radiolabel, and % purity: LY139603, lot# 399SB7, purity 98.5% on as is basis
Formulation/vehicle: solution/water

Methods:
Dosing:

Species/strain: rats/Fischer 344
Doses employed: 0, 1, 10, and 50 mg/kg/day, dose volume of 10 ml/kg
Route of administration: orally/gavage
Study design: 10-day old animals were treated with atomoxetine by oral gavage from postnatal day 10 through maturation (approximately 77 days), through mating and until Gestation day 6 (females) or prior to termination (males). After approximately 77 doses, animals were cohabitated for up to two weeks within treatment groups. Treated males were euthanized and discarded without necropsy after the completion of the mating period. Females were terminated on Postmating Day 13, and external body surfaces and orifices, thoracic, abdominal, and pelvic cavities and viscera, cervical tissues and organs were examined.
Number/sex/group: 20/sex/group

Observations and times:
Survival and clinical observations: animals were examined daily for survival, general physical condition, and behavior. Daily observations evaluated muscle tone, condition of pelage, color, appearance of eyes, respiration, posture, locomotion, and presence of external lesions or growths. Rats were observed at approximately 2 and 6 hours postdose on Test Day 0 through 4 for clinical signs of toxicity.

Body wt and food consumption: all rats were weighed on Test Days 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, 74, and 77 (treatment phase). During the mating phase, body wts were collected for all males and unmated females on Test Days 81, 84, 88, and 91 (mating phase). Females were weighed on Postmating/Gestation Days 0, 3, 6, 10, and 13.
Food consumption was measured on Test Days 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, 74, and 77 (treatment phase) for both males and females. Food consumption was measured for females on Postmating/Gestation Days 0, 3, 6, 10, and 13.

Mating performance and fertility: time to mating, male mating index, female mating index, male fertility index, and female fertility index were measured.

Maternal reproductive parameters: uteri were weighed and opened to measure the number and distribution of implantations, live conceptuses and resorptions. The ovaries were removed and the number of corpora lutea for each ovary were recorded.

Results:
Survival and clinical observations: two males at HD died, one died on day 3 of treatment and according to the sponsor the death was a gavage error since the death occurred immediately after dosing and soiled muzzle was detected indicating lung intubation. The second death occurred on Test Day 48 and the sponsor considered it compound unrelated on the basis that there were no preceding abnormal clinical sings or any signs of deterioration in the rest of rats in the group after treatment. One male in the MD was euthanized for humane reasons (broken nose).

Clinical signs observed were mainly increased activity (7/20 M at HD and 6/20 F at HD) and intermittent muscle tremors (5/20 M at HD and 3/20 F at HD). According to the sponsor these signs were observed only at the 2-hour observation time and not at the 6-hour observation time. Enlarged eyes were observed in 2 M at HD and 2 F at MD. According to the sponsor upon ophthalmic examination one of F at MD were considered normal and the other one was diagnosed as buphthalmus cataract and synechia and buphthalmus for the two M at HD. The sponsor considered these observations as drug unrelated because of "low incidence and unilateral occurrence". Other signs were observed (alopecia, haircoat soiling, soft feces, and skin scab and red) but they were sporadic and seen in control and treated groups.

Body weight and food consumption: body wt was decreased (6% compared to control) in M at HD starting on day 2 and lasted throughout the study and it was decreased by 12% at the end of the study. The decrease was also seen at the MD (3%), however, it was first statistically significant from control on day 22 and continued to be lower with sporadic statistical significance till the end of the study when it was 5% compared to the control. Decreases in M during mating period were also observed (up to 12% decrease compared to control, but it was not statistically significant). Decreases were also observed in F, however, they were less than those in M (started on day 2 as a 4% decrease, was statistically significant only between days 2 and 10 and days 29 and 72, and by the end of the study the decrease was still 4% compared to the control). A decrease (5%) in mean body wt was also observed in F during the gestation period at HD even though it was not statistically significant.

Food consumption was decreased by 10-15% in M starting from day 22 to the end of the study at HD. Decreases (3-7%) were also observed in M at MD but were statistically significant only sporadically between days 46 and 77. Decreases in food consumption (ranged between 6-10%) were also seen in females during treatment but mainly at the HD and was statistically significant from day 29 to day 77. Decreases in food consumption (~10% compared to control) were observed in F between gestation days 3 and 10 at HD only.

