The Investigator reported the event as not related to the study drug or study procedures.

Category 4 (Event reported as a seizure, but not considered a generalised tonic-clonic seizure based on the information provided in the report)

Six events (5 patients) were categorised Category 4. Two were classified Class A with the remainder classified as Class B (i.e. clear or possible confounding factors identified in all reports).

Two events of 'seizure' were coded for a [redacted] with a prior history of seizure and abnormal EEG (Class A). However the MAH state that patients with a history of seizure were excluded from all trials. The MAH should be requested to explain this.

'Possible partial syncopal seizure' was reported in a [redacted]. The syncopal episode followed a dental procedure that included blood loss and anaesthesia (Class A).

The third case is that of a [redacted] who suffered 'psychomotor seizure' (MedDRA Preferred Term 'Partial complex seizures'). The [redacted] continued treatment with atomoxetine for 2 more years at higher doses with no further similar episodes (Class B).

The fourth case is of 'possible seizure' in a [redacted] who went on to continue treatment with atomoxetine for 3 more months at higher doses with no further similar episodes (Class B).

The final case in Category 4 is of a 'focal convulsion' in a [redacted] with a history of complicated pregnancy with forceps delivery and a family history of seizure.

<u>*Clinical Trial Reports Related to Seizure (atomoxetine/placebo/methylphenidate)*</u>
In the 31 clinical trials, 13 patients experienced at least one seizure-related event (12 children/adolescents and 1 adult).

Table 1 below provides the number of possible seizure adverse events by treatment and analysis group.

Table 1

		Atomoxetine		Placebo	Methylphenidate	p-value*
		n/N	Crude incidence	n/N	n/N	
Paediatric Trials	**Controlled Trials†**	1/1614	0.06%	0/849	0/523	1.000
	Overall§	12/5083	0.2%	N/A	N/A	N/A
Adult Trials	**Controlled Trials†**	0/270	N/A	0/266	N/A	N/A
	Overall§	1/748	N/A	N/A	N/A	N/A

† Controlled trials - data from acute-treatment period of double-blind placebo controlled or comparator-controlled studies with atomoxetine.

§ Overall atomoxetine group – data from all phases of clinical trials regardless of indication with an atomoxetine treatment arm.
* p-value corresponds to exact Chi-squared test comparing incidence rates across three treatment groups.

The MAH calculate that clinical trial reporting rate for reports related to seizure in paediatric patients was 0.2% (12/5083) patients. For adults the reporting rate was calculated to be 0.1% (1/748).

The 1 case of seizure (classified "nontonic-clonic seizure"by the MAH) in the controlled-group phase occurred in study LYBR (comparative study with methylphenidate).

Assessor's comments: According to the MAH analysis, confounding or contributing factors were found in 16 of the 17 AEs (12 in Class A and 4 in Class B) (or 12 out of 13 case reports). The clinical trial data do not provide strong evidence of a causal link of seizure events with atomoxetine.

The MAH should be requested to explain the confounding factor 'previous medical history of seizure' in a [redacted] given that the methodology section states that all patients with a history of seizure (excluding febrile seizures) were excluded from clinical trials.

3.0 Cumulative review of Spontaneous Adverse Event Reports of Seizure (data lock 26 November 2004)

Spontaneous reports of seizure events among patients taking atomoxetine following US approval in 2002 have been the most common serious adverse event reported by health care professionals and consumers. The spontaneous reporting rate for seizure events with atomoxetine remains higher than expected based on data from clinical trials (although patients with a prior history of seizure were excluded from clinical trials).

Methodology
The MAH's atomoxetine safety database was searched for all potential reports of seizure by searching on MedDRA Preferred Terms suggestive of a generalised tonic-clonic seizure. The following 47 MedDRA Preferred Terms were identified and used:

Seizure event terms: *complex partial seizures, convulsion, epilepsy, epilepsy congential, grand mal convulsion, partial seizures, partial seizures with secondary generalisation, petit mal epilepsy, simple partial seizures, status epilepticus, tonic convulsion.*

Event terms suggestive of generalised tonic-clonic seizure: *anticonvulsant drug level decreased, anticonvulsant level increased, anticonvulsant toxicity, aura, coma, conversion disorder, cyanosis, depressed level of consciousness, exectroencephalogram abnormal, eye rolling, faecal incontinence, fall, foaming at mouth, hypertonia, incoherent, incontinence, loss of consciousness, movement*

disorder, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, nystagmus, oculogyration, opisthotonus, postictal state, strabismus, syncope, syncopal vasovagal, tongue biting, tonic clonic movements, trismus, urinary incontinence.

The diagnostic categorisation and the etiological classification systems used are identical to those used in the clinical trial and are outlined in the relevant section above.

Summary of Clinical Evaluation and Report Categorisation

A total of 507 events were identified using the search terms outlined above. Of these, 80 were grouped in Diagnostic Category 1 (probable/possible generalised tonic-clonic seizure), 4 in Category 2 (status epilepticus), 74 in Category 3 (seizure classification indeterminate due to insufficient information), and 25 in Category 4 (event not considered to be tonic-clonic seizure).

A total of 324 case reports were grouped in diagnostic Category 5 (event was determined not to be a seizure based on the information provided in the report). These reports are not discussed further in the MAH's report.

Assessor's comments: The MAHs designation of reports into Category 5 seems appropriate from the line listing provided.

Category 1. Reports of Probable/Possible generalised Tonic-Clonic Seizure (80 reports)

A total of 36 of the 80 case reports were considered by the MAH to have clear confounding or contributing factors and were classified Class A. In summary, the 'clear' confounding/contributing factors included: a diagnosis of benign Rolandic epilepsy (autosomal dominant disorder of childhood); concomitant medication (mainly bupropion) known to cause seizures; and a history of seizures or other conditions/events which predispose to seizures. In eight reports the seizure event occurred after discontinuation of atomoxetine (onset ranges from 1 week to 8 months after discontinuing treatment). An overdose of atomoxetine (alone) was reported in one case (patient also on concomitant bupropion treatment although did not overdose on bupropion). A number of reports contained more than one of the above mentioned confounding/contributing factors.

Twenty-eight of the 80 reports in Category 1 had possible confounding or contributing factors (Class B). 'Possible' confounding/contributing factors reported by the MAH include: negative rechallenge or no further events on continuing treatment (in 1-4 months duration of treatment after event); family history of seizures; concomitant fever; history of head trauma, microencephalopathy, Autism, Asperger's, sleep disorder/deprivation; and concomitant drug therapy (risperidone, escitalopram, sertraline, methylphenidate).

Thirteen of the 80 reports in category 1 were classified into Class C as having indeterminate etiology with insufficient information for evaluation of the seizure event.

Three of the 80 reports in Category 1 were classified into Class D. These reports have no apparent confounding or contributing factors and have sufficient information available to evaluate the event. These three cases are discussed in more detail below.

Case [redacted] is that of an [redacted] who received atomoxetine 18mg daily for ADHD. The atomoxetine dose was titrated up to 40mg daily over about 4 weeks. The patient also received amphetamine/dextroamphetamine which was discontinued during the first week of atomoxetine therapy. Two months after starting atomoxetine the patient experienced a witnessed seizure characterised by tonic-clonic activity and loss of consciousness. The patient also experienced faecal and urinary incontinence and extreme sedation. The patient was treated in the emergency room where [redacted] vital signs and pupils were normal. There were no neurological deficits postictally. A CT scan of the head, bloodwork (including chemistry), complete blood cell count, and drug screen were all within normal ranges. Atomoxetine was discontinued. Subsequent EEG and neurological exam were normal. The patient was restarted on amphetamine/dextroamphetamine. Ten days after discontinuing atomoxetine, the patient had experienced no further seizure activity. The patient had no personal or family history of seizure. No other relevant medical history.

Case [redacted] is that of a [redacted] who experienced a grand mal seizure four days after starting atomoxetine 25mg daily for ADD. The seizure was witnessed by family members and was described as tonic-clonic activity with loss of consciousness. The seizure was not preceded by an aura and it is unknown if there was loss of control of the bowel or bladder. Pupils were normal and there were no neurological deficits following the event. There were no vocalisations, cyanosis, pooling of secretions, postictal paralysis, postictal weakness, confusion, agitation, headache, fatigue or muscle pain following the event. The seizure was not preceded by fever, neck stiffness, headache or sleep deprivation. EEG was normal. Atomoxetine was discontinued 2 days after the seizure and was not rechallenged. Four months after discontinuation the patient had not experienced any further seizure activity. The patient was receiving no concomitant medication and had no personal or family history of seizures or any other relevant medical history.

The third case ([redacted]) concerns a [redacted] patient who received atomoxetine 40mg for ADD and experienced feeling tired and woozy. The events continued to get worse so atomoxetine dose was tapered to 30mg 7 days after, then to 20mg 9 days after starting treatment with atomoxetine. Nine days after starting atomoxetine the patient experienced a grand mal seizure. Atomoxetine was discontinued. A preliminary EEG was abnormal and the patient was referred to a neurologist. All tests were negative including a 24-hour EEG. Approximately four months after discontinuation of atomoxetine the patient had experienced no further seizures. The patient was taking no concomitant medication. [redacted] had no personal or family history of seizures and was described as "perfectly healthy".

Assessor's comments: The role of atomoxetine can not be excluded in three cases of seizure ([redacted]). All three cases show

a temporal relationship with starting treatment with atomoxetine and a positive dechallenge. No other medication was involved.

The MAH considers that 50 reports are confounded by a prior personal history of seizures. Whilst these reports are indeed complicated by a history of seizure, further examination of the case reports suggests that in a number of instances the possibility an aggravation the underlying seizure disorder by atomoxetine can not be ruled out.

[redacted] describes a [redacted] with a history of "developmental delayed" seizure disorder which had been controlled for 2-3 years prior to starting atomoxetine. After starting atomoxetine (onset unknown) the patient experienced an increase in seizure activity. Approx. 5 months after starting atomoxetine the patient experienced 4-5 seizures in a 24 hour period. The patient was admitted to hospital for 2 days and atomoxetine was discontinued. The patient had not experienced any further seizure activity.

Case [redacted] is that of a [redacted] who was diagnosed with epilepsy 2 years prior to initiating atomoxetine. Eight months prior to starting atomoxetine [redacted] required hospitalisation due to an episode of repeated seizures. The patient had not experienced seizure activity for six months prior to atomoxetine initiation. [redacted] was concomitantly receiving phenobarbital and topiramate for epilepsy. Patient experienced a grand mal seizure the day after starting atomoxetine which was similar to [redacted] previous seizures. A few hours later the patient experienced a second seizure. The patient's seizure medications have remained unchanged since the time of [redacted] last seizure. Atomoxetine was discontinued and after one month the patient had not experienced further seizure activity.

[redacted] describes a [redacted] with a history of generalised epilepsy (1 seizure/month) who, one day after starting atomoxetine 18mg, experienced two tonic-clonic seizures. Concomitant carbamazepine levels were within normal limits.

Case [redacted] is that of a [redacted] with a history of autism who experienced a seizure between 1-5 weeks after starting atomoxetine. The patient was started on valproic acid and atomoxetine was continued. Three weeks later the patient experienced an additional seizure. Valproic acid and atomoxetine were discontinued and the patient started phenytoin and oxcarbazepine. One month later, atomoxetine was restarted. Three weeks after restarting atomoxetine the patient experienced another seizure and was admitted to hospital where the patient continued to experience seizures over the next couple of days. EEG revealed occasional sharp waves in the right frontal area, but was otherwise normal.

In one case, the seizure event followed a close temporal relationship with an increase in dose of atomoxetine. Case [redacted] describes a [redacted] with no previous history of seizures or other relevant medical history who had been receiving treatment with atomoxetine 40mg for 3 months. One day after the dose was increased to 60mg the patient experienced a tonic-clonic seizure with loss of consciousness. The patient was concomitantly receiving sertraline which is known to lower the seizure threshold and this was the confounding factor stated by the MAH. However, atomoxetine was discontinued after the event and sertraline was continued with no further seizure events reported.

Other reports which upon review of the case details the role of atomoxetine can not be ruled out include [redacted]. This is mainly due to a good temporal relationship between starting atomoxetine and onset of seizure events together with a positive dechallenge in those cases where outcome was reported.

Category 2. Reports of Status Epilepticus (4 reports)
Four cases were categorised as status epilepticus. One report was classified Class A due to a prior history of generalised tonic/clonic seizures and mild developmental delay.

Assessor's comments: The first case ([redacted]) had a prior history of seizures and was considered by the MAH to be clearly confounded. However, as with some case reports in Category 1 above, the role of atomoxetine in aggravating the patients underlying epilepsy can not be ruled out.

[redacted] described a [redacted] patient with a history of generalised tonic-clonic seizures, mild developmental delay and family history of seizures. [redacted] baseline seizure rate was one seizure episode every 6 months for which [redacted] was taking valproate on a regular basis and lorazepam as required. The patient started atomoxetine 40mg daily which was increased to 80mg daily after 1 week. After starting the 80mg dose the patient experienced an increase in fit frequency and severity of [redacted] seizure activity to 3-4 seizures weekly. Seizures consisted of loss of consciousness, generalised tonic-clonic movements and postictal confusion and lethargy. The patient experienced status epilepticus (duration greater than 15 minutes) and was hospitalised. Atomoxetine was discontinued. Valproate level was 150 (normal baseline range 106-120). Electrolytes and MRI normal. Toxicology screen was negative. EEG showed spikes with focal spikes of the right and left centro-temporal region indicative of primary generalised seizures. Atomoxetine was not restarted. The worsening of seizures resolved 3 weeks after stopping atomoxetine and the patient had experienced no further seizure activity 5.5 months later. The reporting physician considered the increased in seizure frequency and severity was due to atomoxetine.

Two cases were classified Class B with concomitant medication of citalopram in both cases and a history of mental slowness or learning disabilities.

The final case of Category 2 was placed in Class C. The case was not reported as status epilepticus. However, due to the duration of the seizure events and intubation of the patient, the MAH placed this case in Category 2 Status epilepticus. There is no further discussion of this case in the MAH's report.

Category 3. Event Reported as a Seizure, but the Seizure Classification was Indeterminate Due to Insufficient Information in the Report (74 reports)
A total of 74 reports were assessed as Category 3 by the MAH. Twenty-eight of these reports were considered to have clear confounding or contributing factors. The clear confounding/contributing factors listed by the MAH include a prior history of seizure,

diagnosis of benign Rolandic epilepsy, concomitant medication known to cause seizures (including bupropion, TCAs), overdose of other medication (paroxetine, TCA, diphenhydramine), and drug abuse (PCP, cocaine, heroin). A number of these reports listed more than one of the above mentioned factors.

