

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-411**

**MEDICAL REVIEW**

Review and Evaluation of Clinical Data  
Safety Team Leader Review of Response to the Approvable Letter

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**NDA:** 21-411

**Drug:** Strattera<sup>TM</sup> (atomoxetine, formerly tomoxetine)

**Route:** oral

**Indication:** attention deficit hyperactivity disorder

**Sponsor:** Lilly

**Action Date:** 11-26-02

**Date Review Completed:** 11-19-02

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## 1 Background

Atomoxetine (Strattera<sup>TM</sup>) is intended to treat attention deficit hyperactivity disorder (ADHD) in children six years of age and older, adolescents, and adults. Atomoxetine is predominantly metabolized by the cytochrome P450 isoenzyme 2D6. In an August 12, 2002 approvable letter, the Division requested the following information regarding atomoxetine:

- A description of the relationship between higher levels of atomoxetine (>2000 ng/ml) and the duration of the QT interval, especially in the pediatric population
- An estimate of the proportion of patients who might be expected to achieve higher atomoxetine plasma levels
- Additional long-term safety data in CYP 2D6 poor metabolizers (genotypic PMs) and CYP 2D6 extensive metabolizers (EMs) who are treated concomitantly with potent inhibitors of CYP 2D6 (phenotypic PMs).

In addition, the sponsor has provided a safety update and new labeling proposals.

Dr. Gerard Boehm, the primary safety reviewer for this NDA, has provided a thorough review of the sponsor's response to the approvable letter; therefore, my review will only address key safety issues with this drug.

## 2 Remaining safety issues

### 2.1 QTc effect at high dose levels

In the original NDA safety review, Dr. Boehm identified evidence of QTc prolongation at doses of 60 mg BID and 75 mg BID in genotypic PMs observed immediately prior to dosing. This signal was not confirmed in a similar study that used phenotypic PMs expose to slightly lower serum levels of atomoxetine.

A labeling change recommended by the Division in the approvable letter limited the maximum dose of atomoxetine to 1.2 mg/kg/day or 84 mg in patients < 70 kg (1.2 X 70 = 84) and to 100 mg in patients > 70 kg for efficacy reasons. This dose is one-third lower than the originally proposed dose of 1.8 mg/kg/day in children and adolescents. Due to this lower recommended dose, the proportion of patients expected to reach plasma levels greater than 2000 ng/ml is substantially smaller than previously anticipated. An analysis in pediatric PMs of change in QTc versus atomoxetine plasma concentration 1-5 hours

after dosing revealed no plasma level/QTc relationship. In this analysis, no patient treated with a dose of up to 1.4 mg/kg/day reached a plasma level exceeding 2000 ng/ml. However, in an analysis of plasma levels drawn any time after dosing, 1/65 PM patients treated with a dose of up to 1.4 mg/kg/day reached a plasma level exceeding 2000 ng/ml.

A simulation performed by the sponsor based on the new upper dose limit (1.2 mg/kg/day) to predict the expected peak plasma level exposures for PM patients estimated that 3/100,000 PMs dosed at the upper dose limit would exceed a plasma level of 2000 ng/ml. Our OCPB pharmacometrics consultants did not concur with the sponsor's model, estimating that the model underestimated C<sub>max,ss</sub> by about 40%. With their correction applied, the pharmacometricians estimated that about 7% of PM patients treated with the intended dose of 1.2 mg/kg would have serum levels exceeding 2000 ng/ml; for patients treated with 1.4 mg/kg they estimated that 42% of patients would have serum levels exceeding 2000 ng/ml. In a separate analysis, the pharmacometricians estimated that over an 8-fold increase in serum concentration, the mean increase in QT interval duration would be only 4 msec. At the same time, they could not rule out the potential for variability leading to a more marked increase in QT duration.

Despite the adjustment of the sponsor's simulation by our OCPB consultants leading to more PM patients having a serum level exceed 2000 ng/ml, the sum total of the supplementary data presented suggests that few, if any, PM patients dosed with the newly recommended dose will reach plasma levels exceeding 2500 ng/ml where the QTc signal was observed. Furthermore, the data from LYAE suggests only a minimal increase in QT interval duration associated with a substantial increase in serum atomoxetine concentration.

## **2.2 Long-term safety in CYP2D6 PMs**

Since the safety update, the number of PMs receiving a maximal dose of at least 1.2 mg/kg/day for at least 6 months and at least 12 months increased substantially (13 to 62 and 1 to 17, respectively). The additional long-term experience did not alter the safety profile for PMs compared to EMs with regard to adverse events, vital signs, or laboratory data.

## **2.3 Glucose Abnormalities**

In the safety update included with the response to the approvable letter, there were three serious AEs related to treatment emergent elevations of serum glucose. In the original NDA submission, there were two such SAEs. In total, four of the events occurred in children and one in an adult. Two of the pediatric SAEs did not document the elevated serum level. Of the three levels reported, one case (pediatric) went into the 400 range, whereas the other two were in the 200 range. (See Dr. Boehm's review for additional details of the cases). The glucose laboratory data from the original NDA did not show evidence of a drug-related change.

New onset diabetes would not be unexpected in a pediatric cohort. Furthermore, childhood onset diabetes has a tendency to wax and wane early in the course of the

disease, such that an affected patient may have normal serum glucose levels at times. We will ask the sponsor for follow-up on the five patients described above, as well as asking for expedited reporting of post-marketing cases of glucose abnormalities.

#### **2.4 Labeling**

I concur with Dr. Boehm's labeling recommendations as laid out in the "Discussion/Labeling" section beginning on p. 13.

#### **2.5 Growth**

In the approvable letter, the Division requested that the sponsor consider conducting long-term trials to assess the effect of atomoxetine on growth in children. Lilly responded that they did not feel additional studies were necessary. They did, however, agree to analyze growth data from ongoing long-term atomoxetine trials and stated that they would continue their extension trial LYAI for 5 years and collect additional growth data in this trial.

Based on our experience with other pediatric supplemental NDAs, we have observed that growth data from uncontrolled extension trials is difficult to interpret. As such, the Division has been in discussion with other sponsors, as well as the Division of Pediatric Drug Development, to devise an alternative approach to studying the long-term effect of psychopharmacological drugs on pediatric growth. As the Division develops this approach, we will have further discussions with Lilly regarding conducting such studies with atomoxetine.

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Judith A. Racoosin, MD, MPH  
Safety Team Leader

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Judith Racoosin  
11/21/02 11:03:39 AM  
MEDICAL OFFICER

Review and Evaluation of Clinical Data  
Safety Team Leader Review of NDA

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**NDA:** 21-411

**Drug:** Strattera™ (atomoxetine, formerly tomoxetine)

**Route:** oral

**Indication:** attention deficit hyperactivity disorder

**Sponsor:** Lilly

**Action Date:** 8-12-02

**Date Review Completed:** 7-24-02

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## 1 Background

Atomoxetine (Strattera™) is intended to treat attention deficit hyperactivity disorder (ADHD) in children six years of age and older, adolescents, and adults. The Strattera™ NDA submission includes 17 clinical pharmacology (CP) studies, 14 phase II/III trials (11 in ADHD summarized in the ISS), and one abuse potential study. Dr. Gerard Boehm, the primary safety reviewer for this NDA, has submitted a very thorough review of the atomoxetine safety database; therefore, my review will only address key safety issues with this drug.

## 2 Selected safety issues

### 2.1 *Clinical effect of differential CYP2D6 metabolism*

Atomoxetine is metabolized by the cytochrome P450 isoenzyme 2D6. It is known that about 10% of the general population are poor metabolizers (PM) of 2D6 substrates. As such, poor metabolizers have increased exposure to the drug, with a higher C<sub>max</sub> occurring at a later T<sub>max</sub>. The CP studies indicated that PMs have a mean ten-fold higher exposure to atomoxetine compared to EMs. Based on this observation, the biopharmaceutics reviewer, Dr. Hong Zhao, recommended that the difference in atomoxetine clearance warrants dose adjustment in PM patients, and suggested that not adjusting dose based on 2D6 metabolizer status must be supported by clinical safety data in PM patients.

The sponsor included safety data for 125 PM patients in the original NDA submission; all of these patients are PMs based on their genetic make-up, hence they will be referred to as "genotypic" PMs (GPM). Information on an additional 57 PMs was included in the two-month safety update. Of these 57 new PMs, 46 are identified as a "phenotypic" PM (PPM). The phenotypic PM was created by exposing an EM to an inhibitor of 2D6 (in this case, fluoxetine), and then subsequently exposing them to atomoxetine. The mean increase in exposure of these PPMs to atomoxetine is about 6.5-fold compared to the EMs.

Dr. Boehm's review did not identify important differences between the PM and EM groups in the incidence of serious adverse events (SAEs) or discontinuations due to adverse events (AEs). However, there were common AEs that occurred more commonly

among PMs compared to EMs. Among common adverse events that occurred more frequently in atomoxetine-treated patients than placebo patients, there were four for which the proportion of PMs with the AE exceeded the proportion of EMs with the AE by two-fold [urinary incontinence PM 2.4% (n=3), EM 1% (n=18); syncope: PM 1.6% (n=2), EM 0.3% (n=5); mydriasis PM 1.6% (n=2), EM 0.6% (n=10); albuminuria: PM 0.8% (n=1), EM 0.2% (n=4); refer to p. 36-37 of Dr. Boehm's review]. The sponsor also included a table based on the data submitted in the safety update that displayed AEs that occurred in at least 1% of PM subjects and at least twice as frequently compared to EM subjects (Dr. Boehm's review, p. 36).

AE Risks Occurring in at least 1% of PM subjects and at least Twice as Frequently Compared to EM Subjects from Pediatric ADHD Studies, Safety Update

Event	EM, N=1,974 % (n)	PM, N=181 % (n)	p value
Mood Swings	1.9% (38)	3.9% (7)	.096
Sedation	1.7% (34)	4.4% (8)	.021
Tachycardia NOS	1.1% (21)	2.2% (4)	.152
Enuresis	0.9% (18)	2.2% (4)	.107
Hypersomnia	0.8% (15)	1.7% (3)	.188
Depressed Mood	0.7% (13)	1.7% (3)	.145
Animal bite	0.6% (11)	1.7% (3)	.107
Mydriasis	0.6% (11)	2.2% (4)	.031
Hand Fracture	0.5% (10)	1.1% (2)	.267
Tremor NEC	0.5% (10)	2.2% (4)	.025
Feeling Jittery	0.4% (8)	2.2% (4)	.014
Vision Blurred	0.4% (8)	1.1% (2)	.203
Weakness	0.3% (5)	1.1% (2)	.111
Syncope	0.2% (3)	1.1% (2)	.059
Vasovagal attack	0.1% (1)	1.1% (2)	.020
Laryngitis	0	1.1% (2)	.007

Other events of interest: urticaria: PM 1.1% (n=2), EM 0.6% (n=12), hypertension: PM 0.6% (n=1), EM 0.2% (n=4).

From Sponsor's Table SU.4.6.3, pp.34-44.

For systolic and diastolic blood pressure, there was no substantive difference between EMs and PMs in the mean increase from baseline; however, there was a statically significant difference for pulse increase (EM +6.2 bpm v. PM +10.2 bpm). With regard to weight change, PMs lost a mean 1.2 kg compared to EMs who gained a mean 0.8 kg; this difference was statistically significantly different. The PMs gained less height than the EMs, but the difference was not statistically significant. The differential effect of atomoxetine on the QTc interval of the ECG in EMs and PMs will be discussed below in the QTc interval prolongation section.