Mating performance: there was no differences between treated and control groups in time to mating, male mating index, male fertility index, female mating index and female fertility index.

Maternal reproductive parameters: there was a 12% decrease compared to control in the number of corpora lutea at HD. There was no drug effect on pregnancy, preimplantation loss or postimplantation loss. The number of implantations at the HD were lower than those in the control (~8% less than the control), however, this decrease was not dose dependent and was not statistically significant.

Summary of individual study findings: 10-day old rats (20/sex/group) were treated with 0, 1, 10, and 50 mg/kg/day from PND 10 through maturation (approximately 77 days), through mating and until gestation day 6 (females) or prior to termination (males).

Animals were observed daily, food consumption and body wts were evaluated. Mating performance and fertility were evaluated (time to mating, mating index, and fertility index). Two M at HD died (one was due to gavage error). Increased activity and muscle tremors were seen at HD in both M and F. Body wt was decreased (~12%) at HD in M and a slight decrease (~5%) was seen in F at HD but was not statistically significant at all times. There are no drug effects on mating performance and fertility. There was a 12% decrease in the number of corpora lutea at HD. There were less implantations at HD (8.8 vs. 9.6 in controls), but there was no drug effect on %of conceptuses, pre- or post-implantation loss.

Conclusions: the drug does not appear to affect mating performance (time to mating, mating index and fertility index in both males and females) when young animals were treated from PND 10 through maturation, mating, and until gestation day 6 for females or termination for males. The decrease in the number of corpora lutea that was seen in females did not reflect an effect on pregnancy, pre- or postimplantation loss, however, the slight decrease in implantations (8%) at the HD might reflect this decrease in the number of corpora lutea. However, when ratio of the number of implantations/corpora lutea produced was calculated, there was no difference between drug and control groups (74% in control, 73% in LD, 88% in MD and 76% at HD). In the discussion, the sponsor referred to other studies where in adults treated with this compound there was no effect on the number of corpora lutea (tox rept 9 and 27). However, these studies were in adult rats (weanling males treated for 10 weeks prior to mating and weanling females treated for two weeks prior to mating) while the current study is in juvenile animals (PND 10). Therefore, this observation that the drug has an effect on the number of corpora lutea produced should be taken into consideration when juvenile females are to be considered for treatment with atomoxetine.

Study title: a 75-day repeated dose neurobehavioral study in young Fischer 344 rats administered tomoxetine hydrochloride (LY139603) orally by gavage

Key study findings: decreases in body wt and food consumption and delayed onset of developmental landmarks (incisor eruption). There was an increase in activity but there was no effect on other behavioral tests (auditory startle habituation and passive avoidance).

Study no: R07199,
Volume#, and page #: vol. 44, toxrpt 48 page 1
Conducting laboratory and location: Eli Lilly and Company
2001 West Main Street
Greenfield, IN 46140
Date of study initiation: 02 Aug 1999
GLP compliance: yes
QA reports: yes (x) no ():
Drug, lot#, radiolabel, and % purity: tomoxetine hydrochloride, lot #399SB7, 98.5%
Formulation/vehicle: solution/water

Methods:
Dosing

Species/strain: rats/Fischer 344
Doses employed: 0, 1, 10, and 50 mg/kg/day
Route of administration: orally/gavage

Study design: 10-day old rats (Test Day 0) were treated with atomoxetine by gavage through PND 84 (Test Day 74). On PND 11 through 12 rats were examined for positive signs of incisor eruption and on PND 15 through 18 for positive signs of eye opening. On PND 19 and again on PND 55$\pm$2 auditory startle habituation was monitored. On PNDs 15, 30$\pm$1, and 60$\pm$2 activity levels were monitored in an automated Figure-8 Mazes. On PND 20 and 83 rats were tested in a modified passive avoidance task.
Number/sex/group: 20/sex/group

Observations and times:

Survival and clinical observation: animals were examined daily for survival, general physical condition, and behavior. Muscle tone, condition of pelage, color and appearance of eyes, respiration, posture, locomotion, and presence of external lesions or growths were evaluated daily. Animals were also observed at 2 and 6 hours post dose on Test Days 0 through 4 for clinical signs of toxicity.

Body wt: rats were weighed on Test Days 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, and 74.

Food consumption: on Test Days 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 60, 64, 67, 71, and 74.

Developmental landmarks: rats were examined for incisor eruption on PND 11 through 12 and for eye opening on PND 15 through 18.