Thirteen of the 74 cases had possible confounding or contributing factors and were placed in Class B according to the MAH. The cases were placed in Class B for the following reasons: family history of seizure, seizure event not witnessed and unconfirmed, other medical history (autism, head trauma, sleep disorder, Tourette's disorder, severe mental retardation and concurrent stroke), concomitant medication known to lower seizure threshold or atomoxetine was continued with no further seizure events (4.5 months).

A total of 33 of the 74 cases in Category 3 were classed as Class C (indeterminate etiology with insufficient information for evaluation of the seizure event). These cases are not discussed further in the MAH report.

Assessor's comments: Many of these cases were confounded according to the MAH analysis. On review, in many of the cases there is insufficient information with which to determine both the seizure event and causality. However, there is also insufficient information available with which to completely exclude causality.

Category 4. Event Reported as a Seizure, Not Considered a Generalised Tonic-clinic Seizure Based on the Information Provided in the Report (25 reports)
There were 24 cases categorised in Category 4. Fourteen of these reports were considered to have clear confounding or contributing factors (Class A).

The majority of the 14 cases in Class A were confounded due to a prior history of seizures (11/14). Other confounding factors included a diagnosis of Rolandic epilepsy and negative dechallenge.

Five of the 25 reports in Category 4 were classed Class B (possible confounding/contributing factors present). These were: atomoxetine continued at lower dose with no further seizures, family history of seizures, concomitant medication known to lower the seizure threshold (escitalopram, paroxetine), other medical history (e.g. premature birth, pervasive developmental disorder).

Five cases in Category 4 were placed in Class C. These reports are not discussed further in the MAH's report.

One case report had no apparent confounding or contributing factors and had sufficient information available for evaluation of the seizure event (Class D).

Case [redacted] is that of a [redacted] who experienced a complex partial seizure an unknown time after starting atomoxetine. The seizure occurred in the

morning hours and was characterised by impaired consciousness at onset and tonic-clonic activity. The seizure was not associated with fever. EEG, CT scan and MRI, and electrolytes were all normal an unknown time after the event. The patient continued atomoxetine following the event although it was eventually discontinued (unknown date and reason). The patient had experienced no further seizure activity six months after the event. Patient had no prior history of seizures or any other relevant medical history. It was unknown if the patient was receiving any concomitant medication.

Assessor's comments: A causal relationship between atomoxetine and the onset of complex partial seizure in case [redacted] can not be excluded. Further review of the case details for other reports placed in Category 4 suggests that there are a number of additional cases in which a causal relationship between atomoxetine and the event can not be established but equally can not be excluded either.

Overview of Reports

Table 2 below gives an overview of the report categorisation, including the number of reports with a prior history of seizure (50/183). In a further 41 reports, the seizure history was not provided in the reports.

Table 2

		Diagnostic Category 1	Diagnostic Category 2	Diagnostic Category 3	Diagnostic Category 4	Total
Prior history of seizure		19	1	19	11	50
No prior history of seizure	Confounding / contributing factors (Classes A & B)	38	2	12	7	59
	Indeterminate etiology with insufficient information for evaluation (Class C)	11	1	12	5	29
	No apparent confounding / contributing factors, with sufficient information for evaluation (Class D)	3	0	0	1	4
Seizure history not provided in report		9	0	31	1	41
Total		80	4	74	25	183

A total of four cases were considered to have no apparent confounding/contributing factors, with sufficient information for evaluation.

4.0 Reports of Seizure in Clinical Trials and Post-marketing Database (covering the period 27 November 2004 - 26 May 2005).

The review of seizure events associated with atomoxetine provided by the MAH and discussed above only includes data until 26 November 2004. The most recent PSUR (PSUR 4) includes data from the period 27 November 2004 – 26 May 2005 for both clinical trial data and spontaneous reporting data. This data is discussed below.

The analyses have been carried out using the same methodology described above. However different search terms were used to search the databases from those which were previously used and will be outlined in the appropriate sections below.

Clinical Trial data update (27 November 2004 – 26 May 2005)

The database for locked ADHD clinical trials (27 November 2004 – 26 May 2005) includes 224 children and adolescents exposed to at least 1 dose of atomoxetine for a total of 33.47 PY, and 562 adults exposed to at least 1 dose of atomoxetine for a total of 440.02 PY. Data from 5 clinical trials were reviewed.

A total of 49 MedDRA preferred terms were used to identify reports from the clinical trial database for review. These are based on the 47 terms used to search the post-marketing database previously with the addition of 'psychomotor seizures' and 'dreamy state'.

Seizure event terms: *complex partial seizures, convulsion, epilepsy, epilepsy congential, grand mal convulsion, partial seizures, partial seizures with secondary generalisation, petit mal epilepsy, simple partial seizures, status epilepticus, tonic convulsion., psychomotor seizures, dreamy state, tonic clonic movements.*

Event terms suggestive of generalised tonic-clonic seizure: *anticonvulsant drug level decreased, anticonvulsant level increased, anticonvulsant toxicity, aura, coma, conversion disorder, cyanosis, depressed level of consciousness, exectroencephalogram abnormal, eye rolling, faecal incontinence, fall, foaming at mouth, hypertonia, incoherent, incontinence, loss of consciousness, movement disorder, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, musculoskeletal stiffness, myoclonus, nystagmus, oculogyration, opisthotonus, postictal state, strabismus, syncope, syncopal vasovagal, tongue biting, trismus, urinary incontinence.*

Within the five clinical trials reviewed, there were 2 possible seizure events reported. Both events were identified in the previous review of seizure events (LYBN-017-1709, LYBR 603-6301). No new events were identified during this review.

Spontaneous Post-Marketing Reports of Seizures (27 November 2004 – 26 May 2005)

Fewer MedDRA preferred terms were used to search the post-marketing database than for the previous review (47 terms Vs 24 terms). The MAH should be asked to clarify the reasons for this.

A search of the post-marketing atomoxetine database identified 98 possible cases of seizure events. A total of 61 of these reports are not discussed further by the MAH since they were considered not to be seizure events upon review.

Assessor's comments: None of the 61 reports were reported as seizures.

A total of 37 reports were identified as having possible seizure related events.

Category 1. Reports of Probable/Possible Generalised Tonic-Clonic Seizure (7 reports)
A total of 7 reports were placed in Category 1 by the MAH. Three were considered to have clear confounding/contributing factors (Class A). The confounding factors cited are concurrent post-viral encephalitis, history of seizure disorder and anoxia and concomitant bupropion therapy.

One report was considered to have possible confounding/contributory factors (Class B) which were concomitant fluoxetine and mirtazepine use.

Three reports were classed as having indeterminate etiology with insufficient information for evaluation of the seizure event (Class C).

Category 2. Status Epilepticus (1 report)

One report was categorised as status epilepticus and was considered to have clear confounding/contributory factors (Class A). The main confounding factor cited is a history of unstable epilepsy with previous hospital admission for status epilepticus.

Category 3. Event Reported as a Seizure, but the Seizure Classification was Indeterminate Due to Insufficient Information in the Report (20 reports)
Seven reports were considered to be Class A with clear confounding factors (6 with history of seizures, 1 concomitant bupropion).

Five reports were considered to be Class B with possible confounding or contributory factors (sleep deprivation, concurrent medication, high fever, other medical history, negative dechallenge).

Eight of the 20 cases in Category 3 were classified Class C with indeterminate etiology with insufficient information for evaluation of the seizure event and are not further discussed by the MAH.

Category 4. Event Reported as a Seizure, Not Considered a Generalised Tonic-Clonic Seizure Based on the Information Provided in the Report (9 reports)
Nine reports were placed in Category 4. Five of these reports were considered to have clear confounding factors (all had a history of seizures- although febrile seizures in two cases) and three were considered to have possible confounding/contributory factors (history of Tourette's and OCD, family history of seizures and history of rage attackes and sleep disorder, Asperger's and concomitant mirtazepine). The remaining case was considered to have indeterminate etiology with insufficient information.

Assessor's comments: Of the 37 reports of possible reports of seizure identified from the spontaneous reporting database, 13 were considered to be confounded by a prior history of seizure. Seizure history was not reported in 14 cases. None of the reports were considered by the MAH to be possibly related to atomoxetine.

Two reports [redacted] involve patients with a history of epilepsy who experienced increased seizure activity after starting atomoxetine. In the first case atomoxetine was continued and concomitant valproate was changed to lamotrigine with no change in epileptic control. These two reports were placed in Category 3, Class A (clear confounding) by the MAH. A further report in Category 4 also reports an increase in seizure frequency after starting treatment with atomoxetine. [redacted] describes a [redacted] with a history of seizure disorder (up to 30 seizures/day), a diagnosis of post-herpetic encephalopathy aged 15 months, and a family history of seizures. The patient was receiving oxcarbazepine, mixed amphetamine salts, topiramate, diazepam, guanfacine and trazodone. This case is clearly confounded according to the MAH classification (previous history of seizure). However, two weeks after starting treatment with atomoxetine the patient experienced an increase in seizure frequency from approx. 3 seizures per month to up to 15 seizures daily. The seizures were reported to be complex partial seizures. The patient received atomoxetine for approx. 1 year. Atomoxetine was discontinued and patient was started on a ketogenic diet. The patient's seizure frequency decreased after discontinuation of atomoxetine.

Whilst some reports are clearly confounded, causality assessment for some reports in

Category 3 and 4 is hindered by a lack of information (particularly outcome). In these cases causality can not be established, yet, for the same reason, neither can it be completely excluded.

5.0 Seizures in an ADHD Population Using a Medical Claims Database Epidemiology study of Seizures in an ADHD population

The MAH undertook a health claims database analysis to examine the incidence of seizures in the general paediatric population and various subgroups, including those with and without ADHD. The study also aimed to evaluate a possible association between ADHD medications and new-onset seizures.

Population
Paediatric patients in the Ingenix Research Database. The patients were divided into a number of different groupings:

- **General paediatric sample** (20% random sample of those with at least 1 year continuous enrolment and without any history of seizure or anti-convulsant medication in the 1 year baseline period. (134,888 patients)

- **Non ADHD group** – drawn from the general sample above (127,778 patients)
  - Psychiatric diagnosis group (5127 patients)
  - No psychiatric diagnosis group (122,651 patients)

- **ADHD group** – drawn from the full database of those with at least 1 year continuous enrolment and without any history of seizure or anti-convulsant medication in the 1 year baseline period (34,727 patients)
  - Treated ADHD (28,979 patients)
  - Untreated ADHD (5,748 patients)

Study design
This was a retrospective cohort study using the Ingenix Research Database fro 1/1/2003 to 31/12/2003. The outcome of interest was non-febrile new-onset seizure defined using a claims based algorithm. Time on drug analysis was used to determine the incidence of first medical claim of seizure occurring during time on ADHD therapy compared with time off therapy.
Analyses were carried out with atomoxetine separated from other ADHD treatment, and stratified by prior treatment with any ADHD therapy in the baseline period.

Results
Demographics
Within the general population there were 49% female and 51% male patients, with 58% of patients in the 6-12 yrs category and 42% aged 13-17 years.

Within the ADHD population there were 26% female and 74% males reflecting the known epidemiology of this condition. The age breakdown for treated ADHD patients was similar to that for the general population. For the untreated ADHD population there were 66% in the younger age-group and 34% in the older age-group.

Table F17: Adjusted relative risk of first medical claim of seizure with time on ADHD therapy stratified by use of any ADHD therapy in baseline

	Combined (N=34,727)			Prior Use (N=25,228)			No Prior Use (N=5,502)		
	Adj RR*	95% C.I.		Adj RR*	95% C.I.		Adj RR*	95% C.I.	
ADHD Treatment Type									
Atomoxetine									
Current	1.1	0.6	2.1	1.2	0.4	2.6	2.5	0.9	7.1
Recent	0.8	0.6	3.4	1.2	0.1	5.9	NA	NA	NA
Past or None	ref	-	-	ref	-	-	ref	-	-
Other ADHD Therapy									
Current	0.8	0.6	1.3	1.7	0.9	3.4	0.7	0.2	2.0
Recent	0.9	0.4	1.9	2.0	0.8	5.1	NA	NA	NA
Past or None	ref	-	-	ref	-	-	ref	-	-
Demographics									
Female, Ages 6-12	1.7	0.9	3.3	1.5	0.6	3.3	1.7	0.8	4.8
Female, Ages13-17	1.4	0.7	3.0	1.8	0.8	4.2	0.4	0.1	3.5
Male, Ages 6-12	1.6	1.0	2.7	1.5	0.8	2.8	1.5	0.6	3.6
Male, Ages13-17	ref	-	-	ref	-	-	ref	-	-
Seizure Risk Factors									
Congenital	1.2	0.5	2.4	1.0	0.3	2.5	1.5	0.4	4.9
No Congenital	ref	-	-	ref	-	-	ref	-	-
CNS	4.6	3.0	7.0	5.3	3.1	8.9	3.3	1.6	7.0
No CNS	ref	-	-	ref	-	-	ref	-	-
Systemic	1.1	0.7	1.6	1.2	0.7	1.9	0.9	0.5	1.9
No Systemic	ref	-	-	ref	-	-	ref	-	-
Substance	1.6	1.2	2.6	2.0	1.1	3.3	2.2	0.9	5.4
No Substance	ref	-	-	ref	-	-	ref	-	-

*Adj RR = multivariable relative risk adjusted for all of the covariates above

Table F21: Nested case control - adjusted odds ratios for treatment stratified by prior use in baseline period

	Combined (N=1,100)			Prior Use (N=846)			No Prior Use (N=254)		
	Adj OR[1]	95% C.I.		Adj OR[1]	95% C.I.		Adj OR[2]	95% C.I.	
ADHD Treatment Type									
Atomoxetine									
Current	1.1	0.5	2.4	1.2	0.4	3.1	2.6	0.5	12.1
Recent	0.5	0.1	4.4	0.7	0.1	6.0	NA	NA	NA
Past or None	ref	-	-	ref	-	-	ref	-	-
Stimulants									
Current	0.8	0.5	1.3	1.4	0.7	2.7	0.4	0.1	1.6
Recent	1.3	0.5	3.8	2.2	0.7	6.8	NA	NA	NA
Past or None	ref	-	-	ref	-	-	ref	-	-
Bupropion									
Current	2.7	0.8	11.8	4.1	0.9	18.7	NA	NA	NA
Recent	NA	NA	NA	NA	NA	NA	NA	NA	NA
Past or None	ref	-	-	ref	-	-	ref	-	-

[1] Adj OR = multivariable odds ratios adjusted for ADHD treatment, age, gender, all seizure risk factor categories, outpatient visits, hospitalizations, calendar quarter, and geographical region.