The finding of no difference between EMs and PMs for serious adverse events and discontinuations due to adverse events is reassuring regarding the potential for the higher levels of atomoxetine in the PMs to cause substantial morbidity. It must be recalled, though, that only 136 GPMs have been exposed to atomoxetine in the development program. With regard to pulse increase, weight loss, and the occurrence of some AEs, PMs are at a higher risk than EMs.

One way to alert prescribers to these differential effects of atomoxetine in PMs versus EMs is to include a section in labeling specifically describing the differences.

## 2.2 QTc prolongation

In order to evaluate the effect on the QTc interval of the increased exposure of PMs to atomoxetine, the sponsor conducted specialized clinical pharmacology studies. They also analyzed the QTc data from the phase II/III trials, although the ECGs performed in these trials were not conducted with regard to time of dosing of atomoxetine.

### 2.2.1 LYAE

Study LYAE was designed to test the safety, tolerance, and pharmacokinetics of multiple atomoxetine doses. This study exposed healthy EM and PM adults to equally high or higher concentrations of atomoxetine than were intended to be administered to children in the phase III studies (2mg/kg). The study enrolled 16 healthy adults, 11 male (including 4 PM) and five women (including 2 PM). The dosing regimen is seen in the table below. Twelve lead ECG tracings were performed on study day 5 of periods 1 to 5 at 0,1,2,4, and 12 hours after the morning dose and at the time of final assessment. The sponsor's analyses used Fridericia's correction.

Dose and Schedule of drug administration during study LYAE

Period 1	Placebo	
Period 2	Atomoxetine 30mg bid 5 days	0.7-1.12mg/kg/day
Period 3	Atomoxetine 45 mg bid 5 days	1.05-1.68mg/kg/day
Period 4	Atomoxetine 60mg bid 5 days	1.4-2.24mg/kg/day
Period 5	Atomoxetine 75mg bid 5 days	1.75-2.8mg/kg/day
Period 6	Washout/Observation 5 days	

In the EMs, there was little effect on the QTc interval, and no evidence of a dose response relationship (the largest mean change from baseline was 2.7 msec occurring at the second lowest dose of four doses; Dr. Boehm's review p. 60). When Dr. Boehm broke out the mean change from baseline at the various ECG measurement times, there was no evidence of a dose response relationship for QTc prolongation at any of the time points. No EM patients had an outlier for absolute QTc (QTc>450msec in males and QTc>470msec in females) or change from baseline >60 msec. A plot of change in QTc versus atomoxetine plasma concentration did not indicate a relationship for EMs.

In the PMs, however, there was evidence of QTc prolongation at the two highest doses, particularly at the pre-dose measurement (time 0).

Sponsor's analysis, QTc change from placebo (baseline) for PM subjects

Dose	Time of Measurement Post dose (hr)	Least Square Mean (msec)	Difference from Placebo	p	95% (CI)
0	0	400.3			

30	0	402.7	2.5	.65	-8.3, 13.2
45	0	400.6	0.4	.95	-10.4, 11.1
60	0	417.2	16.9	.0022	6.1, 27.6
75	0	414.9	14.6	.0078	3.9, 25.4
0	1,2,4,12	395.5			
30	1,2,4,12	390.3	-5.2	.1	-11.5, 1.1
45	1,2,4,12	396.9	1.4	.65	-4.8, 7.7
60	1,2,4,12	397.1	1.6	.62	-4.7, 7.8
75	1,2,4,12	401.7	6.2	.053	-0.1, 12.4

When Dr. Boehm broke out the mean change from baseline at the various ECG measurement times, there was evidence of QTc prolongation with the 75 mg dose at most of the time points.

FDA analysis, QTc change from placebo (baseline) for PM subjects by time

Time	30	45	60	75
0	2.4	0.3	16.8	14.6
1	-7.5	5.1	0.5	4.5
2	-5.1	-13.3	8	0.7
4	-7.8	10.4	1	10.4
12	-1.3	3.4	-3.3	8.9

No PM patients had an outlier for absolute QTc (QTc>450msec in males and QTc>470msec in females) or change from baseline >60 msec. When a relationship between serum atomoxetine level and QTc duration was assessed in the PM patients, a statistically significant positive relationship was observed at the pre-dose, 4 hour, and 12 hour time point. The largest effect was at the pre-dose observation with an estimated mean change of 32msec for the *highest* pre-dose concentration and a 10msec change for the *median* pre dose concentration (see pp. 61-62 in the Boehm review).

## 2.2.2 LYAY

Study LYAY was conducted to evaluate the safety and tolerance of co-administration of multiple doses of fluoxetine and atomoxetine in 20 healthy adults (19 EM and 1 PM). By pretreating the patients with fluoxetine, the EM patients were converted to "phenotypic" PMs. All subjects were given fluoxetine 60mg qd for 7 days followed by fluoxetine 20mg qd for 14 days. Subjects were then given atomoxetine 10mg bid and fluoxetine 20mg qd for 5 days. Subjects then got atomoxetine 45mg bid and fluoxetine 20mg qd for five days. Lastly, subjects got atomoxetine 75mg bid for nine doses followed by a dose of placebo and fluoxetine 20mg qd.

Twelve lead ECGs were recorded at baseline. In addition, ECGs were recorded on fluoxetine and on fluoxetine+atomoxetine at pre-dose (time 0) and 1,2,4,8, and 12 hours post dose. The sponsor did not discuss the methods used to measure the QT interval.

The investigators compared the difference between no drug treatment and fluoxetine with placebo to assess the effect of fluoxetine on the particular electrocardiographic variables. The investigators then compared the difference between the fluoxetine with placebo treatment and the fluoxetine with atomoxetine (different doses at different times) to assess the effect that the addition of atomoxetine would have on the particular variable.

In Dr. Boehm's review, he points out that the serum atomoxetine levels attained using this methodology do not reach the levels observed in genotypic PMs. The C<sub>max</sub> in PPMs on fluoxetine+atomoxetine 75 mg approached the C<sub>max</sub> of GPMs taking 60 mg of atomoxetine. In general, the mean C<sub>max</sub> for the PPMs was about 6.5 times that of EMs, compared to 10 times for GPMs.

Comparison of QTc mean change from baseline for fluoxetine alone-treated patients compared to no drug showed a prolongation of 4-5.6 msec. When atomoxetine plus fluoxetine was compared to fluoxetine alone, there was no evidence of QTc prolongation. No patients had an outlier for absolute QTc (QTc>450msec in males and QTc>470msec in females) or change from baseline >60 msec. The plasma atomoxetine concentration versus change in QTc analyses did not indicate a consistent relationship between plasma atomoxetine concentration and QTc.

### 2.2.3 Phase II/III studies

In the ADHD child and adolescent acute placebo controlled analysis group, ECGs were performed at baseline (visits 1 or 2) and at visits 5,9,12,13 and at discontinuation during trials HFBD and HFBK. ECGs were performed at baseline and at visits 2,3,5,7 and at discontinuation during trial LYAC. The protocols for these trials did not specify timing of ECG measurement in relation to last dose or time of day.

The mean change from baseline showed shortening of the QTc for both atomoxetine and placebo treated groups. The proportion of placebo patients with QTc outliers exceeded that of the atomoxetine group. No patient had a QTc that exceeded 500 msec or showed a change from baseline of >60 msec.

Considering the entire cohort of child and adolescents exposed to atomoxetine, there was a mean shortening of the QTc. The following table shows the distribution of outliers using both data-based and Fridericia corrections.

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Table ISS.4.2.19.

**Number of Patients Meeting CPMP Categorical  
QTc Interval Criteria Part I (Numerical Increases)  
Child and Adolescent Overall Integrated  
ADHD Database**

		Atomoxetine			95% CI	
		N	n	%	Lower	Upper
Corrected QT Interval	Criteria*					
QTcD	Increases of at least 30	1880	205	11.0%	9.5%	12.4%
	Increases of at least 60	1880	21	1.1%	0.6%	1.6%
	Increases to Values of > 500	1880	4	0.2%	0.0%	0.4%
QTcF	Increases of at least 30	1880	151	8.0%	6.8%	9.3%
	Increases of at least 60	1880	14	0.7%	0.4%	1.1%
	Increases to Values of > 500	1880	4	0.2%	0.0%	0.4%

Population: All patients with a baseline and a post-baseline measurement, except patients reported as not taking any study drug.

\*Computation based on the maximum treatment period value.

Source data: eagle:/programs\_g/rxp/b423/iss/sect2\_2/rpt/sect2.2.37.sas.

Among adult acute placebo-controlled ADHD studies, ECGs were performed at visits 1,3,4,6,7,8 and at discontinuation during trials LYAA and LYAO. The protocols for these trials did not specify timing of ECG measurement in relation to last dose or time of day.

The mean change from baseline showed shortening of the QTc for the atomoxetine group compared to a slight prolongation for the placebo group. A slightly higher percentage of placebo subjects had increases in QTc of 30 and 60msec compared to atomoxetine regardless of whether corrected using Fridericia's method or a data based correction. No atomoxetine subjects and 1 placebo subject had an absolute QTc>500 in the adult placebo controlled trials.

When PMs were compared to EMs in the child and adolescent ADHD study cohort, the mean change from baseline was shown to be negative in both groups. A higher percentage of PMs (4.5%, 8/176) met increased outlier criteria for QTc (Fridericia's correction and including those with an increase of at least 30 and to at least 435) as compared to EMs (2.1%, 40/1918). A shift table analysis also showed that PMs had an increased risk of shifting from normal to borderline or prolonged as compared to EMs.

Percentage of adolescent and pediatric subjects with a normal QTc at baseline who had a normal, borderline, or prolonged QTc, stratified by metabolic status

	Extensive			Poor		
	At Maximum			At Maximum		
	Normal	Borderline	Prolonged	Normal	Borderline	Prolonged
Overall	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
QTc D	89% (1621)	10% (185)	1.3% (23)	82% (137)	15% (25)	3.6% (6)
QTcF	94% (1759)	5.1% (96)	0.7% (14)	91% (156)	6.4% (11)	2.3% (4)

≥1.2mg/kg /day*						
QTcD	87% (1196)	12% (158)	1.4% (19)	83% (91)	13% (14)	3.7% (4)
QTcF	94% (1314)	5.5% (77)	1% (13)	94% (104)	3.6% (4)	2.7% (3)

Criteria for males: Normal <430, Borderline ≥430 and <450, Prolonged ≥450  
Criteria for females: Normal <450, Borderline ≥450 and <470, Prolonged ≥470  
\* Maximum dose recorded during a study  
Data from Safety Update, Tables SU.4.6.27 and SU.4.6.28, pp.97-98

### 2.3 Appendicitis

During 1,795 PY of pediatric exposure to atomoxetine in the NDA safety database, eight pediatric cases of appendicitis were reported, yielding an appendicitis rate of 4.5/1,000PY. This risk for appendicitis observed in pediatric patients in the atomoxetine ADHD development program was 2.5 times higher than the background rate estimated from 1999 Hospital Discharge Survey data (p=0.11). The observed increased appendicitis risk compared to background did not appear to be due to the age distribution in the study group, as the calculated SMR for appendicitis was 2.4, which was similar to the rate ratio calculated above.

When an adverse event occurs at a measurable rate in a background population, it is always difficult to determine what increase above the background should raise concern that the increased event frequency is drug-related. The 2.5-fold increased rate of appendicitis in the atomoxetine development program is concerning, but may not be substantially different from the background population.