Neurobehavioral measurements:
Auditory startle habituation: at 19 days of age and again at 55 $\pm$ 2 days the test was performed. A test session consisted of a 5-min acclimation period in the test chamber at a background noise level of 70 $\pm$ 4 dBA. Then each rat was presented with a 50-millisecond burst of 120 $\pm$ 4 dBA white noise, and response data were recorded for a 100-millisecond period following noise onset. A total of 50 noise burst presentations was given to each rat at a fixed interval of 8 seconds. The peak amplitude of the startle response and the latency from noise onset to the rat's peak response were recorded. For each rat data were summarized into five consecutive 10-trial mean value (Trial Blocks 1-5).
1-Hour activity: at 15 , 30 $\pm$ 1, and 60 $\pm$ 2 days of age, activity levels were monitored in an automated Figure-8 Mazes instrument. Rats were individually place in the maze and a computer recorded the number of photobeam breaks. Each trial consisted of four consecutive 15-min intervals with the exception of maze activity at 15 days of age, which consisted of three 10-min intervals.

Passive avoidance: at 20 and 83 days of age, all rats were tested in a modified passive avoidance task using the . The testing method consisted of 2 days, a learning day component where shock was administered and a memory component where there was no shock. Before each testing day, a 60-second acclimation period was given. During the learning component, acquisition of passive avoidance behavior was monitored for three consecutive 180-second trials, separated by a 60-second intertrial interval. The shock duration was set at 180 seconds and the shock intensity at 0.5 mA. After the 60-second acclimation period and intertrial intervals, the chamber light turned on in the compartment in which the rat resided. The rats were then required to remain in the lighted compartment in order to avoid shock. If a rat did cross to the dark compartment, it could escape the shock by returning to the lighted compartment. During the memory component of the procedure, a 60-second acclimation period was given and then a single 180-second trial was conducted in which no shock was delivered if the rat crossed to the dark compartment. Computer-recorded data for each rat included the latency to first crossing and the number of crossings during each trial.

Results:

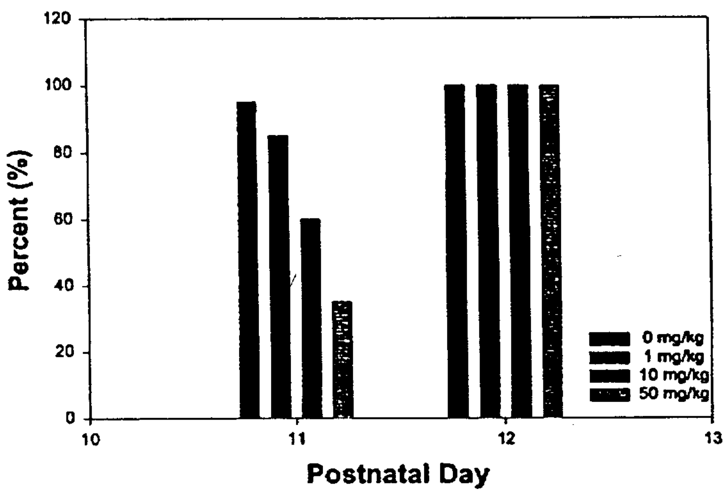
Survival and clinical observations: one M at HD died on Test Day 45. The sponsor indicated that the cause of death was not apparent and negated the possibility that it is drug related "since it occurred during the middle portion of the treatment phase in the absence of adverse clinical observations and there were no signs of deterioration in the surviving rats during the remainder of the treatment phase".
Intermittent tremors were observed in 1/20 M and 1/20 F at HD. These tremors were not observed in any of the other groups. Leg weakness was observed in 2/20 F at HD and was not seen in any of the other F groups nor in M. Increased activity was seen in 4/20 M and 3/20 F at HD. Enlarged eyes were seen in treated groups only in M (3/20 at LD, 2/20 at MD, and 3/20 at HD) and in control and treated animals in F (1/20 control, 2/20 LD, 2/20 MD and 3/20 at HD).
Observations of alopecia, skin, foot, digit, and tail anomalies were seen in both control and treated groups and did not indicate a drug effect.

Body wt: decreases in body wt were seen in M at HD throughout the study (started as a 10% decrease compared to control and reached 22% mid way in the study). Decreases at MD were also seen (~4%) however, they were not statistically significant at all times. Decreases in body wt were also observed in F at HD (~12% compared to control) throughout the study. A slight decrease (~4%) was seen at MD even though it was not statistically significant most of the time.