[2] Adj OR = multivariable odds ratios adjusted for ADHD treatment, age, gender, all seizure risk factor categories except for congenital, outpatient visits, hospitalizations, calendar quarter, and geographical region.

Assessors Comments: There is clear evidence of an increased risk of first claim seizure in patients exposed to atomoxetine who have no prior ADHD therapy use. The relative risk in this group from the cohort study is 2.5 (95% CI: 0.9- 7.1), with a similar odds ratio in the nested case-control study of 2.6 (0.5-12.1). Whilst these are not formally statistically significant, they are certainly suggestive of a signal of seizures related to therapy in this group.

This increased risk is not seen in those who have prior use of ADHD therapies and as these patients constitute the majority of treated ADHD patients the combined results reflect these figures.

It is possible that patients are selectively prescribed atomoxetine if there is a history of seizure risk, for example a family history of seizures, which may not be recorded in the database. It is also possible that patients susceptible to seizures on therapy will have been identified during prior treatment with other therapies. Either of these could lead to channelling of high risk patients.

However, there is no evidence for this channelling in this study and therefore the results should be interpreted as providing evidence of a signal of increased risk of seizures in previously untreated patients until further evidence emerge.

OVERALL DISCUSSION OF SEIZURE EVENTS

Preclinical data and clinical trial data do not suggest that atomoxetine is proconvulsive, however seizure events are the most commonly reported serious adverse event for atomoxetine since US approval in 2002. The spontaneous reporting rate remains higher than expected based on clinical trial data. However these trials excluded patients with a prior history of seizure disorder.

According to the MAH assessment of reported seizure events, there are only four cases (4/183 + 0/37 reports) of seizure events in which the role of atomoxetine can not be excluded. These four patients have no prior history of seizure disorders. Thus, there is some evidence to suggest that atomoxetine causes seizure in patients with no prior history of seizure

The MAH exclude a causal role of atomoxetine in 50/183 and 13/37 reports of seizure events due to a prior history of seizure. However, in a small number of these cases, the possibility that atomoxetine is precipitating the patients underlying seizure disorder can not be ruled out. A more detailed review of the reports revealed a number of cases in which an aggravation of the underlying seizure disorder by atomoxetine could not be excluded. These reports followed a similar pattern in that the patients had been seizure free for some time before atomoxetine was started, subsequently experienced an increase in seizure frequency upon starting atomoxetine, and, in those cases where outcome is provided, have remained seizure free following discontinuation of atomoxetine.

The MAH has concluded that there is insufficient evidence at present to establish a causal association between atomoxetine and the seizure events reported. The MAH states that the reporting rate of seizure events is consistent with the background prevalence and incidence of seizures in the child and adolescent ADHD population. The MAH proposes to continue to closely monitor future reports of seizure associated with the use of atomoxetine.

The MAH's conclusion that the reporting rate of seizure events is consistent with the background prevalence and incidence should be interpreted with caution since the reporting rates are based on spontaneous data which is subject to under-reporting. The fact that seizure has been the most commonly reported *serious* adverse event for atomoxetine since US launch November 2002 is worrying.

The MAH undertook a health claims database analysis to examine the incidence of seizures in the general paediatric population and various subgroups, including those with and without ADHD. The study also aimed to evaluate a possible association between ADHD medications and new-onset seizures. The MAH concluded from this study that there was no evidence to suggest that there is a statistically significant increased risk of new-onset seizures among patients receiving atomoxetine.

However, upon review of the study, there is clear evidence of an increased risk of first claim seizure in patients exposed to atomoxetine who have no prior ADHD therapy use and whilst the relative risks are not formally statistically significant, they are certainly suggestive of a signal of seizures related to therapy in this group.

CONCLUSION

Preclinical data and clinical trial data do not suggest that atomoxetine is proconvulsive, however seizure events are the most commonly reported *serious* adverse event for atomoxetine since US approval in 2002.

There are a small number of reports (4) of seizure events in patients with no prior history of seizures in which a causal relationship with atomoxetine can not be excluded. There are further reports in which an aggravation of a pre-existing seizure disorder by atomoxetine can not be excluded.

Whilst the MAH concludes that the reporting rate of seizure is consistent with background rates in this population, these are based on spontaneous data which is subject to under reporting. It is worrying that seizure events are the most commonly reported serious events since US launch.

The results of the Medical Claims Database study suggest an increased risk of seizure in patients exposed to atomoxetine who have no prior ADHD therapy, although the relative risks were not statistically significant.

The SPC should be updated to include seizure events in section 4.4 (Special Warnings and Precautions for Use), 4.8 (Undesirable Effects) and 4.9 (overdose).

ANNEX 8

Review of Cardiac Disorders associated with Atomoxetine

(pre-clinical/clinical trial/spontaneous reports/Cardiovascular and Cerebrovascular Outcome Study in Adults/WHO SIGNAL article)

REVIEW OF CARDIAC DISORDERS ASSOCIATED WITH ATOMOXETINE

1. Introduction

Atomoxetine is recognised to have effects on the cardiovascular system. Increases in blood pressure, tachycardia, and orthostatic hypotension were observed in clinical trials and are recognised adverse effects of atomoxetine.

At the time of licensing, the clinical trial data relating to the cardiovascular effects of atomoxetine did not raise particular concern in paediatrics, however a potential safety issue was identified in older adults with age related vascular disease. As a result of this, section 4.4 (Special Warnings and Special Precautions for Use) of the Summary of Product Characteristics (SPC) for atomoxetine includes the statement that atomoxetine should be used with caution in patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease. It is also recommended that pulse and blood pressure be monitored periodically while on therapy. Furthermore, the MAH are undertaking a retrospective cohort study (Cardiovascular and Cerebrovascular outcome study in adults) to further evaluate this potential safety signal in adults post marketing.

An overview of the most recent PSUR for atomoxetine (PSUR 4; summary of data attached at Annex 3 of the main risk benefit report) identified a significant number of case reports of QT/QTc interval prolongation associated with the use of atomoxetine. The MAH was subsequently requested to provide a cumulative review of all spontaneously reported cases of cardiac disorders for atomoxetine since first launch.

This assessment report includes previously assessed pre-clinical and clinical trial data and considers the spontaneous adverse event reports relating to cardiac disorders for atomoxetine. In addition, this assessment report considers the ongoing MAH Cardiovascular and Cerebrovacular Outcome Study in Adults (Appendix A) and the most recent (pre-) publication issue (November 2005) of 'SIGNAL', the WHO drug safety bulletin (Appendix B) which includes an article on serious cardiac events associated with atomoxetine.

2. Preclinical Data

In Vitro Studies

Atomoxetine, DM-ATX and 4'-OH-ATX blocked cloned human I_{Kr} (hERG) channel (cloned from human embryonic kidney 293 cells) with IC_{50} of 0.869μM (222ng/ml), 5.71μM (1379ng/ml) and 20μM (5437ng/ml), respectively (Figure 2, below). Atomoxetine inhibited human cardiac I_{Na} (IC_{50} =36.1μM) and I_{Ca2+} channels (IC_{50} = 1.93μM). The effect on I_{Na} was rate and voltage dependent, suggesting that as experimental conditions approach more physiologic levels, blockade is increased.

In Vivo Studies

Cardiovascular effects of ATX in three dog studies (single oral doses in conscious adult dogs, repeated daily oral doses in conscious young dogs and iv infusion in anaesthetised dogs) were investigated. Single oral administration of ATX (0, 4, 8 or 16mg/kg) to telemetered adult mongrel dogs caused no treatment-related effects on heart rate or blood pressure.

ECGs and heart rates were also assessed in telemetered young (8-9weeks of age) beagle dogs, administered ATX (0, 4, 8 or 16 mg/kg/day) orally for 1-month, as part of the sub-chronic toxicity study. No ECG abnormalities attributable to atomoxetine were observed at *ca* 1h post-dose (*ca* C_{max} for ATX).

In anaesthetised dogs cardiovascular effects of ATX (iv infusion, 0.2mg/kg/min for 50min; cumulative doses of 0, 2, 4, 6, 8 or 10mg/kg) were compared to those of amitriptyline. ATX had no effect on blood pressure, peripheral resistance, cardiac output or stroke work index. ATX slightly increased heart rate (cumulative dose ≥2mg/kg) and increased QTc (corrected using Bazett formula) and P-R intervals at cumulative doses ≥6mg/kg and 8mg/kg, respectively.

Assessor's comments

Atomoxetine and 4'-OH-ATX have high affinity and selectivity for norepinephrine transporter (NET) over serotonin & dopamine transporters. 4'-OH-ATX is as active as ATX as an NET inhibitor and may contribute to the pharmacological activity of parent drug. DM-ATX, however, is 20-times less active than ATX as an NET inhibitor. Inhibition of NET by ATX, appears to be stereospecific, S(+)-enantiomer being 10-fold less potent. In general, ATX and its two phase I metabolites (4'-OH-ATX and DM-ATX) had relatively low affinity for other receptors and ion channels. Atomoxetine is a potent and moderately long-lasting inhibitor of NET in vivo.

Atomoxetine, DM-ATX and 4'-OH-ATX inhibited I_{Kr} (hERG) channel [IC_{50} 0.869μM, 5.71μM and 20μM, respectively]. Atomoxetine and DM-ATX are highly bound to human plasma proteins. At therapeutic levels of ATX, as much as a 23.6% and 12.4% I_{Kr} block (Figure 2) is anticipated in CYP2D6 PM and EM subjects, respectively. Plasma C_{max} for unbound ATX after a dose of 1.4mg/kg/d were 0.021μM (CYP2D6 EM) and 0.103μM (CYP2D6 PM). Therefore IC_{50} of ATX in hERG assay is 42.7-fold and 8.4-fold plasma Cmax for unbound ATX in CYP2D6 EM and PM subjects, respectively (see Full company response to Question 8 raised during National application in UK and Tables 8.1 and 8.3, therein). Based on MHRA's assessment of the Company's response to question 8, it is concluded that although hERG K+ channel inhibition predicted for ATX would indicate concern, there were no effects in dogs consistent with this observation. In addition, ATX caused significant inhibition of both human cardiac I_{Na} and I_{Ca2+} channels. Furthermore, inhibition of human cardiac hERG for the DM-ATX and 4'-OH-ATX metabolites at unbound Cmax in PM subjects is negligible (<2%) and is well below the threshold of hERG blockade considered to be predictive for prolongation of QT interval. Finally, this level of hERG inhibition provides >30-fold margin of exposure in PM subjects for the major metabolites. Therefore, there is no substantial clinical risk associated with ATX and its primary metabolites at the recommended clinical doses.

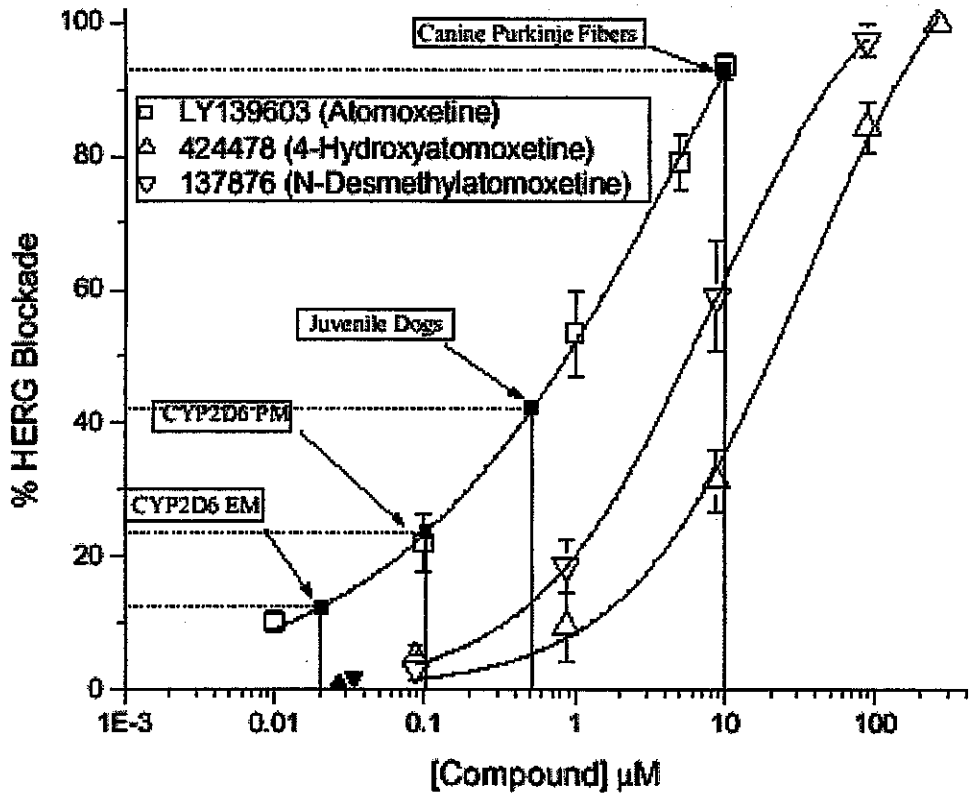

Figure 2. Concentration-response relationship for block of hERG current by ATX and its two principal non-conjugated metabolites.
Plasma Cmax for unbound ATX in poor metabolisers (PM) and extensive metabolisers (EM) are shown superimposed on the ATX curve with the associated predicted hERG blockade. In addition, plasma Cmax for unbound ATX from juvenile dog toxicity study and concentrations tested in dog Purkinje fibres are plotted. Plasma Cmax for unbound metabolites DM-ATX and 4'-OH-ATX are shown on individual metabolite curves (solid triangles)

Plasma C_{max} for unbound DM-ATX measured in humans were 34nM in CYP2D6 PMs and 0.6nM in CYP2D6 EMs. Plasma C_{max} for unbound 4'-OH-ATX measured in humans were 3nM in CYP2D6 PMs and 27nM in CYP2D6 EMs. Therefore predicted I_{kr} block by DM-ATX (0.1% and 2% in CYP2D6 EMs and CYP2D6 PMs, respectively) or 4'-OH-ATX (0.6% and 0.1% in CYP2D6 EMs and CYP2D6 PMs, respectively) is negligible (Figure 2). In addition, the IC_{50} of 4'-OH-ATX and DM-ATX in hERG assay are more than 168-fold their corresponding unbound plasma Cmax in CYP2D6 EM and PM subjects.

In anaesthetised dogs, ATX increased heart rate and QTc (corrected by Bazett formula which overcorrects at high heart rates) interval. However, in conscious adult and young dogs, single and repeated oral doses of ATX, respectively, had no effects on ECG or heart rate at doses up to 16mg/kg/day. At 16mg/kg/day, plasma Cmax for unbound ATX in adult or young dogs was up to 25-fold and 5-fold higher than

predicted Cmax after twice daily doses of 0.9mg/kg to CYP2D6 EM and CYP2D6 PM subjects, respectively.