We will monitor for appendicitis closely during the postmarketing period and ask the sponsor to submit any additional appendicitis cases in an expedited fashion.

### 2.4 Growth

In the placebo-controlled trials in children and adolescents, atomoxetine-treated patients experienced a mean decrease in weight of 0.4 kg compared to a mean increase in weight of 1.5 kg in placebo-treated patients. Mean height increased less in atomoxetine-treated patients (0.9 cm) compared to placebo-treated patients (1.1 cm). The risk of a 3.5% decrease in weight was 32% in atomoxetine-treated patients compared with 6% in placebo-treated patients.

When the child and adolescent cohort was stratified by metabolizer status, the PM patients lost weight (1.2 kg) compared to the EM patients who gained (0.8 kg). PM patients also did not gain as much height as EM patients (1.5 cm vs. 2.2cm).

Adults participating in placebo-controlled trials of atomoxetine showed a similar pattern for weight change. Atomoxetine-treated patients experienced a mean decrease in weight

of 1.2 kg compared to a mean increase in weight of 0.4 kg in placebo-treated patients. The risk of a 7% decrease in weight was 5% in atomoxetine-treated patients compared with 0.4% in placebo-treated patients.

A possible correlate to the loss of weight and/or the lag in height in the atomoxetine-treated children and adolescents is the differential change in serum alkaline phosphatase (AP) observed in the children and adolescents. Alkaline phosphatase typically increases in children up to about age 13 in girls and age 15 in boys, with subsequent decreases in the late teens and stabilization in the 20's.<sup>1</sup> As seen in the table below, placebo patients had the expected mean increase in AP, whereas atomoxetine patients had a mean decrease. PMs had a more marked fall in AP compared to EMs.

Mean change from baseline, Child and Adolescent Acute Placebo controlled trials			
Alk Phos/(U/L)	Atomoxetine (319)	-7.245	<.001
	Placebo (199)	9.201	
Mean change from baseline, EM vs. PM (total child and adolescent cohort)			
Alk Phos/(U/L)	Extensive (1557)	-9.979	.058
	Poor (115)	-16.139	

Not unexpectedly, the adults did not show this pattern for change in AP.

## 2.5 Vital Signs

In general, marketed treatments for ADHD warn about careful use of these drugs in patients with hypertension or cardiovascular disease. Similarly, atomoxetine should be used carefully in such populations. The placebo-controlled trials in children and adolescents identified important mean increases for systolic and diastolic blood pressure, as well as pulse. Atomoxetine-treated children and adolescents also had an increased risk of meeting outlier criteria for blood pressure and pulse compared to placebo. Adults treated in placebo-controlled trials of atomoxetine also showed mean increases from baseline for blood pressure and pulse that differed substantially from the placebo group; however, there was no substantive difference in the proportion of adults meeting outlier criteria between the atomoxetine and placebo groups.

As described above, pulse increases were substantially higher in PMs compared to EMs.

Clinical pharmacology studies identified orthostatic blood pressure changes in atomoxetine treated patients. The falls in systolic blood pressure were more marked for PM patients compared to EM patients.

## 2.6 Q day versus BID dosing

<sup>1</sup> Van der Sluis IM, et al. A Cross-sectional study on biochemical parameters of bone turnover and vitamin D metabolites in healthy Dutch children and young adults. *Hormone Research* 2002; 57:170-179.

As Dr. Boehm pointed out in his review, the sponsor is recommending a maximal dose in labeling that was not tested in a once daily dosing regimen. Although, there was no excess of SAEs or discontinuations due to adverse events in the once daily dosing trial compared to the BID trials, the common adverse event profile differed somewhat, with increased risks for some common AEs in the “q day” regimen compared to the BID regimen (e.g., dyspepsia, palpitation). Should once daily dosing be deemed efficacious, the dosage and administration section of the labeling will need to describe the lower maximum dose recommended for once daily dosing. Additionally, the adverse events section in labeling should include an AE frequency table with side by side comparison of “q day” to BID dosing.

### 3 Discussion

The outstanding safety issue that needs to be grappled with is the potential for PMs to experience QTc prolongation at the highest doses of atomoxetine intended for marketing. Several lines of evidence support the finding that EMs are not at risk for QTc prolongation. However, for PMs, study LYAE showed a positive relationship between serum atomoxetine concentration and QTc prolongation at the highest dose, and the mean change from baseline analyses suggested that a prolongation of 15-17 msec could be observed. This study did not identify outliers >500 msec or with a change from baseline >60 msec, though. The sponsor contends that because the QTc prolongation was not observed in the follow-up study LYAY, we should be reassured regarding the effect of atomoxetine on the QTc interval in PMs. However, the safety review team is not convinced that the approach used in the follow-up study, specifically, the use of pharmacologically created PMs, was capable by design of identifying a signal of QTc prolongation if there was one (because the PPM serum atomoxetine levels did not match the GPM serum atomoxetine levels).

So we are faced with the likelihood that a proportion of patients, probably less than 10%, since not all PMs will be treated at the highest doses, may experience QTc prolongation on the order of about 15 msec. Recently, the division has had experience with a drug that had a mean change from baseline for QTc around 15 msec, without a substantial number of outliers greater than 500 msec. In that case, the drug, ziprasidone, was labeled with a detailed Warnings statement for QTc prolongation, and a contraindication for use with other drugs known to prolong the QTc interval. The difference between ziprasidone and atomoxetine, however, is that with ziprasidone there was no way to predict who would be most likely to experience QTc prolongation. With atomoxetine, determination of metabolizer status and subsequent dose adjustment for PMs prior to drug initiation would avoid exposing at-risk patients to potentially harmful drug levels.

Would additional study lessen our concern about the QTc signal from LYAE? We don't know much about the effect of atomoxetine on the QTc interval in children and adolescents, who account for a major proportion of the intended treatment population. One thing observed in the phase II/III trials was that a higher percentage of pediatric PMs met increased outlier criteria for QTc than pediatric EMs (4.5% vs. 2.1%). A shift table

analysis also showed that PMs had an increased risk of shifting their QTc interval from normal to borderline or prolonged as compared to EMs.

A clinical pharmacology type study similar to LYAE conducted in genotypic PM children would provide important information regarding their risk of QTc prolongation. However, a negative study in this population would not likely eliminate all our concern about the LYAE signal. Given the ethical dilemma of conducting a clinical pharmacology trial in children, one could argue that in the interest of patient safety, the prudent recommendation would be to determine CYP2D6 metabolizer status prior to prescribing.

#### 4 Labeling Recommendations

I concur with Dr. Boehm's edits and additions to the proposed Strattera<sup>TM</sup> labeling. My additional comments follow below.

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Judith A. Racoosin, MD, MPH  
Safety Team Leader

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

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Judith Racoosin  
7/24/02 04:55:57 PM  
MEDICAL OFFICER

## Review of Clinical Data

NDA: 21-411  
Drug Name: Generic Name: Atomoxetine  
Trade Name: Strattera  
Sponsor: Eli Lilly and Company  
Material Reviewed: Response to Approvable Letter, Safety, 9/26/02, 10/18/02  
Reviewer: Gerard Boehm, MD, MPH  
Date Completed: 11/19/02

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### Background

The division made several requests for additional safety data and analyses in the atomoxetine approvable letter dated 8/12/02. The division requested an updated assessment of long term safety in PM subjects. The division asked Lilly to provide a comprehensive report addressing the relationship between QTc and higher plasma levels of atomoxetine (>2,000ng/mL). The division asked that the comprehensive report provide an estimate of the proportion of patients expected to achieve these higher plasma levels and consider pediatric patients. The division also asked Lilly to consider long-term trials to assess the effects of atomoxetine on growth.

On 9/26/02, Lilly submitted their response to the atomoxetine approvable letter that included the following sections:

- Updated poor metabolizer safety data
- Assessment of QTc in CYP2D6 PM patients treated with atomoxetine
- A safety update report
- Labeling proposals
- An update of the world wide literature
- Protocol for long term efficacy study
- Regulatory status update

In addition, the sponsor submitted additional cardiovascular labeling and plans for additional studies examining the effect of atomoxetine on growth on 10/18/02.

### Updated long-term safety for PM subjects

The division asked Lilly to update long-term safety data in PM patients. In several analyses that follow, Lilly compares AE and outlier risks (#events/#subjects) for PM subjects to EM subjects. While the division prefers person time based analyses since they consider duration of exposure, Lilly's comparisons appear to be valid since the mean duration of atomoxetine exposure was similar for EMs and PMs (207 and 206 days, respectively, Response p.21).

### *PM Exposure*

In their response to the approvable letter, Lilly updated the number of PM subjects exposure to atomoxetine to 226 subjects. Forty-six of these subjects were genotypic EM patients who experienced increased atomoxetine plasma levels due to concomitant use of fluoxetine, a CYP2D6 inhibitor (Response, p.11). The following table compares the number of PM subjects exposed in the two-month safety update to the response to the approvable letter by time, and by time and maximal dose.

FDA Table 1. PM Exposure through the safety update and the response to the approvable letter by time and by maximal dose and time

PMs Exposed	Through Safety Update	Through Response to Approvable letter
<b>Overall</b>	<b>180</b>	<b>226</b>
At least 6 months	34	90
At least 1 year	14	33
<b>Max dose <math>\geq</math>1.2mg/kg/day</b>	<b>112</b>	<b>162</b>
At least 6 months	13	62
At least 1 year	1	17

While exposure has increased since the safety update, the number of PM subjects exposed to atomoxetine for 6 months and 1 year remains relatively small.

*PM Serious Adverse Events*

There have been no deaths in the atomoxetine development program. The six identified serious adverse events among PM subjects did not suggest a pattern unique to this population subset. Lilly listed all reported serious adverse events for PM subjects and I replicate that list below:

- HFBE-023-0887 Hostility
- LYAB-089-6441 Road Traffic Accident and Splenic Injury
- LYBB-035-6545 Pathological Fracture
- LYBB-206-8588 Accidental Injury
- LYAF-601-7009 Gastrointestinal Infection NOS
- LYAF-652-9053 Confusional State and Abnormal LFTs

*Discontinuation for Adverse Events*

The sponsor reported that 7.5% (17/226) of atomoxetine exposed PM subjects discontinued for adverse events compared to 5.1% (147/2,910) EM subjects. Except for constipation (1.3%, 3/226), no AE led to discontinuation of more than one PM subject.

Considering only those with at least 6 months of exposure, no PM subjects, and 1.6% (21/1,245) of EM subjects discontinued for adverse events (Response, p.22).

*Treatment Emergent Adverse Events*

The sponsor provided tables comparing the AE risks for EM subjects to the AE risks for PM subjects. For those exposed at least 6 months, the AE risks for the EM and PM subjects were compared separately. There were relatively few events occurring more frequently among PM subjects in either table.

In the following table, I list the AEs occurring in at least 2% of PM subjects and at least twice as frequently compared to EM subjects.

FDA Table 2. Treatment Emergent AE risks, for events occurring in at least 2% of PM subjects and at least twice as frequently compared to EM subjects

Event	EM n=2,886	PM n=227
Middle insomnia	1.5% (n=42)	4% (n=9)
Sedation	1.7% (n=49)	4% (n=9)
Depression	1.4% (n=41)	3.5% (n=8)
Tremor	0.8% (n=22)	3.5% (n=8)

Early morning awakening	1% (n=28)	3.1% (n=7)
Depressed mood	0.8% (n=23)	2.6% (n=6)
Enuresis	1.1% (n=33)	2.2% (n=5)
Mydriasis	0.6% (n=16)	2.2% (n=5)
Pruritis NOS	1% (n=30)	2.2% (n=5)

Other AEs of interest: Weight decreased EM 3.8% (n=109), PM 5.7% (n=13); Rash NOS EM 3.9% (n=112), PM 4.8% (n=11); Urticaria NOS EM 0.6% (n=17), PM 0.9% (n=2); Syncope EM 0.3% (n=10), PM 1.3% (n=3); Vasovagal attack EM 0.1% (n=2); PM 1.3% (n=3). From Response table 9, pp.28-30, and Appendix Table A1.