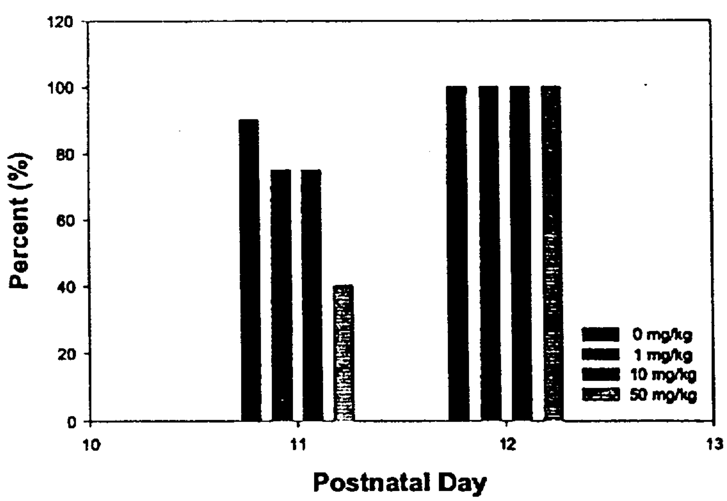
Food consumption: decreases in food consumption (ranged from 7-24% from beginning to the end of study) were observed in M at HD. Decreases (~5%) at MD were also observed however they were statistically significant only at the beginning of the study. Decreased food consumption was also seen in F at HD (ranged from 12-17%) and a slight decrease (~5%) was seen at MD that was statistically significant only at the beginning of the study.

Developmental landmarks:

Incisor Eruption: there was a very slight delay in the onset of incisor eruption in the treated males and females. The average PND of incisor eruption in the 0, 1, 10, and 50 mg/kg treated groups were 11.05, 11.15, 11.4, and 11.65 in males, respectively, and 11.1, 11.25, 11.25, and 11.6 in females, respectively. On PND 11, 95% of control, 85% of LD, 60% of MD, and 35% of HD males showed signs of incisor eruption, while 90% of control, 75% of LD, 75% of MD, and 40% of HD females experienced it. By PND 12, all animals reached this developmental landmark.



Males



Females

Eye opening: there was no apparent drug effect on this developmental landmark.

Neurobehavioral measurements:

Auditory startle habituation: there was a slight increase in the peak startle response in males on day 19 at all doses even though it was not dose dependent (for all trials the increase was 42% at LD, 8% at MD and 40% at HD compared to all trials in the control group). These changes were not statistically significant. The sponsor did not address these observations. No drug effect was seen on day 55.
In females no major effect on peak response were seen on day 19. On day 55, the sponsor acknowledged only one increase at LD (38%) since it was statistically significant even though larger increases were seen in other trials (those seen in trial block 4 at HD on the same day and those seen in males). There was not an apparent drug effect on the latency to peak response in both males and females.

Activity: there was an increase in activity in M at the MD (ranged from 28-38% in the individual trials and it was reflected as 29% in the total) and HD (ranged from 28-42% in the individual trials, and it was reflected as 29% in the total) on day 15. The changes in most of the individual trials were statistically significant but not in the total. In females changes in the individual trials were seen on day 15 at HD (ranged from 17-39% and reflected as 28% in the total), however, these changes were not statistically significant. Some increases in activity were also seen in females on day 30 that were seen mostly at HD (ranged from 18-57% in individual studies and reflected as 31% in the total) but were statistically significant only in the total and not at the level of individual studies. There was no apparent drug effect on activity on day 60 in either males or females.

Passive avoidance: at age day 20, there were some changes in the number of crossings on Test Day 1 in males, which is the learning phase of the testing, where a decrease in the number of crossings that was statistically significant at the MD (31% compared to control) and HD (20%) were seen. An increase (74%) was seen on trial 2 of the same day at HD. On Test Day 2, which is the retention phase of the testing, there was no apparent drug effect on the number of crossing. The changes in the number of crossings on Test Day 1 even though they were statistically significant might not reflect a meaningful effect since they were decreased in one trial and increased in another. There was no apparent drug effect on the number of crossings nor on the latency to the first crossing in females during the learning or the retention phases of the test on Test Day1. Also, there was no drug effect in both M and F when these tests were repeated at age day 83.