High concentration tested in dog Purkinje fibres would be expected to block hERG by 93% in humans (Figure 2). This degree of I_{kr} blockade would be expected to lengthen, not shorten, cardiac APD. Atomoxetine shortened APD by ca 21% in dog Purkinje fibres. The absence of a prolongation of APD in Purkinje fibres is reassuring. In addition, ATX caused significant inhibition of both human cardiac I_{Na} and I_{Ca2+} channels and therefore has an effect at the Na^+ and Ca^{2+} channels co-incident with effect on hERG channel and appears to be a mixed ion channel blocker. Compounds that demonstrate this relationship have not been associated with clinical effects on QT and/or pro-arrhythmia.

In view of the potential of DM-ATX to accumulate in CYP2D6 PM subjects, its potential to prolong QT interval was questioned during the National UK application (see Company's response to Question 8 in Annex 2). This issue and the QT prolongation potential of ATX were adequately addressed during the National application.

3. Clinical Trial Data

Atomoxetine increases noradrenergic tone and is known to affect the cardiovascular response to orthostatic change. In the acute efficacy studies there were just 2 reports of syncope (both in the active atomoxetine group) and no vasovagal attacks. However the data in poor CYP 2D6 extensive metabolisers raise the possibility of drug exposure related cardiovascular adverse effects. It is plausible that cardiovascular adverse events might be caused by the chronotropic and blood pressure effects of atomoxetine disrupting baroreceptor mediated homeostatic processes during postural change.

The detailed reports show that most episodes of syncope and all of the vasovagal attacks were considered not serious and did not result in study discontinuation. Syncope was recorded as a serious adverse event for 2 patients, both of whom were extensive metabolisers, and as the reason for discontinuation for 1 poor metaboliser patient in study LYBG.

The applicant has presented an analysis of the cardiovascular adverse events and haemodynamic changes seen in healthy adults (Phase I studies). In healthy individuals atomoxetine had modest effects on blood pressure (mean increases of 2-3 mm Hg for both systolic and diastolic). However a few subjects demonstrated an exaggerated haemodynamic response resulting in orthostatic hypotension and/or syncope within 12 hours of dosing. There was a clear dose response relationship with cardiovascular effects seen mostly at doses of 40mg and above. There was no clear excess incidence in poor metabolisers, presumably because Cmax is only slightly elevated in this group.

It is likely that atomoxetine can contribute to orthostatic dizziness and syncope in some individuals, as reflected in the SPC. However the pattern of reporting does not

at present indicate any substantial risk in either extensive or poor metabolisers. It was recommended that this should be kept under review in post-marketing surveillance.

Atomoxetine consistently induces a modest sinus tachycardia at therapeutic doses. It is normally asymptomatic and well tolerated. Atomoxetine may also be associated with short-lived orthostatic sinus tachycardia and mild hypotension in both paediatric and adult populations, sometimes producing transient dizziness and possibly very occasionally syncope.

Atomoxetine consistently produces a small increase in diastolic and systolic blood pressures. Very few adverse events have been reported that relate to hypertension and long-term monitoring does not demonstrate any progressive tendency to the development of hypertension.

Effects on blood pressure and heart rate due to increased noradrenergic activity were of an acceptable magnitude and less marked than the changes produced by methylphenidate, which is licensed for ADHD. In paediatric patients the cardiovascular effects of atomoxetine do not give cause for particular concern. However there might be a potential safety issue in older adults with age related vascular disease and it was recommended that this should be the subject of close scrutiny in post-marketing surveillance.

ECG data were collected at baseline and during all studies, and were assessed in a blinded manner. No effect of atomoxetine on the ECG was seen. In particular atomoxetine did not significantly affect QTc in either CYP2D6 poor or extensive metabolisers, and no dose or plasma concentration relationship to QTc was observed.

4. MAH Cumulative Review of Spontaneous Adverse Event Reports of Cardiac Disorders (26 November 2002 – 26 November 2004)

This review includes all spontaneous reports from consumers and healthcare professionals for the period 26 November 2002 to 26 November 2004. An estimated 2.233 million patients have been exposed to atomoxetine during the first two years post launch (minimum of 618,000 patient-years).

During the two year period covered by this cumulative review, a total of 16,792 spontaneous adverse event reports were received by the MAH. These reports contained a total of 41,468 adverse events.

Of the cardiac disorder-related events, 411 were coded to the "Cardiac disorders" system organ class (SOC), and 665 were coded to the MedDRA high level group term (HLGT) "Cardiac and Vascular Investigations" of the "Investigations" SOC.

The MAH has reviewed the reported cardiac adverse events according to the following groups:

- Arrhythmia
  - Supraventricular arrhythmias

Atrial fibrillation, atrial flutter, sinus arrhythmia, supraventricular tachycardia;

- Ventricular arrhythmias
  Ventricular asystoles, ventricular tachycardia, cardiac fibrillation, cardiac arrest, cardio-respiratory arrest;
- Arrhythmia unclassified
  Arrhythmia, extrasystoles, cardiac flutter, heart rate abnormal, bradycardia, heart rate decreased, heart rate irregular, heart rate abnormal;
- Tachycardia
  Heart rate increased, tachycardia, sinus tachycardia;

- Cardiac conduction disorders
  - Cardiac conduction disorders
    Atrioventricular block, atrioventricular block first degree, atrioventricular block second degree, bundle branch block, bundle branch block right, Wolff-Parkinson-White syndrome;

  - ECG QT Prolongation
    Electrocardiogram QT prolonged, electrocardiogram QT corrected interval prolonged;

  - Other ECG abnormalities
    Electrocardiogram abnormal, electrocardiogram QRS complex prolonged, electrocardiogram ST-t abnormal, electrocardiogram ST segment abnormal, electrocardiogram T wave inversion, ECG signs of myocardial ischaemia;

- Other Cardiac disorders
  - Myocardial disorders
    Congestive cardiomyopathy, cardiomyopathy, cardiomegaly, dilation atrial, ventricular dysfunction, ventricular hypertrophy, myocarditis, viral myocarditis, ECG signs of ventricular hypertrophy;

  - Cardiac valve disorders
    Aortic valve incompetence, cardiac valve disease, mitral valve incompetence, mitral valve prolapse;

  - Other cardiac disorders
    Cardiac failure, cardiac failure congestive, cardiac disorder, cardiotoxicity, cardiovascular disorder, myocardial infarction, pericarditis, pericardial effusion.

- Cardiac adverse event reports with a fatal outcome

The MedDRA terms listed above include only those MedDRA terms which have been reported in atomoxetine spontaneous reports.

In their review, the MAH have estimated reporting rates according to CIOMS guidelines. Given an estimated exposure of 2,233,000 worldwide during the

period covered by the review the events are categorised: common – between 1.1% and 10%; uncommon – between 0.11% and 1.0%; rare – between 0.01% and 0.1%; and very rare – less than 0.01%.

Overall summary of reports of cardiac adverse events 26/11/02-26/11/04

Table 1. Reports of cardiac disorders associated with atomoxetine

MedDRA Preferred Term	Number of reactions	Serious	Fatal
Supraventricular Arrhythmias			
Atrial fibrillation	13	10	0
Atrial flutter	4	3	0
Sinus arrhythmia	1	0	0
Supraventricular arrhythmia	4	3	0
Total	**22**	**16**	**0**
Ventricular arrhythmias			
Cardiac arrest	3	3	0
Cardio-respiratory arrest	1	1	0
Cardiac fibrillation	1	1	0
Ventricular extrasystoles	10	5	0
Ventricular tachycardia	6	5	0
Total	**21**	**15**	**0**
Arrhythmias unclassified			
Arrhythmia	10	1	0
Bradycardia	1	1	0
Cardiac flutter	5	0	0
Extrasystoles	3	0	0
Heart rate abnormal	3	0	0
Heart rate decreased	8	0	0
Heart rate irregular	13	0	0
Total	**43**	**2**	**0**
Tachycardia			
Heart rate increased	374	9	0
Tachycardia	164	32	0
Sinus tachycardia	5	2	0
Total	**543**	**43**	**0**
Cardiac Conduction Disorders			
Atrioventricular block	1	1	0
Atrioventricular block first degree	1	0	0
Atrioventricular block second degree	2	2	0
Bundle Branch Block	1	1	0
Bundle branch block right	3	1	0
Wolff-Parkinson-White syndrome	2	2	0
Total	**10**	**7**	**0**
ECG QT Prolongation			
Electrocardiogram QT prolonged	14	14	0
Electrocardiogram QT corrected prolonged	13	13	0
Total	**27**	**27**	**0**
Other ECG abnormality			
ECG signs of myocardial ischaemia	1	1	0
Electrocardiogram abnormal	4	1	0
Electrocardiogram QRS complex prolonged	1	0	0
Electrocardiogram ST segment abnormal	1	0	0
Electrocardiogram St-T segment abnormal	1	1	0
Electrocardiogram T wave inversion	1	1	0
Total	**9**	**4**	**0**
Mycocardial Disorders			

Cardiomegaly	3	2	1
Cardiomyopathy	3	3	0
Congestive cardiomyopathy	2	2	1
Dilatation atrial	1	0	0
Ventricular dysfunction	2	2	0
Ventricular hypertrophy	1	1	0
ECG signs of ventricular hypertrophy	1	1	0
Myocarditis	1	1	1
Viral myocarditis	1	1	0
Total	**15**	**13**	**3**
Cardiac Valve Disorders			
Aortic valve incompetence	2	1	0
Mitral valve incompetence	4	1	0
Mitral valve prolapse	2	2	0
Cardiac valve disease	2	2	0
Total	**10**	**6**	**0**
Other Cardiac Disorders			
Ateriosclerosis	1	1	1
Cardiac disorder	2	1	0
Cardiac failure	1	1	1
Cardiac failure congestive	1	1	0
Cardiovascular disorder	2	1	0
Cardiotoxicity	1	1	0
Myocardial infarction	2	2	1
Pericarditis	1	1	0
Pericarditis effusion	1	1	0
Total	**12**	**10**	**3**
Total (all cardiac disorders)	**702**	**143**	**9 Reactions (relating to 8 fatal case reports)**

NB the fatal congestive cardiomyopathy and cardiac arrest were reported in the same patient.

4.1 Arrhythmia

Supraventricular arrhythmia

A total of 21 case reports of 22 adverse events of supraventricular arrhythmia were identified from the MAH ClinTrace database for the two year period 26 November 2002 to 26 November 2004. This total excludes reports of sinus tachycardia since these reports will be discussed in the section concerning tachycardia below. The following table provides further information regarding both the adverse events reported and the age distribution of these reports. None of the reports had a fatal outcome.

Table 2. Number of adverse events and Case Reports of Supraventricular Arrhythmias

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Atrial fibrillation	0	0	0	3	7	3	0	13	10
Atrial flutter	0	0	1	0	2	1	0	4	3
Sinus Arrhythmia	0	0	0	1	0	0	0	1	0
Supraventricular	0	1	0	1	0	0	2	4	3

arrhythmia									
Total Events	**0**	**1**	**1**	**5**	**9**	**4**	**2**	**22 Events**	**16 SAEs**
Total Unduplicated Reports	**0**	**1**	**1**	**5**	**8**	**4**	**2**	**21 Reports**	**17* Serious Reports**

* Some cases were serious due to other serious events.

Four of the cases were considered non serious. These were three cases of atrial fibrillation and one of atrial flutter. The remaining seventeen of the twenty-one case reports were considered serious. Adverse events of other cardiac disorders were reported in 9 of the 21 cases and that these events are discussed individually under their relevant categories below.

All except one of the patients were receiving treatment with atomoxetine at the time of onset of the event. In the remaining case, atrial fibrillation was identified 4 days after stopping treatment. One case involved an intentional overdose of atomoxetine and other medications. In cases where dosing information is available (14/21) the daily doses ranged from 18mg to 120mg although in the majority of these reports patients were taking either 40mg (7 cases) or 80mg (4 cases). Excluding the case in which onset of the event occurred after stopping treatment, the time to onset ranged from 1 day to about 1 year in the cases where this information was provided (15/20). In the majority of these cases (10/15) time to onset was within the first 2 months of starting atomoxetine.

Of the 21 reported cases, treatment with atomoxetine was discontinued in 20 cases (including 2 cases in which treatment was rechallenged). The action taken with atomoxetine was unknown in the remaining case. In 14 of the 20 cases in which atomoxetine was discontinued the event had resolved or had improved. These 14 reports include the 2 rechallenge cases, indicating negative rechallenges. However, in table 3.2 of the MAH report, no information is provided with regards to the outcome of one of the rechallenge cases (case #6 involving a [redacted]). Table 3.2 of the MAH report merely indicates that the patient recovered and atomoxetine was rechallenged. Thus, we can only be sure of one negative rechallenge. In 2 cases the reaction was ongoing despite discontinuation of atomoxetine and the outcome was unknown in 4 of the cases in which atomoxetine was discontinued.

The MAH evaluated the 21 cases for risk or confounding factors that may have caused or contributed to supraventricular arrhythmia. The MAH considered that 6 case reports were considered to be clearly confounded due to pre-existing cardiac disorders or arrhythmias (including atrial fibrillation). All of these cases were in adult patients. A further nine cases were deemed to have other possible risk or confounding factors which include multiple other medications, history of hypertension or thyroiditis, and a family history of cardiac disorders. According to the MAH four cases lacked sufficient information for analysis including the only case which involved a child. A further case involving a [redacted] did not provide any apparent risk factors for atrial flutter but the MAH state that since the time to onset was ~5 months and that atomoxetine was restarted after the event resolved suggested that atomoxetine was not likely the causative factor. The final case is the case of intentional overdose of atomoxetine and other medications.

The MAH states that supraventricular arrhythmias were reported very rarely during the two year period covered by this review. It is concluded that most of these reports were confounded and that no direct causal relationship of supraventricular arrhythmia with atomoxetine treatment could be established from the data presented.