The following table summarizes the AEs occurring in at least 2% of PM subjects and at least twice as frequently compared to EM subjects for those with at least 6 months of atomoxetine exposure.

FDA Table 3. Treatment Emergent AE risks, for events occurring in at least 2% of PM subjects and at least twice as frequently compared to EM subjects, for those with at least 6 months exposure to atomoxetine

Event	EM n=1,245	PM n=90
Menarche*	0.3% (n=1)	4.5% (n=1)
Nightmare	2.1% (n=26)	4.4% (n=4)
Hand fracture	1% (n=12)	3.3% (n=3)
Middle insomnia	1.6% (n=20)	3.3% (n=3)
Tremor	1% (n=13)	3.3% (n=3)
Agitation	0.7% (n=9)	2.2% (n=2)
Chest discomfort	0.2% (n=2)	2.2% (n=2)
Head injury	1.1 (n=14)	2.2% (n=2)
Hypersomnia	0.8% (n=10)	2.2% (n=2)
Laryngitis NOS	0.1% (n=1)	2.2% (n=2)
Localized infection	0.9% (n=11)	2.2% (n=2)
Mydriasis	0.7% (n=9)	2.2% (n=2)
Skin papilloma	1% (n=12)	2.2% (n=2)
Vasovagal attack	0.1% (n=1)	2.2% (n=2)

\*Denominator restricted to female subjects

From Response table 10, pp.31-34, and Appendix table A2

#### Lab data

Lilly provided update comparisons of mean change and outlier lab data analyses comparing EM and PM subjects, and comparing the subset of EM and PM subjects with at least 6 months of atomoxetine exposure. With few exceptions, neither mean change analyses nor outlier analyses suggested differences in risk for lab result changes when comparing EMs to PMs.

In the following table, I summarize the mean changes for analytes where there appeared to be differences in results between EMs and PMs in the overall analysis or the analysis restricted to those exposed to atomoxetine for at least 6 months.

FDA table 4. Mean changes labs, overall and restricted to those exposed to atomoxetine for at least 6 months, stratified by metabolic status

Analyte (units)	Metabolic status	Mean change from baseline	
		All exposed (n)	≥6months atomoxetine exposure (n)
Alk Phos (U/L)	EM	-10.9 (2699)	-13.46 (1240)
	PM	-22.5 (216)	-15.13 (90)

### Updated QTc and plasma level analyses

In the approvable letter, the division asked Lilly for more data regarding the relationship between QTc and atomoxetine, specifically at atomoxetine plasma levels >2,000ng/mL. The division also asked for estimates for the range of concentrations PM patients are likely to experience and the proportions of patients predicted to achieve higher plasma level exposures.

In their response to the approvable letter, Lilly submitted the following information:

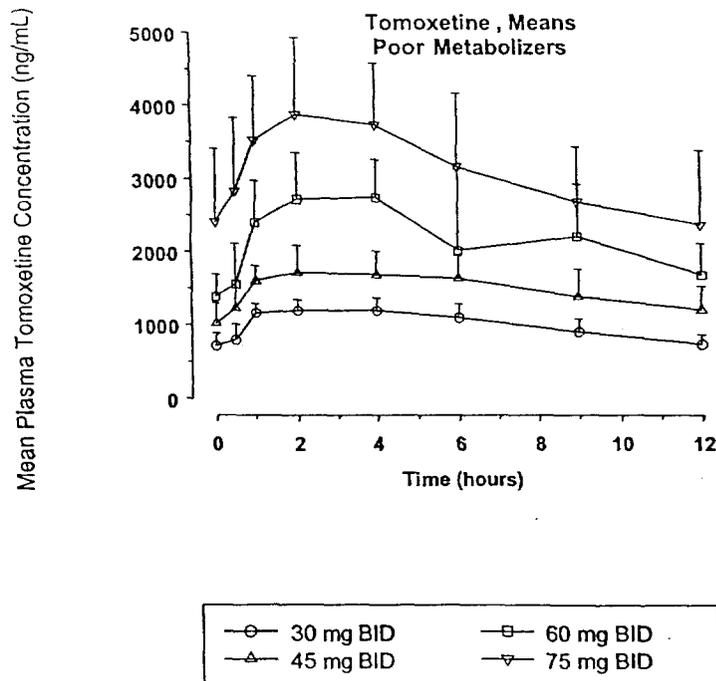
- Data from pediatric patients that were not available at the time of the two-month safety update, along with additional analyses of previously existing data sets
- Updated outlier analyses
- Analyses of likely exposures (pk simulations based on new upper dose limit recommendations)
- Analyses of atomoxetine's effect on heart rate

#### Background

The concerning finding of QTc prolongation identified in the NDA came from study LYAE. PM subjects at the two highest atomoxetine dosages (60mg bid, 75mg bid) had evidence of QTc prolongation, greatest at the pre-dose (0 hour) time point with smaller or no QTc increases on post dosing ECGs. The division requested additional QTc information, particularly for PM subjects with higher atomoxetine plasma level exposures.

#### Lilly's Plasma Concentration Analysis Response

Lilly provided the following graph of atomoxetine plasma data from LYAE in this submission and it is reproduced below.



This graph illustrates that atomoxetine plasma concentrations peaked at 1-5 hours after dosing, and provides the mean plasma concentrations at each administered dose for the PM subjects in this study. (Note: The new recommended atomoxetine maximum dose requested by the division in the approvable letter is 1.2mg/kg/day or 100mg/day).

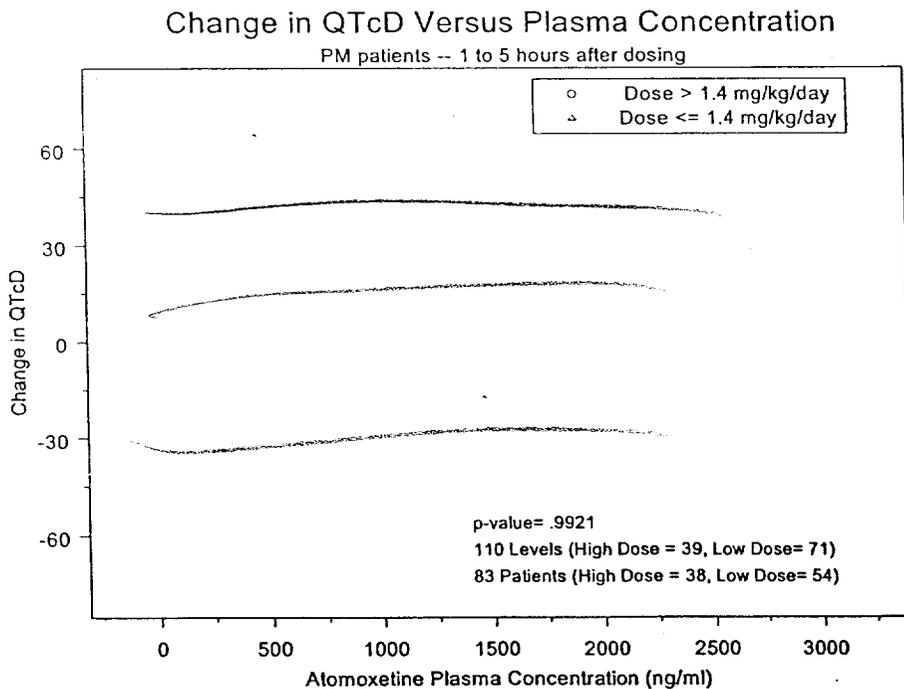
*Data Analyzed in Lilly's Response*

In their response to the approvable letter, Lilly examined ECG data for PM subjects with atomoxetine plasma samples collected at the time of predicted maximal concentration (1-5 hours post dosing) and for PM subjects with plasma samples collected at any time. This group of PM subjects included both the genotypic poor metabolizers and genotypic extensive metabolizers who concomitantly took a CYP2D6 inhibitor (fluoxetine).

In their response to the approvable letter, Lilly identified 100PM subjects with 237 atomoxetine plasma samples. This submission includes 30 additional atomoxetine PM subjects with plasma levels and 97 additional atomoxetine plasma level samples collected since the NDA. Lilly identified one additional PM subject with an atomoxetine plasma level >2,000ng/mL since the NDA.

*Analysis of QTc change and plasma level 1-5 hours after dosing*

Lilly provided a graph for pediatric subjects that compares QTc change from baseline to atomoxetine plasma concentration for subjects with plasma levels 1-5 hours following dosing. That graph is reproduced below.



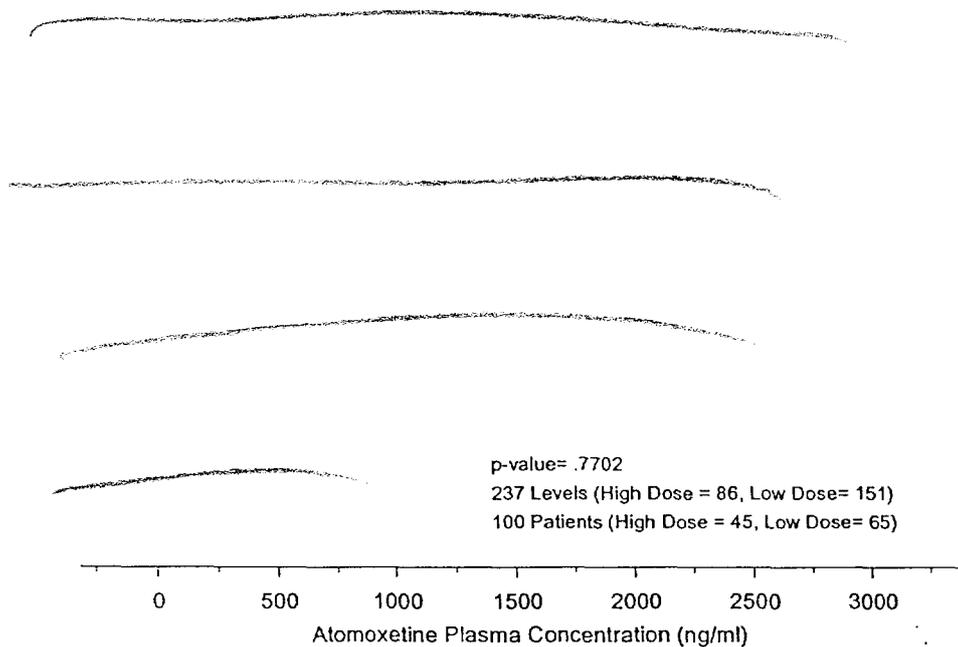
There does not appear to be a plasma level/QTc prolongation relationship among those few subjects with atomoxetine plasma levels >2,000ng/mL. The QTc mean change from baseline for those subjects with plasma levels >2,000ng/mL was -7.6msec (Response,

p.10). Additionally, for subjects receiving doses up to 1.4mg/kg/day, none had atomoxetine plasma levels >1,750ng/mL.

Lilly also plotted the data using only subjects treated with >1.4mg/kg/day (not shown) and again there did not appear to be evidence of a QTc/plasma atomoxetine relationship.