Summary of individual study findings: 10-day old rats were treated with 0, 1, 10, and 50 mg/kg atomoxetine by gavage through PND 84. On PNDs 11 through 12 rats were examined for positive signs of incisor eruption, on PNDs 15 through 18 for positive signs of eye opening, on PND 19 and again on PND 55 auditory startle habituation was monitored, on PNDs 15, 30, and 60 activity levels were monitored, and on PND 20 and 83 rats were tested in a passive avoidance task. In addition animals were observed daily for survival and general physical condition. Body wt and food consumption were measured at certain days. One M at HD died on Test Day 45, the sponsor considered the death drug unrelated. Intermittent tremors were observed at HD in 1 M and 1 F. Leg weakness was observed in 2 F at HD. Increased activity was seen in 4 M and 3 F at HD. Body wt was decreased in M at HD throughout the study (ranged from 10-22% compared to control). Decreases at MD were seen in M but were less (~5%) and not statistically significant at all times. Decreases in body wt (~12% compared to control) were observed in F at HD throughout the study. Food consumption was decreased in M at HD (7-24% at the beginning to the end of the study). Less drastic decreases (~5%) were seen at MD but were not statistically significant. In F decreases in food consumption (~5%) were also seen at HD but were statistically significant only at the beginning of the study. A slight delay in the onset of incisor eruption in M at MD and HD and only at HD in F. However, all animals reached this developmental landmark at PND 12. Eye opening was not affected by drug treatment. On day 19, a slightly higher peak auditory startle response in M at all doses compared to those seen in the control group. These changes were not statistically significant. There was an increase in activity in M at MD and HD and in F at HD on day 15. No meaningful drug effects on the passive avoidance test were observed (decreases in one trial and increases in another on the same day).

Conclusions:
As seen in other studies, the drug decreased body wt and food consumption. An effect of the drug was seen on developmental landmarks such as a delay on the onset of incisor eruption. An increase in activity in M at MD and HD and in F at HD. No remarkable drug effect on the other behavioral tests (auditory startle habituation and passive avoidance test). The increase in activity in animals treated with the compound might be counterintuitive to what the drug is indicated for (hyperactivity).

Juvenile studies conclusion:
As was seen in previous studies in adult animals, the drug resulted in a decrease in food consumption and body wt. The decreases in body wt that were observed with treatment especially at HD indicate that an MTD is reached. The finding that treatment with atomoxetine affects body wt and food consumption could be of credible concern in this population since an effect on growth is possible. Delayed onset of puberty in both males and females and delayed developmental landmarks were observed with treatment. A decrease in developmental landmarks (incisor eruption) was also seen in a previous reproduction study when the progeny of treated females was found to have a decrease in incisor eruption in comparison to the control group (see tox rept. 27 in Reproductive and Development Toxicology section). It is possible that the decrease in body wt and food consumption seen with drug treatment might affect these development of several of these landmarks.

As for the effect of the drug on other fertility parameters (# of corpora lutea produced and decreased number of sperms in the epididymis) these also could be as a result of the effect of the drug on growth. However, other mechanisms might be possible through the effect of the drug on norepinephrine. The decrease in the number of sperms in the epididymis was proposed by the sponsor to be as a result of the effect of the drug on the

contractility in the ducts of the epididymis. However, no studies to support this proposal were provided.
The increase in activity that was seen in the behavioral test of animals and with the increase in activity observed with the daily observations should be taken into consideration since the drug is indicated for hyperactivity. In addition, the sponsor is proposing that this compound is different from other drugs used to treat ADHD in that it is a non-stimulant.

Labeling recommendations: delayed onset of puberty in both male and female rats and decreased epididymal weight with decreased sperm number in the epididymis was observed in rats treated from postnatal day 10 to 84 with 50 mg/kg/day atomoxetine [$\leq$13x the maximum recommended human dose (MRHD) in EM and $\leq$1.5x MRHD in PM based on AUC values). However, eventually all animals reached puberty and there was no malformations of the vagina or prepuce/glans penis. The decreased number of sperm in the epididymis with the decreased weight of the structure did not appear to affect the fertility of animals. A slight increase in activity on PND 15 but not on PND 60 was seen in rats treated with the same dose and duration. Females treated with the same dose from PND 10 through mating and gestation had a decrease in the number of corpora lutea.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Pharmacology: the reviewed studies had indicated that there is minimal effect of atomoxetine on other transporters and a variety of other receptors compared to its effect on the NE transporter.