Assessor's comments:
The majority of reports of supraventricular arrhythmias occurred in adults (≥18 years). Of note, the most frequently reported supraventricular arrhythmia was atrial fibrillation. All 13 cases of atrial fibrillation occurred in adult patients, the youngest of whom was [redacted] Five of these reports were considered to be confounded due to prior cardiac history (chronic heart failure, atrial fibrillation, coronary artery disease, mitral valve prolapse, ventricular hypertrophy) including the case in the 25-year old (prior atrial fibrillation). The remaining 8 cases were considered by the MAH to be possibly confounded due to concomitant medication, family history of cardiac disorders, history of hypertension, obesity, use of alcohol and caffeine. However, it is noted that the concomitant medications quoted in the reports are not recognised to cause atrial fibrillation themselves (fluticasone, fexofenadine, sertraline, lisinopril, atorvastatin etc) although in the case of lisinopril and atorvastatin these medications are indicative of other potential confounding factors such as an underlying cardiovascular disorder. Atomoxetine was dechallenged in all eight of the possibly confounded cases. Positive dechallenges were reported in 6 of the 8 cases (including one in which treatment with a beta-blocker was initiated), negative dechallenge was reported in one case and the outcome was unknown in the final case.

Two of the 21 reports were reported in children/adolescents. These were 1 case of supraventricular tachycardia in a [redacted] year old patient of unknown sex and 1 case of atrial flutter in a [redacted]. Limited information was available regarding the [redacted]-year old. The [redacted] developed 'arrhythmia' and 'atrial flutter' 5 months after starting atomoxetine 80mg daily. The patient had no pre-existing heart conditions. Atrial flutter is uncommon in children and this patient appears to have no other risk factors, however there was a negative rechallenge in this case. A risk factor for atrial flutter is systemic arterial hypoxia and a causal link between atomoxetine and peripheral ischaemia including Raynaud's phenomenon is likely given its pharmacological actions (see also review of Raynaud's phenomenon associated with atomoxetine in PSUR4). The other three reported cases of atrial flutter concerned adult patients ([redacted] olds) all of whom had apparent risk factors (history of AF and hypertension, history of high cholesterol and concomitant use of cardiovascular medicines, and history of autoimmune thyroiditis with adjustment of thyroid medication just prior to onset of the events).

There were four cases of supraventricular tachycardia (including the case in the [redacted]). Very limited details were available in 3 of the 4 cases. The fourth case occurred in a [redacted] with a history of gouty arthritis who was not taking any concomitant medication. Sinus tachycardia is a recognised adverse effect of atomoxetine and is listed in section 4.8 of the SPC.

The MAH should continue to closely monitor cases of atrial fibrillation and atrial/cardiac flutter.

Ventricular arrhythmia

A total of 21 reports containing 21 adverse events (15 serious) of ventricular arrhythmias were reported during the two year period covered by this cumulative review. The following table provides further information regarding both the adverse events reported and the age distribution of these reports. Three of the reports had a fatal outcome.

Table 3. Number of adverse events and Case Reports of Ventricular Arrhythmias

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Cardiac arrest	0	0	2	0	1	0	0	3	3
Cardio-respiratory arrest	0	1	0	0	0	0	0	1	1
Cardiac fibrillation	0	0	0	0	0	0	1	1	1
Ventricular extrasystoles	1	4	3	1	1	0	0	10	5
Ventricular tachycardia	0	0	2	1	2	1	0	6	5
Total Events	**1**	**5**	**7**	**2**	**4**	**1**	**1**	**21 Events**	**15 SAEs**
Total Unduplicated Reports	**1**	**5**	**7**	**2**	**4**	**1**	**1**	**21 Reports**	**15 Serious Reports**

Adverse events relating to other cardiac disorders were reported in 10 of the 21 case reports. These adverse events are discussed separately in their relevant categories. Other serious adverse events reported in these cases include angioneurotic oedema, chest pain, suicide attempt, convulsion, loss of consciousness, life support, anoxic encephalopathy, brain death, sudden death, hepatitis acute and hepatic enzymes increased.

All patients were taking atomoxetine at the time of onset of the events. One of the cases of ventricular tachycardia involved intentional ingestion/overdose of atomoxetine, narcotics and other drugs. Excluding this overdose case, in cases where dosing information is available (16/20) the daily doses ranged from 20mg to 100mg although in the majority of these reports patients were taking 40mg (6 cases), 60mg (4 cases) or 80mg (3 cases). The time to onset ranged from 1 day to about 15 months in the cases where this information was provided (17/20). Time to onset was within the first 2 months of starting atomoxetine for 11 of these 20 cases.

Three cases of ventricular arrhythmia had a fatal outcome. These three cases involved 2 young males and one adult female. The causes of death are listed as anoxic encephalopathy due to cardiac arrest, sudden unexplained death in childhood, and congestive cardiomyopathy. Fatal cases are discussed in further detail in section 4.7 below.

Of the 18 non-fatal cases, treatment with atomoxetine was discontinued in 15 cases. In 10 of the 15 cases in which atomoxetine was discontinued the event had resolved or had improved. In 1 case the reaction was ongoing despite discontinuation of

atomoxetine and the outcome was unknown in 4 of the cases in which atomoxetine was discontinued. Treatment with atomoxetine was rechallenged in another case. The outcome of the rechallenge is unknown. The action taken with atomoxetine and the outcome of the events were unknown in the remaining 2 cases.

The MAH evaluated the 21 cases for risk or confounding factors that may have caused or contributed to ventricular arrhythmia. The MAH considered that 4 case reports were considered to be clearly confounded due to pre-existing cardiac disorders or arrhythmias. A further 11 cases were deemed to have other possible risk or confounding factors which include multiple other medications, or a family history of cardiac disorders. According to the MAH four cases lacked sufficient information for analysis for the aetiology of the events. A further case involving a [redacted] old patient did not provide any apparent risk factors for ventricular extrasystoles. The final case is the case of intentional overdose of atomoxetine and other medications.

The MAH states that ventricular arrhythmias were reported very rarely during the two year period covered by this review. The MAH concludes that most of these reports were confounded and that no direct causal relationship of ventricular arrhythmia with atomoxetine treatment could be established from the data presented.

Assessor's comments
The majority of the cases of ventricular arrhythmias occurred in children and adolescents under the age of 18 years (13 reports in children and adolescents Vs. 7 reports in adults).

The most frequently reported ventricular arrhythmia was ventricular extrasystoles (10 out of 21 reports) and the majority of these cases concerned children and adolescents (8 out of 10 reports). One of the 10 cases was considered to be clearly confounded due to prior cardiac murmur and use of amphetamine/dextroamphetamine. A further 6 cases were considered by the MAH to be possibly confounded due to family history of cardiovascular disorders (including premature ventricular contractions), or concomitant medication (montelukast, budesonide, loratadine and fluticasone, methylphenidate). There were 2 cases in which the role of atomoxetine was 'indeterminate' and one case which was not apparently confounded. However, limited information and varying times to onset in these three cases makes causality assessment difficult. Ventricular extrasystoles are relatively common and are usually of no clinical significance. None of the reported cases of ventricular extrasystoles were associated with possible serious consequences such as ventricular fibrillation.

There were 6 reported cases of ventricular tachycardia (VT), four of which occurred in adults over the age of 18 years. Two of the six cases were considered to be clearly confounded (history of AF and ventricular hypertrophy, progressive dilated cardiomyopahty due to congential disorder) and a further three cases were considered to be possibly confounded (pre-existing sleep apnoea and use of morphine, concomitant venlafaxine, doxepine and fexofenadine, and history of mild hypertension). The sixth and final case involved a [redacted] with a history of depression who took an overdose of atomoxetine, a narcotic and other unspecified substances in a suicide attempt. The two cases which occurred in children are the mixed overdose case and the clearly confounded case in which the [redacted] old patient

had pre-existing progressive dilated cardiomyopathy due to congential disorder. Three of the cases of ventricular tachycardia were associated with atrial fibrillation although these cases were considered to be clearly or possibly confounded. The MAH should continue to closely monitor cases of ventricular tachycardia.

There were three cases of cardiac arrest, two of which were fatal and one case of cardio-respiratory arrest which was fatal. The three fatal cases are discussed in more detail in section 4.7 of this report. The non-fatal cardiac arrest concerned a [redacted] patient who reportedly recovered after dechallenge of atomoxetine however further details concerning the case are not available (the reporter was a friend of the patient and refused to provide further information).

Arrhythmia unclassified

A total of 42 reports containing 43 adverse events (2 serious) of 'rate and rhythm disorders NEC' (MedDRA HLGT), 'heart rate abnormal', 'heart rate decreased', and 'heart rate irregular' (MedDRA preferred terms) were reported during the two year period covered by this cumulative review. Reports of tachycardia are discussed in section 4.2 below. The following table provides further information regarding both the adverse events reported and the age distribution of these reports. None of the reports had a fatal outcome.

Table 4. Number of adverse events and Case Reports of Arrhythmia unspecified

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Arrhythmia	0	4	2	1	3	0	0	10	1
Bradycardia	0	0	0	1	0	0	0	1	1
Cardiac flutter	0	0	1	1	1	0	2	5	0
Extrasystoles	0	0	0	2	1	0	0	3	0
Heart rate abnormal	0	0	1	1	0	0	1	3	0
Heart rate decreased	0	4	1	1	2	0	0	8	0
Heart rate irregular	0	4	1	6	0	1	1	13	0
Total Events	**0**	**12**	**6**	**13**	**7**	**1**	**4**	**43 Events**	**2 SAEs**
Total Unduplicated Reports	**0**	**11**	**6**	**13**	**7**	**1**	**4**	**42 Reports**	**7* Serious Reports**

* Some cases were considered serious due to other serious adverse events

The two serious cardiac adverse events were 1 case of 'bradycardia' with loss of consciousness and 1 case of 'arrhythmia'. The remaining 5 cases were deemed serious due to serious events of 'loss of consciousness' (2), atrial fibrillation (1), 'ventricular tachycardia', 'akinesia' and 'syncope'. A total of 12 of the 42 cases contained other cardiac adverse events and these are discussed in their relevant sections.

All patients were taking a therapeutic dose of atomoxetine at the time of onset of the events except one patient who took twice the prescribed dose for 25 days and was found to have an irregular heart beat. None of the cases had a fatal outcome. The MAH states that 'the events reportedly resolved when atomoxetine was discontinued in some cases, and was continued in others' and that 'some cases provided limited information with no event outcomes'.

The MAH has only provided details for the two serious cardiac events which are categorised as 'arrhythmia unspecified'. The first serious case is that of a [redacted] who was taking an unknown dose of atomoxetine and developed loss of consciousness, bradycardia, skin discolouration, nausea, headache and dizziness. The time to onset was reportedly <1month. Heart rate was about 30bpm. Atomoxetine was discontinued and the patient recovered. The patient had no history of cardiac disorders. The second serious case report is that of a [redacted] who was receiving atomoxetine 25mg for an unknown period of time and developed arrhythmia. Atomoxetine was continued at 18mg daily and the outcome of the event is unknown. The patient was not receiving any concomitant medication. [redacted] medical history is unknown.

No details are provided for the remaining 40 reports and the MAH has not presented an evaluation of these 40 cases for risk or confounding factors.

In their summary the MAH states that adverse events of arrhythmias including bradycardia were considered very rarely reported during the reporting period.

Assessor's comments:
The most frequently reported unclassified arrhythmias were 'heart rate irregular' (13/43), 'arrhythmia' (10/43) and 'heart rate decreased' (8/43). More reported cases of unclassified arrhythmias concerned adult patients over the age of 18 years than child or adolescent patients (21 adults Vs 18 children and adolescents).

Two case reports were considered to be serious. These were a case of bradycardia, loss of consciousness, skin discolouration, nausea, headache and dizziness in a [redacted] and a case of arrhythmia in a [redacted]. Limited details are available for the serious case of arrhythmia. The case of bradycardia is the first to be reported for atomoxetine however there are a further 8 cases of 'heart rate decreased' for which no further details are provided by the MAH. These cases are interesting given that atomoxetine is recognised to cause tachycardia. The serious case of bradycardia presented appears to be apparently unconfounded with an onset on less than one month and a positive dechallenge. Another interesting point concerning this case of bradycardia is that the patient also experienced skin discoloration which could potentially be a peripheral cyanosis although no further details regarding this are available.

The MAH has not provided case details or a discussion of causality for the 40 non-serious case reports of unclassified arrhythmia, thus further analysis of these cases in this assessment report is not possible. The MAH should be requested to provide case details for the 40 non-serious cases of unclassified arrhythmias.

4.2 Tachycardia

As a direct consequence of its mechanism of action (selective inhibition of noradrenaline reuptake) atomoxetine is expected to increase heart rate. Tachycardia is listed in section 4.8 (side effects) of the SPC for atomoxetine.

A total of 542 case reports of 543 adverse events (43 serious) coding to the MedDRA preferred terms 'tachycardia', 'sinus tachycardia' and 'heart rate increased' were reported during the 2 year period covered by this cumulative review. None of the reports had a fatal outcome.

Table 5. Number of adverse events and Case Reports of Tachycardia

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Heart rate increased	3	134	71	75	52	4	35	374	9
Tachycardia	1	72	35	21	11	3	21	164	32
Sinus tachycardia	0	1	2	2	0	0	0	5	2
Total Events	**4**	**207**	**108**	**98**	**63**	**7**	**56**	**543 Events**	**43 SAEs**
Total Unduplicated Reports	**4**	**206**	**108**	**98**	**63**	**7**	**56**	**542 Reports**	**69* Serious Reports**

* Some cases were serious due to other serious events

In most of the cases patients were taking therapeutic doses of atomoxetine at the time of onset of tachycardia. However the MAH state that in 32 cases the patients were prescribed a dose that exceeded the maximum recommended dose according to the labelling. A further 14 cases involved intentional or accidental overdoses of atomoxetine from 60mg to 1200mg.

Of the 69 serious reports of tachycardia, 15 were associated with atomoxetine overdose (intentional, accidental or prescribed). The MAH states that 27 of the 69 cases contained serious events of tachycardia, sinus tachycardia or heart rate increased, a further 16 cases contained serious events of tachycardia along with other serious adverse events and there were 26 reports in which there were other serious events reported but the tachycardia was not considered serious. A total of 36 adverse events relating to other cardiac disorders were reported in 27 cases. These adverse events are discussed separately in their relevant categories.

The most frequently reported adverse events reported other than tachycardia in the 542 cases include: dizziness (58), blood pressure increased (57), insomnia (51), nausea (50), chest pain (43), feeling abnormal (43), fatigue (42), somnolence (36), headache (36), hyperhidrosis (35), anxiety (34), dyspnoea (32), decreased appetite (27), palpitations (24), drug ineffective (22), and dry mouth (21). The MAH states that the serious adverse events in these cases included loss of consciousness (4), syncope (4), hypertension (4), blood pressure increased (4), chest pain (3), and suicide attempt (2).

According to the MAH's report, in cases where the outcome was provided most of the patients recovered either on withdrawal of atomoxetine or on continuing treatment with atomoxetine.

The MAH has provided no further details of these reports.

The MAH states that tachycardia were reported very rarely (reporting rate 0.02%) during the two year period covered by this review.