*Analysis of QTc change and plasma level any time after dosing*

Lilly provided a graph comparing QTc change from baseline versus atomoxetine plasma levels for all patients with data regardless of time since last dose (see below). There did not appear to be a QTc prolongation/plasma concentration relationship from these data. There was one subject (1/65) with an atomoxetine level >2,000ng/mL (roughly 2,300ng/mL) among those treated with <=1.4mg/kg/day.



Source data: eagle:\programs\_g\mp\b4z2\regulatory response\apvbltr\plasma vs ecg -- all.sas

**Figure 4. Change in QTc and plasma atomoxetine concentration sampled any time after dosing.**

**Updated QTc Outlier Analysis**

*QTc outlier risks, EM vs. PM, overall*

Lilly combined newly available data with data that they had submitted in the NDA and two-month safety update and performed outlier analyses comparing QTc prolongation risks for EMs and PMs. This analysis results from pooling of data from trials of different designs and different durations, complicating the interpretation of these results. This analysis appears to include both adults and pediatric patients.

**Table 1. Analyses of categorical changes in QTc interval associated with atomoxetine at any dose**

	EM Patients			PM Patients			Fisher's Exact
	N	n	%	N	n	%	P-value
Increase >30 msec	2792	270	9.7%	218	23	10.6%	0.636
Increase >60 msec	2792	17	0.6%	218	5*	2.3%*	0.018*
Increase to >500 msec <sup>a</sup>	2788	2	0.1%	218	2*	0.9%*	0.028*

Abbreviations: EM = extensive metabolizer; PM = poor metabolizer.

<sup>a</sup> Patients with > 500 msec at baseline were excluded from this analysis.

\* The ECG data for patient 6067 from Study B4Z-MC-LYAF are presented here as originally read, however manual review of the ECG shows that it exhibits electrical interference and is uninterpretable with respect to assessment of QT interval. Copies of these tracings are included in Attachment 1. Reanalysis of the data excluding patient 6067 yields the following proportion of patients with an increase of 60 msec or greater or an increase to 500 msec or greater: increase > 60 msec = 4/217 (1.8%) and increase to at least 500 msec = 1/217 (0.5%). The corresponding probabilities for the comparisons to EM patients are not significant (.060 and .201 respectively). Further, patient 723 from study HFBE, another PM originally included in the > 60 msec category, has, on review, an IVCD that makes interpretation of the QT interval unreliable (tracing also included in Attachment 1), further reducing the number of unambiguous increases > 60 msec to 3/216 or 1.4%.

Source Data: eagle:\programs\_g\rmpl\b4zs\regulatory response\apvbltr\cyp2d6  
\rpt\cyp21.sas

When the analysis was restricted to patients who received at least 1.2mg/kg/day, the results were similar for the two groups (data not shown).

The sponsor also provided a listing for the outlier subjects that provided all QTc results and the dosages taken at the time of the ECG. This listing demonstrated that the outliers were generally intermittent and did not necessarily occur at the highest dose a subject received (i.e QTc shortened with higher atomoxetine doses in some subjects).

*QTc outlier risks, Placebo controlled trials*

In a somewhat easier to interpret analysis, the sponsor provided the outlier risks for placebo controlled trials, updated to include additional data collected since the NDA submission. There did not appear to be substantial differences in QTc outlier risks by treatment. Lilly's outlier risk table is provided below.

**Table 4. Analyses of Categorical Changes in QTc Interval in Acute Placebo Controlled Studies**

	Atomoxetine			Placebo			Fisher's Exact
	N	n	%	N	n	%	P-value
Increase > 30 msec	497*	31	6.2%	333	25	7.5%	0.483
Increase > 60 msec	497	1**	0.2%	333	0	0.0%	1.00*
Increase to > 500 msec <sup>a</sup>	496	0	0.0%	333	0	0.0%	1.00*

\* Includes 486 EM patients and 11 PM patients

\*\* The one patient with a 60 msec increase was an EM patient

<sup>a</sup> Patients with > 500 msec at baseline were excluded from this analysis.

Source Data: eagle:\programs\_g\rmplb4zs\regulatory  
response\apvbltr\cyp2d6\cpt\ecgcatgplaempm.sas

Lilly provided a graph of QTc change from baseline for 130 PM subjects (genotypic and phenotypic) recorded within 5 hours of last dose plotted against dose. There did not appear to be a dose/QTc relationship from this graph (data not shown).

**Exposure simulations**

Lilly performed PK simulations to estimate the expected peak plasma level exposures for PM subjects given the new upper dose limit suggested by the division in the approvable letter (1.2mg/kg/day). To provide some allowance for deviation from recommended use in clinical practice, Lilly used 1.4mg/kg/day as the upper dose limit in their simulations. Lilly performed their simulation for 1,000 PM subjects and their results are displayed in the following table.

**Table 5. Simulated C<sub>ss, max</sub> for Poor Metabolizer Pediatric Patients After a BID Dosing Regimen**

Dose (mg/kg/day)	Poor Metabolizer Patients					
	Mean	Median	SD	5 <sup>th</sup> Percentile	95 <sup>th</sup> Percentile	% Values >2000 ng/mL
1.0	827	819	125	640	1037	0.0
1.2	986	975	145	766	1237	0.0
1.4	1164	1152	171	891	1456	0.0
1.6	1316	1296	190	1036	1641	0.2
1.8	1482	1467	221	1151	1854	1.8

Lilly estimated a mean peak atomoxetine plasma concentration of 1,164ng/mL at the 1.4 mg/kg/day dose with a standard deviation of 171. Using these parameters, Lilly estimated that 3/100,000 PMs dosed at the upper dose limit would achieve a peak plasma level >2,000ng/mL based on the clinical trial data. Lilly noted that if population variability is greater than that observed in the clinical trials, a higher proportion of patients exposed to the upper dose limit could achieve peak plasma levels in excess of 2,000ng/mL.

Plasma data from 65 patients in clinical trials included 1 subject treated with a dose  $\leq$ 1.4mg/kg/day who had an atomoxetine plasma level >2,000ng/mL (2,250ng/mL).

#### FDA Pharmacometric Review

In a FDA pharmacometric memo, the division's consultant reviewed Lilly's plasma level simulation results. Our consultant felt that Lilly's model under-predicted atomoxetine plasma concentration values at higher plasma concentrations. Comparing predicted atomoxetine plasma concentration results to sampling data from an actual patient, our consultant concluded that there was a bias in Lilly's model fit around the  $C_{max}$  value. Our consultant estimated that  $C_{max}$  was under predicted by 40% on average. Our consultant provided a table with predicted  $C_{ss,max}$  for several atomoxetine doses, corrected for the observed bias. That table is reproduced below.

**Table 4. Corrected predicted  $C_{ss,max}$  for poor metabolizer pediatric patients after a BID dosing.**

Dose (mg/kg/day)	Mean (ng/mL)	Median	SD	5th Percentile	95th Percentile	% Values >2000 ng/mL
1.0	1378.3	1365	208.3	1066.667	1728.333	0.0
1.2	1643.3	1625	241.7	1276.667	2061.667	7
1.4	1940	1920	285	1485	2426.667	42
1.6	2193.3	2160	316.7	1726.667	2735	72
1.8	2470	2445	368.3	1918.333	3090	90

In a separate table, our consultant predicted that for PM patients dosed at 1.2mg/kg/day, 0% of atomoxetine  $C_{ss,max}$  values would exceed 2,500ng/mL and that for PM patients dosed at 1.4mg/kg/day, 2.5% of atomoxetine  $C_{ss,max}$  values would exceed >2,500ng/mL. Our consultant's predictions appear to be more in line with Lilly's graph of actual dose/plasma concentration data which depicted that 1 atomoxetine plasma concentration >2,000ng/mL among 65 PM patients dosed at  $\leq$ 1.4mg/kg/day.

Our consultant modeled QTc versus atomoxetine concentration using data from study LYAE and the resulting slope was described as very shallow (4msec increase with an 8-fold concentration difference) suggesting that increases in atomoxetine concentrations may not cause significant QTc prolongation. Our consultant could not rule out clinically significant prolongation due to the variability present in the data used in the model.

#### Atomoxetine and Heart Rate

In the final section of their presentation, Lilly argued that atomoxetine's effect of increasing heart rate would protect against Torsades de pointes. Lilly pointed out that Torsades de pointes is precipitated by slow heart rate. Lilly suggested that even if atomoxetine prolonged repolarization, the associated risk of Torsades would be mitigated by the increase in heart rate.

### **Safety Update**

As part of the response to the approvable letter, Lilly submitted a Safety Update for atomoxetine. This is Lilly's second safety update for atomoxetine. Lilly's first safety update was submitted 12/01 and was reviewed with the NDA. In the most recent safety update, Lilly updated exposure, serious adverse events and discontinuations due to adverse events through the Safety Update cutoff date of July 31, 2002.

#### *Exposure*

Lilly updated the exposure through the safety update cutoff date at 4,007 individuals with 2,855 person years exposure to atomoxetine. Lilly identified 3,536 pediatric and adolescent subjects exposed to atomoxetine for 2,541 person years and 471 adult subjects exposed to atomoxetine for 314 person years. Lilly considered these exposure estimates to be conservative since some subjects were in blinded studies and not all data had been received (Safety Update, p.6).

#### *Deaths*

There have been no deaths in the atomoxetine ADHD development program through the latest Safety Update cutoff date.

#### *Serious Adverse Events*

Lilly provided a listing of Serious Adverse events recorded since the last safety update, cutoff 11/15/2001, through 7/31/2002, the cutoff date of this safety update (Safety Update p.7). One SAE occurring after 7/31/2002 was included in the listing because it was a possible appendicitis case, and the division has expressed interest in these events. One included SAE occurred in a sibling of a study participant who overdosed on the study subject's medication.

The SAE list included 37 subjects with confirmed atomoxetine exposure and 3 subjects from trials whose treatment was blinded at the time of the Safety Update cutoff. I read through the narrative summaries that Lilly provided for these events and there appeared to be few new types of SAEs included in this safety update. I have included the list of the safety update serious adverse events as an appendix to this review. Lilly identified no SAEs of hepatic failure, acute renal failure, aplastic anemia, rhabdomyolysis, or serious skin reactions.

The SAE list included 2 new cases of appendicitis through the safety update cutoff and one additional possible case reported after the safety update cutoff. Using the pediatric exposure estimate provided above and the appendicitis cases reported through the safety update cutoff date, the incidence of appendicitis among pediatric patients through the Safety Update (3.9/1,000PY; 10/2,541PY) is similar to the incidence reported in the NDA safety review (4.5/1,000PY; 8/1,795PY).

Below I summarize selected SAEs submitted with the Safety Update.

#### **Appendicitis**

**LYAB-057-5331** This 14 year old male had been receiving atomoxetine for 18 months when he developed abdominal pain and was diagnosed with appendicitis (operative note reported "acutely inflamed appendix"). Following appendectomy, he remained in the study.

**LYAB-096-6162** This 12 year old female developed abdominal pain after receiving atomoxetine for more than 2 years. She was diagnosed with appendicitis and underwent appendectomy. She continued in the trial following the appendectomy.

**LYAW-098-7407** This eight year old male developed abdominal pain and vomiting seven weeks after starting atomoxetine. His condition initially improved, but then worsened and an abdominal CT demonstrated mesenteric adenitis, which was treated with IV antibiotics. Symptoms recurred and the patient had an ultrasound that demonstrated an inflamed appendix with swollen adjacent lymph nodes. Surgery was planned for later that day for possible appendicitis with outcome not provided in the narrative.