Pharmacokinetics: the drug has a variable oral bioavailability between species. The drug appears to distribute quickly to tissues and it is excreted in milk and passes through the placenta. It is extensively metabolized and the two major phase I metabolites are 4-hydroxyatomoxetine and N-desmethylatomoxetine which were detected in rats, dogs, mice, rabbits, rhesus monkeys and humans. In humans aromatic hydroxylation appears to be mainly mediated by CYP2D6. The major route of elimination was in the urine and some was seen in the feces mostly due to biliary elimination of metabolites. The drug is highly protein bound. Major induction of CYP450 enzymes in mice (CYP2B) and moderate induction in rats (1A and 2B).

Safety pharmacology: The pharmacodynamic effects of tomoxetine HCl in the preclinical studies, with relevance to human safety, are primarily observed in the central nervous and cardiovascular systems. In rodents, tomoxetine HCl resulted in deaths associated with clonic convulsions at very high oral doses (13.5X-18X the MRHD on a BSA basis), myoclonic jerking, decreased body temperature, decreased motor activity, lethargy, irritability, leg weakness, jerky gait, exophthalmos, and piloerection, tremors, grasping loss, pinna reflex, mydriasis, lacrimation, vibrissal response, analgesia, placing loss, decreased abdominal tone, corneal loss, righting loss, and increased hexobarbital sleeping time. No increase in locomotion was observed in the rodents, suggesting a low potential for producing psychomotor stimulation in clinical use. In young beagle dogs administered up to 16 mg/kg/d PO tomoxetine HCl (2.6X the MRHD in poor metabolizers and 7.6X the MRHD in extensive metabolizers on an AUC basis), the pupillary light reflex was decreased and the incidence of mydriasis increased, but there were no other treatment-related effects in the neurological examination. Tomoxetine increased cocaine-like responding rates in rats, but not in monkeys.

In the cardiovascular toxicity studies, tomoxetine decreased the maximum rate of rise of the action potential (Vmax) in isolated canine cardiac purkinje fibers at a concentration of 10^{-5} M, suggesting a potential for interference with cardiac conduction, although tomoxetine was half as potent as the approved antidepressant drug amitriptyline in this effect. Tomoxetine and the metabolites N-desmethyltomoxetine and 4-hydroxytomoxetine also blocked the I_{Kr} (HERG) channel in transfected human embryonic kidney cells at clinically relevant concentrations, suggesting a potential for Q-T prolongation and predisposition to the occurrence of ventricular arrhythmias. In the *in vivo* model in anesthetized dogs, IV tomoxetine administration increased heart rate to a lesser extent and increased respiratory rate to a similar extent compared to IV amitriptyline. There was no effect on the QRS duration, but a negative dromotropic effect with prolongation of the P-R interval was observed after both tomoxetine and amitriptyline. Tomoxetine increased the Q-TC interval as much as 22%-32% at 10 mg/kg IV with and without pretreatment with atropine and propranolol, although the changes were not statistically significant. Oral tomoxetine HCl had no effects on heart rate, respiratory rate, and ECG parameters at single doses up to 5X the MRHD on a BSA basis in conscious dogs, and after daily oral administration at up to 2.6X the MRHD in poor metabolizers and 7.6X the MRHD in extensive metabolizers on an AUC basis for 4 weeks in young beagle dogs. However, the results of *in vitro* and anesthetized dog studies indicate that careful ECG monitoring should be conducted in the clinical setting.

Tomoxetine HCl had no effects on respiratory function at up to 9X the MRHD in rats. The renal effects in rats were similar to those observed by the antidepressant drugs imipramine and desipramine, and included mild, dose-related diuresis, decreased osmolality, increased creatinine excretion and decreased creatinine concentration, without changes in the concentrations of sodium, potassium and chloride at up to 4.5X the MRHD in the rats. No agonist effects were observed in isolated guinea pig ileum and rabbit jejunum, and there were no effects on gastrointestinal motility in mice. Tomoxetine HCl had no effects on immune response in male mice. The results of the receptor-binding and *ex vivo* studies suggested a low potential for interaction with the sympathetic and parasympathetic control of peripheral organ function.