Assessor's comments: Atomoxetine affects adrenergic tone and is recognised to cause sinus tachycardia. The EU SmPC for atomoxetine lists sinus tachycardia in the side effects section.

4.3 Cardiac Conduction Disorders

Cardiac Conduction Disorders

The MAH used the MedDRA HLGT term 'Cardiac conduction disorders' to search their ClinTrace database for reports of cardiac conduction disorders associated with atomoxetine. A total of 10 reports of 10 reactions (7 serious) of cardiac conduction disorders were reported during the period 26 November 2002 – 26 November 2004. The table below provides further information on the events reported and the age distribution of the reports.

Table 6. Number of Adverse Events and Case Reports of Cardiac Conduction Disorders

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Atrioventricular block	0	0	0	0	0	1	0	1	1
Atrioventricular block first degree	0	1	0	0	0	0	0	1	0
Atrioventricular block second degree	0	1	1	0	0	0	0	2	2
Bundle branch block	0	0	0	1	0	0	0	1	1
Bundle branch block right	0	1	1	0	1	0	0	3	1
Wolff-Parkinson-White syndrome	0	2	0	0	0	0	0	2	2
Total Events	**0**	**5**	**2**	**1**	**1**	**1**	**0**	**10 Events**	**7 SAEs**
Total Unduplicated Reports	**0**	**5**	**2**	**1**	**1**	**1**	**0**	**10 Reports**	**7 Serious Reports**

Three adverse event reports were considered to be non-serious. The first of the non-serious cases was atrioventricular block first degree and nausea in an [redacted] who had no relevant history. The patient had received atomoxetine 25mg for 4 days. ECG was borderline normal/abnormal. Atomoxetine was continued. The patient is

asymptomatic. The second of the non-serious case is an [redacted] who developed bundle branch block right after several days of treatment with atomoxetine 25mg. The patient had no relevant history. Atomoxetine was continued and the patient was asymptomatic. According to the MAH the cardiologist stated that the event was not due to atomoxetine. The final non-serious case of cardiac conduction disorder is a case of bundle branch block right, bone pain, pain, headache, feeling abnormal and dyspnoea in a [redacted]. The patient had received atomoxetine 25mg for 3 days. The event resolved after withdrawal of atomoxetine treatment. The MAH states that the ECG was performed when taking atomoxetine for a duration of 3 days, amphetamine/dextroamphetamine, aspirin, unspecified anti-allergic medicine and chlorpheniramine.

Other cardiac disorders were reported in three of the ten reports and these are discussed in the relevant sections of this report. Other serious adverse events reported in these cases included blood pressure increased and aggression.

All of the patients were receiving treatment with atomoxetine at the time of onset of the events. Dosing information is available for 8 of the 10 case reports and the daily doses in these cases ranged from 25mg to 80mg. Time to onset (information available in 9 cases) ranged from 3 days to about 5 months.

None of the case reports had a fatal outcome. Treatment with atomoxetine was discontinued in 6 cases and in all 6 cases the patient recovered. A further two patients underwent a negative rechallenge with atomoxetine. Two patients were continuing on treatment with atomoxetine and were asymptomatic, however no information is provided as to whether the observed ECG abnormalities remained.

The MAH evaluated the 10 cases for risk or confounding factors. The MAH considered that 6 case reports were clearly confounded. In these cases the confounding factors were considered to be: prior history of atrial fibrillation in a [redacted] who developed atrioventricular block, atrial flutter, blood pressure increased, mitral valve incompetence, chest discomfort, pain in extremity, electrocardiogram ST segment abnormal; a diagnosis of congential Wolff-Parkinson-White syndrome in a [redacted] patient who reported congestive cardiomyopathy, WPW syndrome, heart murmur, weight decreased and fatigue; a history of Dandy-Walker syndrome, enlarged heart and illegal substance use in a [redacted] who reported bundle branch block and aggression; a family history of supraventricular tachycardia and diagnosis of congential WPW syndrome in a [redacted] who reported WPW syndrome and mitral valve incompetence; a prior history of second degree heart block in a [redacted] who reported second degree heart block less than one month after starting atomoxetine; and a history of first degree heart block in a [redacted] who reported atrioventricular block second degree.

A further two cases were deemed to have other possible risk or confounding factors. The first of these cases involved a [redacted] who was also taking simvastatin and therefore appeared to be at high risk of cardiovascular disorder. There was a negative rechallenge of atomoxetine in this case. The second case involved a [redacted] who had no prior history of cardiac disorders who was found to have an abnormal ECG when taking atomoxetine for 3 days along with several other

medications (amphetamine/dextroamphetamine, chlorpheniramine, aspirin). [redacted] ECG had normalised after discontinuation of atomoxetine.

According to the MAH in the remaining 2 cases causality was considered by the MAH to be 'indeterminate'. These cases involved two [redacted] who had no baseline ECG and developed borderline abnormalities of cardiac conduction (atrioventricular block first degree and bundle branch block right). Both patients continued on treatment as both were asymptomatic, however there is no information provided with regards to outcome of the observed ECG changes.

The MAH states that cardiac conduction disorders were reported very rarely during the two year period covered by this review and the reporting rate was even less than that seen in the general population. The MAH concluded that no direct causal relationship of cardiac conduction with atomoxetine treatment could be established from the data presented and propose to continue to closely monitor cardiac conduction disorders.

Assessor's comments:
The majority of the reports of cardiac conduction disorders occurred in children and adolescents under the age of 18 years (7 out of 10 reports). However, two of the reports in [redacted] were of Wolff-Parkinson-White Syndrome which is a congenital cardiac conduction disorder. The remaining reports in children and adolescents were of atrioventricular block 1st degree (1), atrioventricular block 2nd degree (2) and right bundle branch block (2). Two of the reports in [redacted] were confounded by a prior history of second degree heart block and first degree heart block. One report of right bundle branch block in a [redacted] was considered possibly confounded due to concomitant medication (amphetamine/ dextroamphetamine, aspirin, unspecified anti-allergic medicine and chlorpheniramine). The remaining two cases in the two [redacted] with first degree AV block and right bundle branch block were considered 'indeterminate'.

In the three cases involving adult patients, there were clear confounding factors in two cases and possible confounding factors in the third case (concomitant simvastatin, alendronate and estrogens, negative atomoxetine rechallenge).

At present there is not enough evidence to suggest a causal relationship between atomoxetine and AV block or bundle branch block. Atomoxetine is recognised to cause tachycardia and thus it would not be expected to cause conduction disorders such as AV block or bundle branch block. However, there are 9 reported cases of bradycardia and decreased heart rate (discussed in the section above) which are more likely to be associated with AV block or bundle branch block. The MAH should continue to closely monitor such events.

4.4 ECG QT Prolongation

The MAH used the MedDRA preferred terms 'electrocardiogram QT interval prolonged' and 'electrocardiogram QT corrected interval prolonged' to search the ClinTrace data base for reports relating to prolongation of the QT interval associated with the use of atomoxetine. The database was searched for the 2 year period 26 November 2002 – 26 November 2004.

A total of 27 case reports (of 27 reactions) relating to QT interval prolongation were identified. All cases were considered serious. There were no reported adverse events coding to 'long QT syndrome' or 'torsades de pointes' on the database for atomoxetine. An additional text string search using "QT" of the case narrative field of all atomoxetine reports was performed. No additional cases were identified. The table below provides further information on the reported events and the age distribution.

Table 7. Number of Adverse Events and Case Reports of ECG QT Prolongation

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Electrocardiogram QT interval prolonged	0	9	2	3	0	0	0	14	14
Electrocardiogram QT corrected interval prolonged	0	6	5	1	1	0	0	13	13
Total Events	**0**	**15**	**7**	**4**	**1**	**0**	**0**	**27 Events**	**27 SAEs**
Total Unduplicated Reports	**0**	**15**	**7**	**4**	**1**	**0**	**0**	**27 Reports**	**27 Serious Reports**

A value of corrected QT interval was provided in 22 of the 27 reports (that is the QTc interval as reported). In the 5 remaining cases a value for QT or QTc interval is not provided. It is noted that corrected QT interval is generally calculated from the value of the QT interval and ventricular rate using Bazett's correction method (QTcB). However, Bazett's correction method tends to overestimate QTc interval length where the heart rate is increased. It is also noted by the MAH that 1) the majority of the reports of QT/QTc interval prolongation occurred in young patients who tend to have higher heart rates than adults; 2) atomoxetine is a drug which is known to cause tachycardia; and 3) tachycardia or increased heart rate was reported in nine of the 27 case reports and a ventricular rate of 99bpm or more was reported in a further 4 reports. Thus, where values for the QT interval and ventricular rate are provided (12/22 cases), the MAH has calculated the corrected QT interval using Fridericia correction method (QTcF) and the data correction method (QTcD).

The MAH states that the upper limit of normal length of QTc interval is currently described as 450 milliseconds. QTc intervals ≥ 500msec or QTc interval changes ≥ 60sec from baseline are considered medically significant due to increased risk of torsades de pointes. The MAH categorised case reports of QT/QTc interval prolongation based on QTc interval values provided. Table 8 below summarises the MAH categorisation of these reports.

Table 8

QTc (msec)	>500	<500, >450	≤450	Unknown	Total
No. of cases	4	10	8	5	27

In three of the four cases in which the QTc interval was >500msec the QTc interval was 60msec greater than baseline. In one of the ten cases in which the QTc interval was <500 - >450 msec the QTc interval was 60msec greater than baseline. Thus,

according to the MAHs definition of medically significant QTc interval prolongation given above, a total of 5 reports involved medially significant QTc interval prolongation. These cases are summarised as follows:

Case [redacted] is that of a [redacted] who received atomoxetine 40mg for 2 days. [redacted] QTc interval (as stated by the reporter) was 526 msec. Atomoxetine was dechallenged and the event resolved. The patient had a history of hypokalaemia and was taking concomitant potassium.

Case [redacted] is that of a [redacted] who took an intentional overdose of 1200mg atomoxetine alone. [redacted] QTc interval was reportedly 607msec (QT interval = 416, Ventricular rate = 128, QTcF = 536, and QTcD = 559) and he also experienced convulsions. The patient was taking concomitant risperidone, bupropion and alprazolam. The patient recovered.

Case [redacted] involved a [redacted] who took an intentional overdose of 1200mg atomoxetine, 36000mg oxcarbazepine and 9000mg quetiapine. [redacted] QTc interval was reportedly 510msec (QT interval = 397, Ventricular rate = 99, QTcF = 469, and QTcD = 483). In this case QTc values were provided by the reporter, but not the QTcB. The patient also experienced depressed level of consciousness followed by aggression and agitation with severe hallucinations after the overdose. The patient recovered. Urine test was positive for marijuana.

Case [redacted] involved a [redacted] patient who took one dose of atomoxetine 40mg and was reported to have a QTc interval of 480msec (QT interval = 404, Ventricular rate = 85, QTcF = 454, and QTcD = 463). Atomoxetine was dechallenged and the event resolved. The patient was taking a first dose of bupropion with atomoxetine and sulfamethoxazole/trimethorpim and antibiotics.

Case [redacted] is that of a [redacted] who took atomoxetine 60mg for 'months'. [redacted] QTc interval was reported to be 514 during a treadmill test. Treatment with atomoxetine was discontinued but the outcome is unknown. The patient has a prior history of borderline QT prolongation and a family history of unspecified cardiac disorders. [redacted] was taking piruterol and fluticasone concomitantly.

The MAH considers cases [redacted] and [redacted] to be clearly confounded. Case [redacted] was considered to be possibly confounded. Cases [redacted] and [redacted] were overdose cases and were considered by the MAH to be situations that do not represent the pharmacological properties of atomoxetine within the normal therapeutic dose range.

Of the 27 reports of QT/QTc interval prolongation, there were two reports in which the patients had stopped atomoxetine treatment 2 weeks before the QT/QTc interval prolongation was detected. Four more reports involved overdose (2 prescribed, 2 intentional) and are discussed above. The MAH considers that these overdose cases are unlikely to be related to atomoxetine since these cases are not representative of atomoxetine at therapeutic doses.

In the remaining 21 reports, the daily dose of atomoxetine was provided in 17 cases and ranged from 25mg to 100mg and the duration of treatment, where provided (13/21 cases), ranged from 1 day to about 5 months.

The event of QTc interval prolongation was the only adverse event reported in 11 of the 27 cases. Other cardiac disorders were reported in 10 cases and are discussed in the relevant sections of this report. Other serious adverse events reported in these cases of QTc interval prolongation include drug interaction, angioneurotic oedema, serotonin syndrome, convulsion, suicide attempt, aggression, agitation, abnormal behaviour, hallucination auditory, hallucination visual, depressed level of consciousness, and loss of consciousness.

None of the reported events of QTc interval prolongation resulted in a fatal outcome and according to the MAH no serious arrhythmias were reported with the events of QT/QTc interval prolongation. Treatment with atomoxetine was discontinued in 18 of the 27 reports. In 15 of these cases the patient recovered after discontinuation of treatment and the outcome was unknown in the remaining three cases. Treatment with atomoxetine was continued in 4 cases and in all 4 cases the events continued. Atomoxetine was rechallenged in 2 cases, the events resolved in one of these cases and the outcome was unknown in the other. The action taken with atomoxetine and the outcome of the event were unknown in the remaining 3 of the 27 cases.

The MAH evaluated the 27 cases for risk or confounding factors that may have caused or contributed to QT/QTc interval prolongation in these cases. Four cases were not considered by the MAH to represent the pharmacological properties of atomoxetine at therapeutic doses since they involved overdoses (2 intentional and 2 prescribed). These cases are discussed above. There were also 2 cases in which the QTc interval prolongation was identified about 2 weeks after atomoxetine was discontinued. A further 4 cases were considered to have clear confounding/risk factors (prior history of QTc prolongation (2 cases), possible hypokalaemia (1 case), and pre-existing cardiac disorder (1 case)). Eleven cases were considered by the MAH to be possibly confounded due to concomitant medication. However, QTC interval prolongation is not listed as a recognised adverse effect at therapeutic doses of the medication listed in 7 of these cases. There were four cases in which the relationship between atomoxetine and the reported events was considered to be 'indeterminate' due to lack of information available, however in two of these cases a positive dechallenge of atomoxetine was observed.

There were a further 2 cases in which no apparent confounding factors were presented. Both male children experienced borderline QTc prolongation (446msec and 462msec) less than 2 months after starting atomoxetine 25mg. Both continued on treatment and the events continued. These reports were reported by the same reporter who also reported 2 further similar cases involving young male patients who developed QTc intervals of 448 and 445msec less than 2 months after starting atomoxetine 25mg. These two cases were considered to be possibly confounded by concomitant medication by the MAH (fluoxetine and bupropion) however neither concomitant medication is recognised to cause QTc prolongation at therapeutic doses. These two cases are included in the eleven possibly confounded cases discussed in the paragraph above.