#### Wolff-Parkinson-White Syndrome

**LYAB-101-5825** This 14 year old male had received atomoxetine for 443 days when an ECG revealed a shortened PR interval which was interpreted as Wolff-Parkinson-White Syndrome (WPW). The patient's study drug was discontinued. A pediatric cardiologist subsequently evaluated the patient and reviewed all available ECGs and determined that the patient did not have WPW, confirmed the shortened PR interval and commented that it was of no clinical significance.

**LYAF-650-8162** This 13 year old male was diagnosed with possible WPW syndrome after 71 days of atomoxetine, after completing controlled trial but prior to enrolling in an open label extension. The patient stopped atomoxetine and was evaluated by a pediatric cardiologist who felt the ECG was suggestive but not absolutely diagnostic for WPW. The patient's echocardiogram exam was described as essentially normal. The patient was discontinued from the trial. Lilly noted that the patient's father had WPW, which was treated with catheter ablation.

#### Renal Cell Carcinoma

**LYAR-063-5501** This 53 year old male who received 370 days of atomoxetine treatment was diagnosed with renal cell carcinoma and had a total right nephrectomy.

#### Elevated Blood Glucose

In their safety update, Lilly identified three atomoxetine-exposed subjects with elevated blood glucose SAEs. I summarize those cases below.

**LYAF-570-1890** This 6 year old male developed high blood glucose (216 mg/dL) with associated excessive thirst and lethargy 102 days after starting atomoxetine. A fasting blood sugar six days later was 109 mg/dL. Blood sugars were monitored over the following weeks and remained high. Concomitant medications were beclomethasone (route not specified), paracetamol, and salbutamol.

**LYAF-621-5076** This 12 year old male developed a high non-fasting blood glucose (440 mg/dL highest recorded) after 72 days of atomoxetine treatment. The subject was withdrawn after 93 days of treatment.

**LYAI-650-6406** This 10 year old male was hospitalized for elevated blood glucoses that began after 153 days of treatment with atomoxetine. He continued in the study.

I reviewed the SAE listings from the NDA and first safety update and found two additional elevated blood glucose SAEs. Those cases are described below.

**LYAR-081-5953** This 35 year old male developed elevated blood glucoses (451mg/dL highest reported) after 3 months of atomoxetine treatment. His baseline non-fasting blood glucose was 105mg/dL. He was hospitalized and treated with insulin. His listed height was 5'6" and weight was 137.5 lbs. His family history was not known since his parents "left him at a young age."

**LYAI-018-3325** This 11 year old male developed elevated blood sugars and was hospitalized for this finding approximately 5 months after starting atomoxetine. He had ketones present in his urine. He was diagnosed with juvenile onset diabetes and treated with insulin. He continued on study drug. The patient had a maternal uncle with juvenile onset diabetes.

To further explore the relationship between atomoxetine and glucose abnormalities, I re-reviewed NDA adverse event listings, laboratory mean change from baseline analyses and laboratory outlier analyses from the NDA and safety updates. I did not identify any additional glucose related adverse events. There did not appear to be differences in mean changes from baseline for glucose when comparing atomoxetine to placebo or EM subjects to PM subjects. There were no remarkable differences in risk for high glucose outliers when comparing atomoxetine to placebo or EM subjects to PM subjects.

#### *Discontinuations for Adverse Events*

Lilly provided a listing of 96 patients who discontinued from atomoxetine trials from 9/1/2001 through 7/31/2002. Lilly identified 53 subjects who were taking atomoxetine, 40 subjects taking blinded treatment, and 3 subjects taking placebo or no drug at the time of discontinuation. The listed AEs leading to discontinuation were similar to the events described in the NDA. I read through narratives for these events and there was generally little information provided about the events. Lilly identified no adverse events of hepatic failure, acute renal failure, aplastic anemia, rhabdomyolysis, or serious skin reactions leading to discontinuation.

#### **Comments About Additional Atomoxetine Growth Studies**

In the approvable letter, Lilly was asked to consider conducting long-term trials to assess the effect of atomoxetine on growth. In a submission dated 10/18/2002, Lilly acknowledged omitting their response to the approvable letter request and provided their position on future atomoxetine growth studies. While Lilly commented that they were willing to discuss growth studies, they did not feel that additional studies were practical or necessary. Lilly suggested that controlled studies using non medication based comparators would not be possible due to the belief that medication is superior to non medication based therapies for ADHD. Lilly believes that the methodology they used to analyze growth related data is satisfactory. Lilly did commit to analyzing growth data from ongoing long term atomoxetine trials and stated that they would continue their extension trial LYAI for 5 years and collect additional growth data in this trial.

#### **Regulatory Status Update**

Lilly informed the division that atomoxetine is currently not being marketed in any country and that applications are pending in Australia, New Zealand, and Canada.

#### **Literature Search**

Lilly provided the articles from an updated search of the medical literature for publications on atomoxetine. They attest that these articles reveal no new safety information for atomoxetine.

#### **Discussion/Labeling**

Lilly has provided a complete response to division's approvable letter. Neither the update of PM safety data, nor the safety update identify previously unrecognized atomoxetine related adverse effects or modify the understanding of the atomoxetine safety profile.

The identification of three additional atomoxetine subjects (5 total) with serious glucose elevation events is of potential interest. The narratives that Lilly submitted for these events contained little information and Lilly should provide additional follow up for all 5 glucose related SAE cases (LYAF-570-1890, LYAF-621-5076, LYAI-650-6406, LYAR-081-5953, LYAI-018-3325) as well as a review of their database for any other evidence of an effect of atomoxetine on glucose. Lilly should also immediately forward post marketing reports of glucose abnormalities to FDA.

In the following paragraphs I discuss safety labeling changes that the division raised in the approvable letter and Lilly's responses. I have also included labeling language proposals for the division review team's consideration. I discuss the safety issues in the order they appear in labeling. The division's labeling proposals that Lilly has accepted without revision are not presented.

#### QTc

Within the recommended dose range, there is no evidence of QTc prolongation in either EM subjects treated with a CYP2D6 inhibitor or PM subjects and therefore, I do not believe that the atomoxetine labeling requires language about an effect on QTc. The QTc prolongation signal observed in study LYAE was not convincingly supported by other ECG data in the atomoxetine safety database and at 50mg bid (1.2mg/kg/day), the new recommended target atomoxetine dose, few patients will achieve the exposure where the QTc prolongation signal was observed. Whether or not atomoxetine can prolong QTc at dosages higher than the maximum recommended dose is not definitively known.

In the atomoxetine NDA, Lilly provided results from clinical pharmacology study LYAE that suggested a possible atomoxetine effect on QTc among PM subjects. In study LYAE, PM subjects exposed to atomoxetine 60mg bid and 75 mg bid had statistically significant QTc prolongation at pre-dose time points. The lack of significant prolongation at other time points admittedly made this an unusual finding. In a follow up study where EM subjects were treated concomitantly with a CYP2D6 inhibitor there was no evidence of QTc prolongation albeit at lower mean atomoxetine plasma levels compared to PMs treated with atomoxetine in LYAE. For the remaining development program ECG data, there did not appear to be consistent evidence of an atomoxetine/QTc prolongation relationship.

The main concerns arising from the NDA review regarding ECG data were incomplete QTc information at higher doses and plasma levels among PM patients, and lack of QTc information in pediatric subjects. Lilly's response to the approvable letter addressed these concerns. Lilly's depiction of QTc data in PM children at higher plasma levels does not demonstrate QTc prolongation/plasma level relationship, although the data are scant. The reason for the lack of data is that few patients achieved these plasma levels.

According to Lilly's simulations, very few PMs will achieve atomoxetine plasma levels >2,000ng/mL. Our pharmacometric consultant predicted a higher proportion of atomoxetine plasma concentration values >2,000ng/mL among PMs treated with 1.4mg/kg/day. Our consultant estimates that 42% percent of plasma concentration values could exceed 2,000ng/mL at the 1.4mg/kg/day dose but that only 2.5% will exceed 2,500ng/mL. The limited amount of QTc data available for this plasma level range did not suggest atomoxetine-related prolongation of cardiac repolarization.

Lilly argues that the effect of atomoxetine on heart rate (increases) is protective in preventing torsades de pointes. Although Lilly's assertion seems logical, based on currently available knowledge, I do not believe we can routinely dismiss QTc prolongation signals for drugs just because they are also known to increase heart rate.

#### *Growth*

Lilly disagrees with the growth labeling proposed by the division in the approvable letter and offers their arguments with their labeling proposals. Lilly is concerned that the atomoxetine label includes more information about growth effects than the labeling for currently approved ADHD drugs. Lilly disagrees with the division's interpretation of the atomoxetine growth data.

Lilly's first disagreement with the division's proposed labeling is the apparent suggestion of a differential effect of atomoxetine on growth when compared to the language present in the labels of other treatments approved for the treatment of ADHD. The type of information included in labeling evolves and hopefully improves over time. As better data are collected and data are better analyzed, additional important information becomes available for prescribers and is included in labeling. The consequence of this progress is that the information available for newer drugs is different than the information for older drugs. The mention in labeling of a particular characteristic of a newer drug that does not also appear in labeling for older drugs may not mean that the characteristic is not present across the therapeutic class. It may only mean that the characteristic was identified for the newer drug because of improved data collection or more thorough analyses of data. Lilly is concerned that the growth related labeling language proposed by the division for atomoxetine may incorrectly suggest differential effects when compared to other treatments approved for the treatment of ADHD. While the division does not intend to suggest differences in the absence of such evidence, our overriding concern in this instance is providing the most complete information about atomoxetine to prescribers and patients and their parents. If truly interested in clarifying the relative effect of different ADHD treatments on growth, Lilly could conduct a study capable of examining this question.

Lilly expressed concern that the division would include weight data from a fixed dose study that demonstrated a clear dose response for weight loss. Lilly argues that data from all placebo controlled trials (fixed dose and flexible dose) be combined and presented because providing data only from one study with smaller sample size could incorporate more random error. I believe that the language proposed by the division clearly illustrates an effect of the drug on weight and documents that the effect increased with increasing dose, using the only data available to evaluate dose response. Whether it is adequate to state the effect without providing the data in labeling is a matter of opinion. I believe it is useful to prescribers to see the data used to support the conclusion of a dose response but I recognize that labeling can be shortened if the specific data are not included.

The height-labeling issues raised by Lilly arise from differences in opinion about the interpretation of the height data. Lilly would state in labeling that there is no evidence of an initial significant decrement from expected growth rates and again during long term treatment growth rates are at or close to expected rates. Lilly suggests that the observed mean z-score and percentile decreases aren't clinically important. To revisit the findings, I supply the following paragraphs from the NDA safety review to review the data as well as Lilly's interpretation of these data as summarized in their 2-month safety update.