General toxicology: the major effect of atomoxetine was the decrease in food consumption and body wt that was observed mainly in rodents (dogs did not reflect this in the 1-year study, and only food consumption appeared to be affected when the drug was given IV for two weeks). In view of the decrease in body wt observed in rats, an MTD is considered to be met in rat studies. As for dogs, an MTD can be considered met in view of the physical signs observed (tremors that lasted for several weeks in animals treated with HD). The liver appears to be the organ that is mostly affected by atomoxetine with changes in its wt and other gross and histopathological changes (pallor, mottling and vacuolation). However, dogs did not reflect hepatotoxicity as a result of treatment with the drug.

Genetic toxicology:
Tomoxetine was negative for mutagenicity in the standard Ames test and negative for clastogenicity in the *in vitro* assays for unscheduled DNA synthesis in adult rat hepatocytes (UDS assay), forward mutations at the TK locus in L5178Y mouse lymphoma cells, and ~~chromosome~~ aberrations in Chinese hamster ovary cells, and the *in vivo* assays for sister chromatid exchange in Chinese hamster bone marrow and induction of micronuclei in mouse bone marrow cells. However, in Chinese hamster ovary cells there was a slight increase in the percent of cells with diplochromosomes suggesting increased endoreduplication. The metabolite nortomoxetine HCl (Compound 137877) was negative in a standard battery that included the Ames test for gene mutation in bacteria, *in vitro* assays for clastogenicity measured by induction of DNA repair synthesis (UDS) and forward mutation at the TK locus of mouse lymphoma cells, and an *in vivo* assay on induction of sister chromatic exchange in Chinese hamster bone marrow. However, the dose selection in the *in vivo* study was not supported by data indicating nortomoxetine-induced toxicity.

Carcinogenicity: please see the conclusion at the end of the carcinogenicity section.

Reproductive and developmental toxicology: an MTD can be considered met in the rat studies based on the decreases in body wt and body wt gain seen in treated males and females and in rabbits based on the deaths that were observed at the HD (150 mg/kg in one study when the dose was dropped to 100 mg/kg) . From fertility studies conducted in rats, it appears that the drug does not affect fertility. However, a slightly higher incidences of early resorptions were observed in both rabbits (both Dutch Belted and White New Zealand) and rats (CD and Wistar), even though this observation was not acknowledged by the sponsor. The drug had the following effects on fetuses and progeny: decreased live fetuses (New Zealand rabbits) and progeny survival (Wistar rats), decreased female fetal wt (CD rats and New Zealand rabbits) and female weight in the progeny of Wistar rats from days 1-7, and a delay in physical landmarks or "developmental landmarks" as called by the sponsor (incisor eruption and eye opening) in CD rats. In addition, fetal "malformations" and specifically the origin of the carotid artery in New Zealand rabbits (these "malformations" were called "deviations" in another study) and missing subclavian artery were observed. The malformations (or deviations) in the origin of the carotid artery were seen in two separate studies in New Zealand white rabbits, however the sponsor attributed these findings to the higher incidence of background levels of this anomaly in these rabbits. Incomplete ossification in various bones in both CD rats and New Zealand rabbits (called "malformations" in rats and "deviations" in rabbits) were seen.
Some of the effects of the drug on fetal wt and fetal development could be attributed to the general effect of the drug on body wt and food consumption (both decreased) in the dams. If these were the only effects of the drug it is probably considered cautiously safe

to give it to pregnant women. However, due to the other effects seen (decreased progeny survival and malformations in major blood vessels) it is recommended that the drug not be used in women of child-bearing potential.

Special toxicological studies (juvenile animals): the decreases in body wt that were observed with treatment especially at HD indicate that an MTD is reached. The finding that treatment with atomoxetine affects body wt and food consumption could be of credible concern in this population since an effect on growth is possible. Delayed onset of puberty in both males and females and delayed developmental landmarks were observed with treatment. A decrease in developmental landmarks (incisor eruption) was also seen in a previous reproduction study when the progeny of treated females was found to have a decrease in incisor eruption in comparison to the control group (see tox rept. 27 in Reproductive and Development Toxicology section). It is possible that the decrease in body wt and food consumption seen with drug treatment might affect the development of several of these landmarks.
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General Toxicology Issues:
Recommendations:

Labeling with basis for findings:

X. APPENDIX/ATTACHMENTS:

Addendum to review:

Other relevant materials (studies not reviewed, appended consults, etc.):

Any compliance issues:

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

/s/

Ikram Elayan
8/5/02 04:55:08 PM
PHARMACOLOGIST

Barry Rosloff
8/5/02 05:12:54 PM
PHARMACOLOGIST
Concur with approvability recommendation. See my memo of 8/5/02 for further comments.