The table below provides details of the MAH's aetiological analysis of Adverse Events of ECG QTc prolongation.

Table 9 Aetiological analysis of Adverse Events of ECG QTc Prolongation

Etiological Classes	Clearly confounded	Possible confounded	Indeterminate	Not apparently confounded	ATX overdose	Not during ATX treatment	Total
QTc >500	2	0	0	0	2	0	4
QTc <500, >450	0	4	1	1	2	2	10
QTc <450	1	6	0	1	0	0	8
QTc unknown	1	1	3	0	0	0	5
Total	4	11	4	2	4	2	27

The MAH concludes that QT/QTc interval prolongation was very rarely reported and that therapeutic doses of atomoxetine do not appear to be associated with clinically significant QTc prolongation which is consistent with preclinical and clinical trial data. The MAH considers that changes to the SPC and/or labelling are un-necessary and propose to continue to closely monitor adverse events relating to delayed myocardial repolarisation associated with atomoxetine.

Assessor's comments:
The majority of the reports of QT/QTc interval prolongation were reported in children and adolescents under the age of 18 years (22 out of 27 reports), however this may merely reflect the prescribing patterns of the drug.

Five of the 27 cases involved medically significant QTc interval prolongation (QTc>500msec or QTc change >60msec from baseline). Two of these reports were considered to be clearly confounded (history of hypokalaemia and concurrent treatment with potassium, and prior history of borderline QT interval prolongation) and one was considered to be possibly confounded (taking 1st dose of bupropion with atomoxetine, sulfamethoxazole/trimethoprim and other unspecified antibiotics). The remaining two cases occurred following overdoses, one of which was a mixed overdose, the other involved an overdose of atomoxetine alone.

The case of overdose in which the only drug taken in overdose was atomoxetine (case US_040102075) has been excluded from further discussion by the MAH who states that this case does not represent the pharmacological actions of atomoxetine at therapeutic doses. However, this was an overdose of atomoxetine alone and thus does not rule out a causal association with the drug. The overdose case may be indicative of a dose response and may warrant updating of the overdose section of the SPC. Two further cases may also indicate a dose response effect of atomoxetine on QT interval prolongation. In these two reports the MAH states that the events of QT interval prolongation occurred whilst the patients were receiving a prescribed daily dose of atomoxetine that exceeded the maximum recommended dose. These events were categorised as overdose cases by the MAH and were not considered to represent the properties of the drug at therapeutic doses and thus were not considered further. The first of these cases involves a [redacted] who had a QTc interval of 480msec (QT interval = 350, VR = 113, QTcF = 432, QTcD = 448) after <2 months treatment with atomoxetine 120mg (2.3mg/kg daily). Atomoxetine was dechallenged

and the event resolved. No possible risk or confounding factors are discussed by the MAH for this case. The second case involves a [redacted] whose QTc interval was reported to be 456msec (QT interval = 330, VR = 115, QTcF = 409, QTcD = 425) an unknown time after starting atomoxetine 40mg (2.1mg/kg daily). Again there was a positive dechallenge of atomoxetine and no possible risk or confounding factors are discussed/provided by the MAH. These cases would therefore seem to add some support to possibility of QT interval prolongation at higher doses/overdoses of the drug.

There are two cases in which the role of atomoxetine can not be completely excluded at therapeutic doses. Two male children experienced borderline QTc prolongation (446msec and 462msec) less than 2 months after starting atomoxetine 25mg. Both continued on treatment and the events continued. These reports were reported by the same reporter who also reported 2 further similar cases involving young male patients who developed QTc intervals of 448 and 445msec less than 2 months after starting atomoxetine 25mg. The MAH have categorised these 2 further cases as possibly confounded due to concomitant medication (bupropion and fluoxetine). However, neither bupropion nor fluoxetine are recognised to cause QT interval prolongation at therapeutic doses.

The data suggest that atomoxetine may be associated with prolongation of QTc interval in cases of overdose. There are a further two cases of borderline prolongation of the QTc interval at therapeutic doses in which no other alternative causes could be identified. In addition there are at least 7 other cases in which (despite concomitant medication) the role of atomoxetine can not be excluded. Furthermore, in eighteen of the cases in which atomoxetine was discontinued, 15 of the patients recovered after drug withdrawal and the outcome was unknown in the remaining three cases.

4.5 Other ECG Abnormality

In this section, the MAH have included all adverse events which code to the MedDRA preferred terms in the MedDRA HLT ECG investigations, excluding electrocardiogram QT prolonged and electrocardiogram QT corrected prolonged which have been discussed in the section above.

A total of 10 adverse events were identified for the period 26 November 2002 – 26 November 2004. One of these adverse event reports 'electrocardiogram abnormal' was also coded to the preferred term 'ECG signs of ventricular hypertrophy' and is discussed in myocardial disorders below. It is not discussed further in this section of the report. Further details of the remaining nine reports together with the age distribution of the reports are provided in the table below.

Table 10. Number of Adverse Events and Case Reports of Other ECG Abnormal

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
ECG signs of myocardial ischaemia	0	0	0	0	1	0	0	1	1

Electrocardiogram abnormal	0	1	1	2	0	0	0	4	1
Ele1ctrocardiogram QRS complex prolonged	0	0	1	0	0	0	0	1	0
Electrocardiogram ST segment elevated	0	0	0	0	0	1	0	1	0
Electrocardiogram ST-T segment abnormal	0	0	0	1	0	0	0	1	1
Electrocardiogram T wave inversion	0	0	1	0	0	0	0	1	1
Total Events	**0**	**1**	**3**	**3**	**1**	**1**	**0**	**9 Events**	**4 SAEs**
Total Unduplicated Reports	**0**	**1**	**3**	**3**	**1**	**1**	**0**	**9 Reports**	**6* Serious Reports**

* Some cases were considered serious due to other serious events

Three of the cases were considered to be non-serious. The first of the non-serious cases involved a [redacted] who developed chest pain, heart rate increased, hypoaesthesia, electrocardiogram abnormal and anxiety after receiving atomoxetine 40mg for less than 2 months. The patient has a history of depression. The patient recovered and atomoxetine was re-challenged. According to the MAH no evidence of cardiac abnormality was found and the cardiologist suggested that the events were possibly related to anxiety. The second of the non-serious cases involves a [redacted] who developed palpitations, electrocardiogram abnormal, headache, insomnia, disorientation and anger whilst taking 10mg atomoxetine with kava kava. A drug interaction was suspected. Atomoxetine was continued and the event resolved when kava kava was discontinued. The third and final non-serious case involves a 12-year old patient of unknown sex who developed electrocardiogram abnormal after taking an unknown dose of atomoxetine for an unknown duration. The events recovered when atomoxetine was de-challenged. The patient had a history of heart surgery to fix an unspecified abnormality.

Adverse events relating to other cardiac disorders were reported in 6 of the nine reports and these events are discussed in the relevant sections of this report.

Other serious adverse events were reported in 6 cases and these included reports of blood pressure increased, serotonin syndrome, suicide attempt, convulsion, loss of consciousness, life support, dizziness, chest pain, headache, flushing, hypertension, troponin increased, hepatitis B, and dyspnoea.

All except one of the reported events occurred whilst the patient was receiving treatment with atomoxetine. This patient intentionally took an unknown amount of atomoxetine together with narcotics and other drugs. Out of the remaining eight cases, dosing details were available for 7 cases. The daily dose ranged from 10 to 120mg. Details regarding the duration of treatment were available in 5 cases and this ranged from 2 days to approximately 4 months.

None of the reported cases of 'other ECG abnormalities' resulted in a fatal outcome. In five cases treatment with atomoxetine was discontinued and in all of these five

cases the patient recovered. Two patients continued on treatment with atomoxetine and the events had resolved in both cases. Treatment with atomoxetine was rechallenged in a further two cases and in both cases the patients were reported to have recovered.

The MAH evaluated the 13 cases for risk or confounding factors that may have caused or contributed to the reported 'other ECG abnormalities'. The MAH considered that 4 case reports were clearly confounded. In these cases the confounding factors were reported to be pre-existing cardiac disorders in two cases (atrial fibrillation in a patient who developed AV block, atrial flutter, increased BP, increased HR, mitral valve incompetence and ECG ST segment abnormal and a prior history of heart surgery in a patient who reported electrocardiogram abnormal); and a positive de-challenge of other drugs whilst treatment with atomoxetine was continued in two cases.

Three cases were considered by the MAH to be possibly confounded. Two of these were considered to be possibly confounded due to prior history (history of high cholesterol in a patient who developed dizziness, HR increased, AF, atrial flutter, ECG signs of myocardial ischaemia and a history of benign positional vertigo and drug abuse in a patient who developed electrocardiogram abnormal with hepatitis B, increased liver enzymes, urticaria, pruritus, vomiting, nausea, confusional state and dyspnoea). The third case involved a [redacted] patient who developed serotonin syndrome with tachycardia, ECG QT prolonged, ECG ST-T segment abnormal, nightmares, anxiety and dyskinesia after 2 weeks of treatment with atomoxetine 80mg. The patient was also taking sertraline. The patient recovered and atomoxetine was re-challenged (negative re-challenge).

One case was considered to have 'indeterminate' aetiology by the MAH. This case involved a [redacted] patient who reported ECG abnormal following chest pain and heart rate increased. The MAH state that it is not clear whether the ECG was taken prior to or after discontinuation of atomoxetine. Cardiac consultation following recovery did not show any evidence of cardiac abnormality and it is reported that the cardiologist suggested that the events were due to anxiety attacks.

The final case involves [redacted] who took an overdose of atomoxetine together with narcotics and other drugs in a suicide attempt. The reported cardiac events in this overdose case were ventricular tachycardia and electrocardiogram QRS complex prolonged. The patient had a history of depression.

The MAH states that adverse events relating to other ECG abnormalities were very rarely reported and that many of them were considered to be confounded. The MAH concludes that a causal relationship between atomoxetine and the reported adverse events could not be established.

Assessor's comments:
The most frequently reported other ECG abnormality was 'Electrocardiogram abnormal' (4 out of 9 cases). Four reports involved children or adolescents under the age of 18 years.

Three of the cases of electrocardiogram abnormal were considered to be clearly

(positive dechallege of kava kava and prior history of heart surgery) or possibly confounded (concomitant trazodone and lithium). The fourth case was considered 'indeterminate' and was considered likely due to anxiety by the reporter.

The other ECG abnormalities reported were single cases of each reported event and the majority involved concomitant medication, overdose or other possibly confounding factors.

4.6 Other Cardiac Disorders

In this section the MAH discusses cardiac adverse events related to pathologic structural changes including myocardial disorders, cardiac valve disorders and other unclassified disorders.

Myocardial Disorders

The MAH searched their ClinTrace database for myocardial disorders using the MedDRA HLGT 'Myocardial disorders' and the 2 MedDRA preferred terms 'ECG signs of ventricular hypertrophy' and 'viral myocarditis'.

A total of 13 case reports of 15 adverse events (13 serious adverse events) of myocardial disorders were identified in the MAH ClinTrace database for the period 26 November 2002 to 26 November 2004. Three of the reports had a fatal outcome. The following table provides further information regarding both the adverse events reported and the age distribution of these reports.

Table 11. Number of Adverse Events and Case Reports of Myocardial Disorders

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Category of Cardiomyopathy									
Cardiomegaly	0	2	0	0	1	0	0	3	2
Cardiomyopathy	0	1	2	0	0	0	0	3	3
Congestive cardiomyopathy	0	1	1	0	0	0	0	2	2
Dilatation atrial	0	0	0	1	0	0	0	1	0
Ventricular dysfunction	0	1	0	0	1	0	0	2	2
Ventricular hypertrophy	0	1	0	0	0	0	0	1	1
ECG signs of ventricular hypertrophy	0	1	0	0	0	0	0	1	1
Category of Myocarditis									
Myocarditis	0	1	0	0	0	0	0	1	1
Viral myocarditis	0	0	0	1	0	0	0	1	1
Total Events	**0**	**8**	**3**	**2**	**2**	**0**	**0**	**15 Events**	**13 SAEs**
Total Unduplicated Reports	**0**	**6**	**3**	**2**	**2**	**0**	**0**	**13 Reports**	**12* Serious Reports**

* One serious case report contained two serious adverse events

All adverse event reports were considered serious except one. The report which was considered to be non-serious was a case of atrial dilatation, tachycardia and palpitation in a [redacted]. Adverse events of other cardiac disorders were reported in 5 of the 13 cases and these events are discussed individually in their relevant categories.

Other serious adverse events reported in these cases included pancreatitis, chest pain, death, hepatitis C positive, HIV test positive, chromosomal mutation, hepatitis acute, and hepatic enzyme increased.

All of the patients were receiving treatment with atomoxetine at the time of onset of the events. Dosing information is available for all 13 case reports and the daily doses ranged from 25mg to 120mg. Time to onset (information available in all cases) ranged from 13 days to 9 months.

Three of the case reports had a fatal outcome. These were myocarditis, upper respiratory tract infection, and nausea in a [redacted]; prescribed overdose, drug ineffective, hepatic cirrhosis, cardiomegaly, constipation, irritability and wound in a [redacted]; and congestive cardiomyopathy, cardiac arrest, hepatitis acute, hepatic liver enzyme increased, listless, dyspnoea, syncope, epistaxis, headache, nausea, vomiting, dehydration, abnormal behaviour, and decreased appetite in a [redacted]. These cases are discussed in further detail in section 4.7 of this report.

Of the 10 non-fatal cases, treatment with atomoxetine was discontinued in 8 cases. In 4 of these 8 cases the patient had recovered, in two cases the events continued and in 2 cases the outcome was unknown. A further two patients discontinued atomoxetine and were subsequently rechallenged and were reportedly "doing well".

The MAH evaluated the 13 cases for risk or confounding factors that may have caused or contributed to the reported myocardial disorders. The MAH considered that 4 case reports were clearly confounded. In these cases the confounding factors were: multiple sclerosis, heart damage and ventricular dysfunction due to prior use of Phen-Fen; viral infection with negative rechallenge of atomoxetine; history of congestive cardiac failure, diabetes and alcoholism; and inherited degenerative disorder (Friedereich ataxia) and idiopathic cardiomyopathy diagnosed.

A further six cases were deemed to have other possible risk or confounding factors which were stated to be: family history of ventricular hypertrophy and diagnosed with ventricular hypertrophy after 1 month of atomoxetine treatment; diagnosed with congenital WPW syndrome and idiopathic cardiomyopathy; patient died due to lymphocytic myocarditis of viral origin following URTI; multiple other medications; the patient died of dilated cardiomyopathy 15 days after starting treatment; and in the final possible confounded case the possible risk/confounding factors were considered to be negative rechallenge of atomoxetine for 6 weeks after recovery of cardiomyopathy.