**FDA summary of weight and height data from NDA safety review**

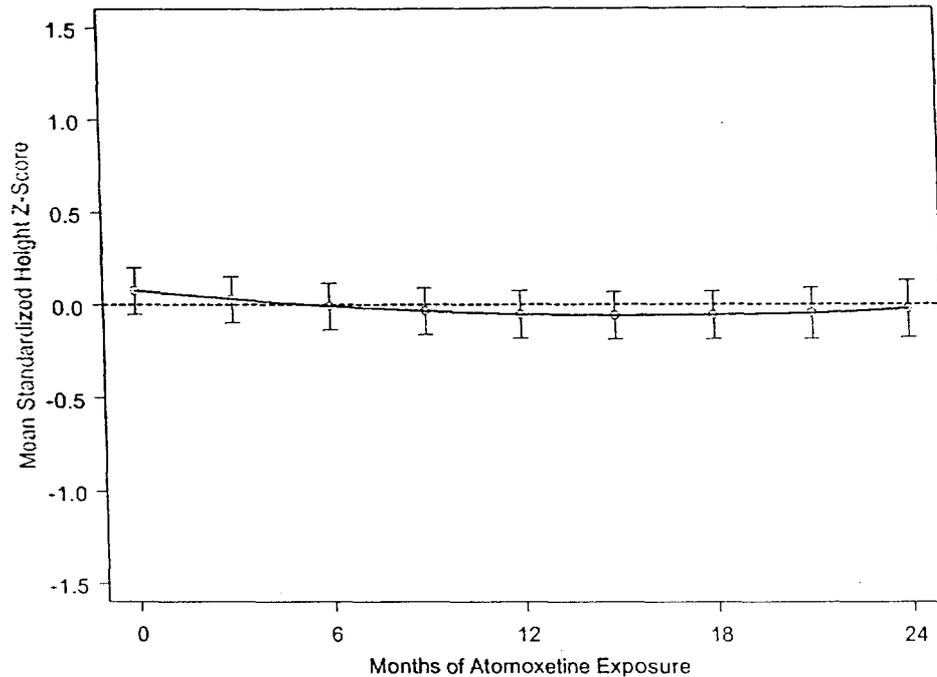
In their long-term analyses, the sponsor considered those 423 pediatric and adolescent subjects exposed to atomoxetine for at least 1 year and separately those 74 subjects exposed for at least 1.5 years. They then compared mean z score at baseline for these groups to several points throughout the observation periods. While exposed subjects had a mean increase in weight for one year (4 kg) and 1.5 years (6.5kg) there was a mean decrease in z scores of .25 and a mean decrease in weight percentile of 7.1 at one year. The sponsor also noted a mean decrease in weight z score of .28 and a mean decrease in weight percentile of 7.3 at 1.5 years (Safety update, p.115). This indicates that compared to the general population, the observed weight gain was less than predicted. Since these subjects were on average heavier than the general population at baseline, even after the observed changes, the mean percentile at endpoint was 54. The sponsor provided a plot of z scores over time for this population. It appeared that most of the mean decrease in z scores occurred in the first 3 months of exposure with suggestion of stabilization around 1 year, followed by an increase that does not return to baseline.(Source: NDA Safety Review p.54)

Using data for subjects exposed to atomoxetine for at least 1 year, the mean increase in height was 6.4cm with a decrease in mean z score of 0.16. Percentile for height decreased from 52 at baseline to 47 at endpoint (Safety update, p.121). Using data for subjects exposed to atomoxetine for at least 1.5 years, the mean increase in height was 9.3cm with a decrease in mean z score of 0.14. Percentile for height decreased from 54 at baseline to 49.5 at endpoint (Safety update, p.121). (Source NDA Safety Review p.57)

Lilly provided the following graph of mean height z-scores for subjects with at least one year exposure to atomoxetine in the 2 month safety update.

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Fitted line is a least square line from the statistical model with effects for baseline, days of exposure, and days of exposure squared  
 Source data: eagle:/programs\_g/rmp/b4zs/is2s/height and weight/z-score repeated by month.sas

Note: Error bars represent 2 standard errors of the mean (SEM)

Model: dependent variable: height Z-score; independent variables: baseline height Z-score, days, days squared

**Figure SU.5.4.1. Repeated measures mean height Z-scores over time, patients with at least 1 year of atomoxetine treatment, Two-Month Update Growth Analysis Group.**

The above graph suggests that for those with at least 1 year of exposure, mean z-scores decreased through month 12. Interpretation of results beyond month 12 becomes more difficult because patients begin dropping out and the analysis is based on fewer individuals as time proceeds. If one looks at the mean change in z-score from baseline in the table provided below, at months 18 and on, the mean change also remains negative.

Assessment of Changes in Standardized height z score over time for patients with at least 1 year of atomoxetine treatment

Duration (months)	N	Height z score mean change from baseline	95% CI
0	266		
2	54	-0.02	(-0.10, 0.06)
3	197	-0.03	(-0.08, 0.01)
6	162	-0.10	(-0.15, -0.05)
9	123	-0.08	(-0.16, 0.00)
12	183	-0.16	(-0.23, -0.09)
15	94	-0.12	(-0.21, -0.04)

18	49	-0.18	(-0.31, -0.05)
21	34	-0.10	(-0.29, 0.09)
>21	14	-0.02	(-0.34, 0.30)

From sponsor's table SU.5.4.4, p.123.

The following paragraph includes Lilly's interpretation of the height data provided in the safety update (Safety Update p.126).

Among patients treated with atomoxetine for at least 1 year, mean height increased statistically as well as clinically significantly. There was a small, but statistically significant decrease relative to baseline Z-scores and percentiles. For patients treated for at least 1 year, the mean decrease in height Z-score represented approximately 1.1 cm. That is, patients gained an average of 1.1 cm less than if their Z-score at endpoint was the same as at baseline. After 1 year of atomoxetine treatment, height relative to population norms stabilized, suggesting that patients were gaining height at a rate similar to that of other children of the same age and gender. The decrease in Z-score was greatest in the tallest group of patients and did not decrease statistically significantly in the shortest group of patients. Thus, with respect to risk assessment, patients most at risk (that is, the shortest patients) maintained their baseline Z-scores at endpoint.

Overall, the magnitude of the change in height Z-score was small, and does not appear to represent a clinically important effect at the current time. Ongoing studies will eventually provide more definitive information as the sample of patients who have been exposed over periods of 2 years increases.

Changes in height were not statistically significantly correlated with modal atomoxetine dose. This could be related to the fact that these changes were quite modest and may not represent true drug effects, or, alternatively, there may be an effect that is too small to be detected in the sample studied.

In the approvable letter, the division included a comment about the decrease in mean height z-score and percentile findings in proposed labeling without including the specific data. We acknowledge that the findings cannot be interpreted as definitively proving that atomoxetine suppresses height/growth. Without long term-controlled data, we will not be able to discern whether the observed effect is due to drug or due to differences in the population studied compared to the general population, which produced the normative data. Even if we were able to determine that atomoxetine was responsible for the given finding, determining whether effect is clinically important is admittedly difficult for at least two reasons. I do not believe the data are capable of providing accurate point estimates for a height effect since protocols did not include specific instruction for height measurements or specify accurate measurement methodology (e.g. use of stadiometers). Secondly, decisions about clinical significance can vary and may be influenced by the clinical circumstances for a particular patient. Since there is some disagreement about the interpretation and clinical importance of the data, I propose for consideration labeling language that includes the actual weight and height changes from baseline and mean weight and height percentile changes from baseline. This approach would inform prescribers of the available data and allow them to interpret the significance of these findings in the context of particular treatment decisions.

## 2<sup>nd</sup> Proposal:

Growth should be monitored during treatment with STRATTERA. During acute treatment studies (up to 9 weeks), STRATTERA-treated patients lost an average of 0.4 kg, while placebo patients gained an average of 1.5 kg. In a controlled trial that randomized patients to placebo or one of three atomoxetine doses, 1.3%, 7.1%, 19.3%, and 29.1% of patients lost at least 3.5% of their body weight in the placebo, 0.5mg/kg/day, 1.2mg/kg/day, and 1.8mg/kg/day STRATTERA dose groups, respectively. During acute treatment studies, STRATTERA-treated patients grew an average of 0.9 cm, while placebo-treated patients grew an average of 1.1 cm. There are no long-term, placebo-controlled data to evaluate the effect of STRATTERA on growth. During ~~open-label~~ open-label studies, patients treated with STRATTERA for at least 18 months gained an average of 6.5kg while mean weight percentile decreased from 68 to 60. For this same group of patients, the average gain in height was 9.3cm with a decrease in mean height percentile from 54 to 50. Among patients treated for at least 6 months, mean weight gain was lower for poor metabolizer (PM) patients compared with extensive metabolizer (EM) patients (+0.7 kg compared with +3.0 kg), while mean growth for PM patients was 4.3 cm and mean growth for EM patients was 4.4 cm. Whether final adult height or weight is affected by treatment with STRATTERA is unknown. Patients requiring long-term therapy should be monitored ~~patients who are not growing or gaining weight~~

## Effects on Blood Pressure and Heart Rate

Lilly disagreed with the division's analysis of pulse and blood pressure outliers, which identified subjects with at least one recorded high pulse or blood pressure reading during placebo controlled trials. Lilly commented that a more clinically useful analysis would identify sustained increases in pulse or blood pressure. Lilly submitted a proposal that would identify subjects with pulse or blood pressure elevations at the subject's final study visit. The division agreed that sustained increases of pulse or blood pressure are of interest but disagreed with Lilly's approach of identifying subjects with elevations at their final study visit since this definition could miss subjects who had sustained increases at other points in the study. The division proposed an analysis that would compare the percentages of subjects with at least two outlier increases for pulse or blood pressure by treatment. Lilly agreed, conducted the analysis and submitted the following labeling proposal incorporating their results.

## General

Effects on blood pressure and heart rate — STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following STRATTERA dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute. No pediatric subject had a heart rate increase of at least 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion. Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients 10.4 beats/minute.

STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of Strattera treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic blood pressure

measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of Strattera treated subjects and 1.5% (3/200) placebo subjects. [High systolic and diastolic blood pressure measurements were defined as those exceeding the 95<sup>th</sup> percentile, stratified by age, gender, and height percentile - National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.]

In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of 5 beats/minute compared with placebo subjects. Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.

STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pressure measurements  $\geq$ 150 mm Hg compared with 1.2% (3/256) of placebo subjects.

At the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements  $\geq$ 100 mm Hg compared with 0.4% (1/257) of placebo subjects.

Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated subjects. STRATTERA should be used with caution in any condition that may predispose patients to hypotension.

Lilly should provide the percentage and n/n for the pediatric placebo subjects with heart rate increases of at least 25 bpm and with heart rates of at least 110bpm at final visit. I recommend no other changes to above labeling.

#### *Symptoms of Bladder Outlet Obstruction*

Lilly proposed changing the title of the section from \_\_\_\_\_ to be consistent with other section titles (ex. Effects on Blood Pressure and Heart Rate). We will recommend that the title for this section be *Effects on Urine Outflow from the Bladder*.

#### *Comparison of AEs in EMs and PMs*

In the approvable letter, the division proposed including a separate table comparing AE risks in EMs to PMs. We included this table because we felt that if metabolic status was known, prescribers would have some information about AE risks differences for the different groups. In their response, Lilly deleted that table and provided risk comparisons in individual warning and precaution sections that discuss specific topics. Lilly's rationale for their proposal is that the event profiles are qualitatively similar for the different metabolic groups and that for individual patients with AEs, prescribers would make dosage adjustment or discontinuation decisions regardless of the CYP2D6 genotype. Provided our biopharmaceutics consultants agree with Lilly's plasma level analysis results and we do not believe PMs are at risk for QTc prolongation, I do not think assessment of metabolic status will be necessary prior to initiating atomoxetine therapy. I see Lilly's point that a separate table comparing AE risks for the different metabolic groups may not be useful clinically if CYP2D6 metabolic status is not determined prior to initiating atomoxetine treatment. Therefore I agree with deleting the table and including useful difference by metabolic status information under specific warning or precaution sections.

### *Information for Patients*

In the approvable letter, the division asked Lilly to provide a rationale for their *Information for patients* statement that asks patients to inform physicians if they are taking vitamins, natural supplements, or herbal remedies. Lilly would include this statement because it is good medical practice for the physician to know what a patient is taking, although they deleted vitamins from their latest proposal. I have no objections to this statement.

### *Laboratory Tests*

Lilly proposed the following changes in the *Laboratory Tests* section of labeling:

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Lilly argued that knowledge of CYP2D6 status will not aid in optimizing therapy since there are no data to guide differential dosing or demonstrate differential dose response and that dose adjustments should be based on clinical response. I agree with the above labeling proposal to strike

### *Other Adverse Events Table*

In the approvable letter, the division requested a listing of all adverse events observed during clinical trials. Lilly disagreed with that request and cited an FDA draft guidance that recommends not including such listings in labeling. While a list of all adverse events observed during clinical trials may include drug related adverse events that occurred too infrequently to meet inclusion criteria in the common drug adverse event tables, the list would also include many events not related to drug. Therefore, with little confidence that an other adverse events list would include useful, interpretable information, I would lean towards not including such a table in atomoxetine labeling.

In the approvable letter, the division's proposed labeling requested that Lilly provide separate common AE listings for the QD and BID regimens and that the AE table include events in at least 2% of atomoxetine subjects and greater than placebo. These requests resulted in the inclusion of additional observed AEs and a more complete illustration of the atomoxetine AE profile than was present in Lilly's initial proposed label.

### *Dosing Information-Tapering*

Lilly disagreed with the division's proposed labeling language that recommended

The division's recommendation was based on a pooled analysis of two studies that appeared in the atomoxetine NDA that found 5.5% (4/73) of abruptly discontinued adults reported dizziness compared to 0/94 tapered adults ( $p=.035$ ).

In their response to the approvable letter, Lilly provided several pieces of information to support their argument against recommending

Lilly pointed out that no pediatric atomoxetine subjects reported dizziness during two studies with discontinuation phases. Lilly stated that in the pooled adult analysis, 5.5% (4/73) of atomoxetine abrupt discontinuation subjects experienced dizziness compared to 2.6% (5/196) placebo subjects ( $p=0.5$ ). The placebo data were not included in their NDA analysis. Lilly pointed out that all four of the adult subjects with

abrupt discontinuation emergent dizziness were from study LYAA while no dizziness discontinuation events were identified for the abruptly discontinued atomoxetine subjects in study LYAO.

Using the LYAA data set submitted with the NDA, I identified the four-atomoxetine subjects with discontinuation emergent dizziness to characterize these events. One of the subjects (1110) had the event on the day of randomization to abrupt discontinuation, meaning that the event apparently preceded discontinuation of atomoxetine. For the three remaining subjects, the events were described as mild for 2 (2191,2755) and moderate for one (2770). The subject with the moderate event had a brief duration of dizziness (1 day).

Upon further consideration, I do not think that the data strongly support that \_\_\_\_\_ and I agree with Lilly that the proposed \_\_\_\_\_ language be removed from labeling. The finding of discontinuation emergent dizziness events in only one out of four studies with discontinuation phases suggests a lack of consistency with respect to the finding. Furthermore, one of the subjects identified as having discontinuation emergent dizziness apparently had the event prior to discontinuation, reducing the magnitude of the finding.

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Appendix- Serious Adverse Events from the Safety Update, Lilly table 4.2.1

Patient #/ Patient # in Parent Study if Applicable	MedDRA Preferred Term (actual term)	Date Reported	ATX	PBO/ ND	Blinded
LYAB-032-6046	MAJOR DEPRESSIVE DISORDER NOS (reoccurrence major depressive episode) <sup>b</sup>	7/18/02	X		
LYAB-052-5144	NEGATIVISM (oppositional defiant disorder) <sup>b</sup>	5/3/02	X		
LYAB-053-5168	SUICIDE ATTEMPT (suicidal gesture) <sup>b</sup>	10/25/01	X		
LYAB-057-5331	APPENDICITIS (appendicitis)	2/26/02	X		
LYAB-089-6441	SPLENIC INJURY (lacerated spleen) ROAD TRAFFIC ACCIDENT (motor vehicle accident)	12/10/01	X		
LYAB-096-6162	APPENDICITIS (appendicitis) <sup>a</sup>	8/13/02	X		
LYAB-101-5825	WOLFF-PARKINSON-WHITE SYNDROME ACQUIRED (Wolff-Parkinson-White syndrome) <sup>b</sup>	1/21/02	X		
LYAF-512-2019	INTESTINAL OBSTRUCTION NOS (acute bowel obstruction) <sup>b</sup>	11/30/01	X		
LYAF-530-1605	GASTROENTERITIS VIRAL NOS (gastrointestinal infection) <sup>b</sup>	2/18/02	X		
LYAF-570-1890	THIRST (excessive thirst) BLOOD GLUCOSE INCREASED (high blood sugars) LETHARGY (lethargy)	3/21/02			X
LYAF-591-4015	[MEDDRA PT NOT YET MAPPED] (hospitalization for Nissan operation (Laparoscopic) <sup>c</sup>	Unknown			X
LYAF-600-6066	ABDOMINAL PAIN LOWER (abdominal pain lower)	1/7/02	X		
LYAF-620-5012	TONSILLITIS NOS (angina/tonsillitis) <sup>b</sup>	3/1/02	X		
LYAF-621-5076	DIABETES MELLITUS NOS (diabetes mellitus) <sup>b</sup>	1/25/02	X		
LYAF-621-5078	SCHOOL REFUSAL (school refusal)	1/14/02	X		
LYAF-650-8162 / LYAI-650-6402	WOLFF-PARKINSON-WHITE SYNDROME ACQUIRED (Wolff-Parkinson-White syndrome) <sup>b,d</sup>	12/11/01	X		

Patient #/ Patient # in Parent Study if Applicable	MedDRA Preferred Term (actual term)	Date Reported	ATX	PBO/ ND	Blinded
LYAI-012-3444 /LYAC-012-7110	SUICIDAL IDEATION (suicidal ideation) <sup>b</sup>	5/15/02	X		
LYAI-013-4540/ LYAT-013-3163	CELLULITIS ORBITAL (left periorbital cellulitis) SINUSITIS NOS (pan-sinusitis)	2/1/02	X		
LYAI-015-4625/ LYAT-015-3212 LYAI-017-4682 <sup>e</sup>	INTENTIONAL SELF-INJURY (suicidal ideation/gesture) OVERDOSE NOS (overdose)	10/25/01 12/6/01	X X		
LYAI-019-4774 /LYBB-019-8941	DEHYDRATION (dehydration due to vomiting on codeine)	3/6/02	X		
LYAI-021-4029/ LYAT-021-3356	SUICIDAL IDEATION (threatened suicide) <sup>b</sup>	12/6/01	X		
LYAI-032-6651 /LYAQ-032-3327	NEGATIVISM (oppositional behavior)	3/4/02	X		
LYAI-044-7081 /LYBB-044-7027	FALL (accidental fall) DEMENTIA NOS (concussion with "post-concussion syndrome")	12/14/01	X		
LYAI-087-8525 /LYBB-087-8106	PSYCHOTIC DISORDER NOS (onset of psychotic symptoms) <sup>b</sup>	11/19/01	X		
LYAI-088-8566 /LYBB-088-8164	EPISTAXIS (nasal bleeding)	4/2/02	X		
LYAI-089-8611 /LYAQ-089-3771	AGGRESSION (aggression) <sup>b</sup>	12/10/01	X		
LYAI-098-8967 /LYBB-098-8530	DENGUE FEVER (dengue fever) <sup>b</sup>	5/17/02	X		
LYAI-221-3005 /LYAS-221-4462	PERIANAL ABSCESS (perianal abscesses)	3/22/02	X		
LYAI-530-5323 /LYAF-530-1611	ABDOMINAL PAIN NOS (abdominal pain)	4/26/02	X		
LYAI-581-6002/ LYAF-581-1561	PNEUMONIA NOS (pneumonia)	3/6/02	X		
LYAI-650-6406 /LYAF-650-8166	GASTROENTERITIS NOS (gastroenteritis) BLOOD GLUCOSE INCREASED (high blood glucose)	4/24/02	X		
LYAR-063-5501/ LYAA-063-2602	RENAL CELL CARCINOMA STAGE I (right renal cell carcinoma-type one)	2/11/02	X		

Patient #/ Patient # in Parent Study if Applicable	MedDRA Preferred Term (actual term)	Date Reported	ATX	PBO/ND	Blinded
LYAR-072-5101/ LYAA-072-2152	DIVERTICULITIS NOS (diverticulitis)	12/26/01	X		
LYAR-082-6151 LYAO-082-3302	COMA (coma) <sup>b</sup> SUBDURAL HAEMATOMA (right subdural hematoma with delayed intraparenchymal bleed) CRANIOTOMY (right craniotomy with evacuation of subdural hematoma)  CONTUSION (contusions arms and right leg) EPISTAXIS (epistaxis) RIB FRACTURE (fractured ribs (3)) LOSS OF CONSCIOUSNESS (loss of consciousness) LACERATION (multiple lacerations) LIMB INJURY NOS (open wound on right thigh)  HAEMATOMA NOS (scalp hematoma) SPINAL FRACTURE NOS (transverse process fractures to T4,T9,T10)	6/8/02    4/8/02	X		
LYAR-097-5666 LYAA-097-2783	CALCULUS RENAL NOS (kidney stones) <sup>b</sup>	1/7/02	X		
LYAS-012-4108	CONSTIPATION (constipation) ABDOMINAL PAIN UPPER (stomach pain)	2/21/02	X		
LYAW-098-7407	APPENDICITIS (appendicitis) LYMPHADENITIS NOS (mesenteric adenitis)	4/19/02	X		
LYBH-042-3160	DEHYDRATION (dehydration)	3/12/02			X
LYBH-089-3316	ASTHMA NOS (shortness of breath secondary to acute asthma)	7/3/02	X		

(Footnotes for Table 4.2.1)

a Patient LYAB-096-6162 had a serious adverse event of appendicitis which occurred after the data cut-off.

This event is included here because of the special interest in cases of appendicitis.

b Patient discontinued due to the serious adverse event (see Table 4.3.1).

c Reported by investigator, data not yet available in ClinTrace.

d Event occurred during the patient's transition from study LYAF to the open-label extension study LYAI.

Patient summaries have been provided for both studies.

e This is the identifier for the study patient, not the person with the adverse event (family member ingested patient's study medication).

Abbreviations: ATX = atomoxetine, PBO/ND = placebo/no drug.

Source: ClinTrace

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/s/

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Jerry Boehm  
11/19/02 01:49:15 PM  
MEDICAL OFFICER

Judith Racoosin  
11/19/02 01:54:19 PM  
MEDICAL OFFICER

## REVIEW AND EVALUATION OF CLINICAL DATA

### APPLICATION INFORMATION

NDA 21-411

SPONSOR: Eli Lilly and Company

Date Submitted: October 12, 2001

User Fee Date: August 12, 2002

### DRUG NAME

Generic Name: atomoxetine hydrochloride

Proposed Trade Name: Strattera

### DRUG CATEGORIZATION

Pharmacological Class: Norepinephrine Reuptake Inhibitor

Proposed Indication: Attention Deficit Hyperactivity Disorder

Dosage Forms: 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, or 60 mg.

### REVIEWER INFORMATION

Medical Officer: Roberta L. Glass, M.D.

Review Completion Date: July 1, 2002

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