According to the MAH in the remaining 3 cases, no confounding factors were present however, causality was considered by the MAH to be 'indeterminate' in these cases since the short time to onset in these cases suggested the limited role of atomoxetine

in these events. The first patient was diagnosed with cardiomegaly after 1 month on existing condition or allergic reaction. In the second case, the time to onset of diagnosis of severe congestive heart failure, severe mitral regurgitation and cardiomyopathy was 40 days. The cardiomyopathy was considered likely congenital in origin (possibly exacerbated by viral infection) by the reporter. The third patient was diagnosed with dilatation of left atria by ECG only without further testing after 2 weeks of treatment with atomoxetine.

The MAH states that myocardial disorders were reported very rarely during the two year period covered by this review and the reporting rate was even less than that seen in the general population. The MAH concluded that most of these reports were confounded and that no direct causal relationship of myocardial disorders with atomoxetine treatment could be established from the data presented.

Assessor's comments:
The most frequently reported myocardial disorders were cardiomyopathy (5) and cardiomegaly (3). The majority of reports involved paediatric patients (11 Vs 4 adults) although this may also reflect the prescribing pattern. Three reports had a fatal outcome, two of which involved patients under the age of 18 years. The fatal cases were 'myocarditis, 'cardiomegaly' and 'congestive cardiomyopathy'. The three fatal cases are discussed in further detail in section 5 of this report.

The four non-fatal cases of cardiomyopathy (3 cases of cardiomyopathy, 1 case of congestive cardiomyopathy) involved paediatric patients. All reports are unlikely related to atomoxetine - Friedreich's ataxia; congenital Wolff-Parkinson-White syndrome; negative rechallenge; negative dechallenge and reporting physician considered the event to be congenital.

The two non-fatal cases of cardiomegaly were considered not related to atomoxetine by the reporting physician. The case of ventricular hypertrophy was considered possibly confounded by a family history of ventricular hypertrophy and the case of ECG signs of ventricular hypertrophy the patient started valproate, clonidine and fluoxetine at the same time as atomoxetine. In all other cases the reported reactions were first cases and/or were confounded.

No update to the SPC with regards to myocardial disorders is required at present.

Cardiac Valve Disorders
The MAH searched their ClinTrace database for reports of cardiac valve disorders associated with atomoxetine using the MedDRA HLGT 'cardiac valve disorders'. A total of 10 case reports of 10 adverse events (6 serious) were reported during the six month period covered by this review. The table below provides further details regarding the reported events and the age distribution of these events.

Table12. Number of Adverse Events and Case Reports of Cardiac Valve Disorders

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Aortic valve	0	0	0	1	1	0	0	2	1

incompetence									
Mitral valve incompetence	0	1	1	1	0	1	0	4	1
Mitral valve prolapse	0	1	0	0	1	0	0	2	2
Cardiac valve disease	0	2	0	0	0	0	0	2	2
Total Events	**0**	**4**	**1**	**2**	**2**	**1**	**0**	**10 Events**	**6 SAEs**
Total Unduplicated Reports	**0**	**4**	**1**	**2**	**2**	**1**	**0**	**10 Reports**	**9* Serious Reports**

* Some cases were considered serious due to other serious events.

All except one of the case reports were considered to be serious. The report which was considered to be non-serious was a case of aortic valve incompetence and heart rate irregular in a [redacted]. Adverse events of other cardiac disorders were reported in 6 of the 10 cases and that these events are discussed individually in their relevant categories.

Other serious adverse events reported in these cases included pancreatitis and blood pressure increased.

All except one of the patients were receiving treatment with atomoxetine at the time of onset of the events. The daily dose was provided in eight of these nine cases and ranged from 18mg to 100mg. The time to onset was provided in the same eight of nine cases and ranged from 14 days to 1 year.

The remaining patient ([redacted]) experienced mitral valve prolapse four months after discontinuation of atomoxetine. The patient had been on atomoxetine 40mg for just 6 days. The patient underwent cardiac surgery and recovered.

None of the case reports had a fatal outcome. Treatment with atomoxetine was discontinued in 5 cases. In 2 of these 5 cases the patient had recovered, in 2 cases the events continued and in 1 case the outcome was unknown. Two patients continued treatment with atomoxetine and the events resolved in both cases. There was one case in which treatment with atomoxetine was re-challenged. The event had reportedly resolved (negative re-challenge). In the final two cases the action taken with atomoxetine is unknown.

The MAH evaluated the 10 cases for risk or confounding factors that may have caused or contributed to the reported cardiac valve disorders. Seven of the ten cases of cardiac valve disorder were considered by the MAH to be unlikely related to treatment with atomoxetine. Details of these cases are as follows. The case of mitral valve prolapse which occurred 4 months after discontinuing 6 days of treatment with atomoxetine was considered not to be drug related by the MAH due to the fact that the event occurred 4 months after discontinuing treatment and that the patient had received atomoxetine for just 6 days. In a further five cases (4 adults, 1 child), severe heart disorders were identified prior to treatment with atomoxetine. The first of these five cases was a [redacted] who developed atrioventricular block, atrial flutter, blood pressure increased, mitral valve incompetence, chest discomfort, pain in extremity, and electrocardiogram ST segment abnormal after 1-2 months of treatment

with atomoxetine 80mg. The patient had a history of atrial fibrillation and hypertension. The second case is that of a [redacted] who developed heart rate irregular and aortic valve incompetence after treatment with atomoxetine (dose and duration of treatment unknown). The patient had a history of congenital tricuspid aortic valve and endocarditis. The third patient is a [redacted] who developed aortic valve incompetence, ventricular dysfunction, pancreatitis and pericardial effusion after 6 months of treatment with atomoxetine 25mg. The patient has a history of multiple sclerosis, heart damage and ventricular dysfunction due to prior use of "Phen-Fen". Atomoxetine was discontinued and the events continued. The fourth case is that of a [redacted] who developed cardiac valve disease and headache following a 'prescibed overdose' of atomoxetine (18mg for 1 month). The patient had a history of congenital transposition of great vessels, pulmonary stenosis and ventricular defect repaired as an infant. Atomoxetine was continued, sertraline was added and the patient was reportedly 'stable'. The fifth case is that of a [redacted] who developed electrocardiogram QTc interval prolonged, tachycardia and mitral valve incompetence after 4 months of treatment with atomoxetine 100mg. The patient had a history of heart murmur prior to atomoxetine treatment and was diagnosed with mitral valve regurgitation after atomoxetine was started. Another child with a family history of supraventricular arrhythmias was diagnosed with congenital Wolf Parkinson White syndrome during evaluation for tachycardia. It was reported that the patient was doing well and that treatment with atomoxetine had been restarted.

According to the MAH, clear causative factors could not be identified in the remaining 3 cases, all of which involved children. These reports were classified 'indeterminate' by the MAH since insufficient information was provided in these cases. The first of these three cases is that of a [redacted] who developed cardiomyopathy, dyspnoea, vomiting, cardiac failure congestive and mitral valve incompetence after 40 days of treatment with atomoxetine 80mg. There was no prior history of such events. Concomitant medication was unknown. Atomoxetine was discontinued and the events continued. The patient was treated with spironolactone. According to the MAH the reporting physician felt that the mitral valve incompetence and congestive heart failure were congenital and possibly exacerbated by a viral infection. The second of these three cases is that of an [redacted] who was found to have a cardiac murmur and cardiac valve disease (unspecified valvular disorders) after 1 year of treatment with atomoxetine. 'Negative history'. Concomitant medication is unknown. 'Heart murmur was detected'. The event was ongoing although the action taken with atomoxetine was unknown. The final of these three cases is that of an [redacted] who was found to have mitral vavle prolapse and chest pain after 7 months of treatment with atomoxetine 25mg. The patient's medical history was unknown and it was reported that intermittent chest pain prompted evaluation. Atomoxetine was continued. The patient received no treatment for the mitral valve prolapse and [redacted] was reportedly 'stable'.

The MAH states that cardiac valve disorders were reported very rarely during the two year period covered by this review and the reporting rate was even less than that seen in the general population. The MAH concluded that most of these reports were confounded and that no direct causal relationship of cardiac valve disorders with atomoxetine treatment could be established from the data presented. The MAH proposes to continue to monitor events of cardiac valve disorder.

Assessor's comments:
Seven out of the 10 cases of valvular disorders were considered to be unlikely related to atomoxetine due to pre-existing cardiac disorders (6 cases) and the event occurring 4 months after discontinuing a 6-day course of atomoxetine in the seventh case.

In the remaining 3 cases (mitral valve prolapse (1), mitral valve incompetence (1) and cardiac valve disease (1)) the relationship between atomoxetine and the reported events was considered 'indeterminate' by the MAH. All three cases involved paediatric patients (aged 8, 13 and 11 years) and times to onset were 7 months, 40 days and 1 year. In one case it is stated that the reporting physician considered the events to be congenital.

No updates to the SPC for atomoxetine are warranted based on this review of cardiac valve disorders.

Other Cardiac Disorders
The adverse events in the cardiac disorders SOC, which were not related to arrhythmia, conduction disorders, myocardial or valve disorders and were considered potentially medically significant are discussed in this section.

A total of 12 case reports of 12 adverse events (10 serious) of other cardiac disorders were reported during the two year period covered by this review. Three reports had a fatal outcome. The table below provides further details regarding the reported events and the age distribution of these events.

Table 13. Number of Adverse Events and Case Reports of Other Cardiac Disorders

MedDRA PT	Age Group							Total	Serious Event only
	0-5	6-12	13-17	18-44	45-65	≥65	Unk		
Arteriosclerosis	0	0	0	1	0	0	0	1	1
Cardiac disorder	0	1	1	0	0	0	0	2	1
Cardiac failure	0	0	0	1	0	0	0	1	1
Cardiac failure congestive	0	0	1	0	0	0	0	1	1
Cardiovascular disorder	0	0	1	0	1	0	0	2	1
Cardiotoxicity	0	0	1	0	0	0	0	1	1
Myocardial infarction	0	1	0	1	0	0	0	2	2
Pericarditis	0	0	0	1	0	0	0	1	1
Pericarditis effusion	0	0	0	0	1	0	0	1	1
Total Events	**0**	**2**	**4**	**4**	**2**	**0**	**0**	**12 Events**	**10 SAEs**
Total Unduplicated Reports	**0**	**2**	**4**	**4**	**2**	**0**	**0**	**12 Reports**	**10 Serious Reports**

Two reports were considered to be non-serious. The first of these reports was of 'cardiovascular disorder' in a [redacted] who had a cardiac stent inserted prior

to starting atomoxetine. There was a negative dechallenge of atomoxetine in this case. The second of the non-serious cases was a case of 'cardiac disorder' in a [redacted] after 3 weeks of treatment with atomoxetine. The event was discovered through echocardiogram. Atomoxetine was discontinued but the outcome of the event is unknown as is the patient's medical history.

Adverse events relating to other cardiac disorders were reported in three of these 12 reports. These other cardiac events have been discussed previously in the relevant sections above.

Other serious adverse events reported in these cases included skin discoloration, multiple drug overdose, convulsion and pancreatitis.

All patients were receiving atomoxetine at the time of onset of the events. The daily dose was provided in nine cases of the twelve cases and ranged from 25mg to 120mg. The time to onset was provided in ten of the twelve cases and ranged from 1 day to 6 months.

Three of the case reports had a fatal outcome. These were intentional overdose, cardiac failure, multiple drug overdose, convulsions, headache, dyspnoea, dizziness, abdominal distention and weight increased in a [redacted] (cause of death cardiac failure likely due to heroin overdose); arteriosclerosis and chest pain in a [redacted] with a history of heart disease and high blood pressure (autopsy confirmed ateriosclerosis); and myocardial infarction in a [redacted] with a history of arthritis and thyroid disorder who was taking many medications (died of a heart attack at a construction site). These reports are discussed in more detail in section 4.7 below.

Excluding the three fatal cases, treatment with atomoxetine was discontinued in eight of the nine remaining cases. In 1 of these 8 cases the patient had recovered, in 4 cases the events continued and in 3 cases the outcome was unknown. In the final case the action taken with atomoxetine is unknown.

The MAH evaluated the 12 cases for risk or confounding factors that may have caused or contributed to the reported cases. The fatal cases are discussed further in section 4.7 below. Three of the nine non-fatal cases involved adult patients with pre-existing cardiac disorders: case of pericarditis in a patient with a history of pericarditis; aortic valve incompetence, ventricular dysfunction, pancreatitis and pericardial effusion in a patient with MS, heart damage and ventricular dysfunction due to prior use of "Phen-Fen"; and cardiovascular disorder in a patient with a cardiac stent placed prior to treatment with atomoxetine.

The six remaining cases involved teenage patients. One of these patients had pre-existing progressive cardiac disorders whose ventricular disorder was identified through data collected from his internal pacemaker/defibrillator device. Another patient had a prior history of 'cardiotoxicity' whilst taking stimulants. In three cases, insufficient information was provided for aetiological classification according to the MAH. The first of these three cases was a [redacted] who experienced an unspecified cardiac disorder whilst taking atomoxetine for an unspecified duration. [redacted] medical history was unknown. The second of these three cases involved a [redacted]

[redacted] patient who had a heart attack whilst taking atomoxetine. Further information was not available regarding this case despite MAH attempts to obtain it. The third case involved a [redacted] who had a cardiac disorder after 40 days of atomoxetine treatment. The reporting physician in this case suspected a congenital cardiac disorder possibly exacerbated by a viral infection. The final case of the six cases involving teenagers was that of a [redacted] who experienced localised skin discolouration possibly due to local vascular or circulation abnormality, which was unlikely a cardiac disorder.

The MAH states that other cardiac disorders including myocardial infarction were reported very rarely during the two year period covered by this review.

Assessor'comments:
There were three cases of other cardiac disorders which resulted in a fatal outcome (cardiac failure following a multiple drug overdose, ateriosclerosis, and myocardial infarction). All three cases involved adults ([redacted]). These reports are discussed in more detail in section 4.7 below.

Of note, the second and non-fatal case of myocardial infarction was reported in a [redacted] patient who reportedly experienced myocardial infarction less than one month after starting atomoxetine 60mg. [redacted] medical history is unknown and the MAH state that they are unable to obtain medical confirmation of this report.

4.7 Spontaneous Reports with a Fatal Outcome due to Cardiac Disorders

A total of 8 case reports of cardiac adverse events resulted in a fatal outcome during the period 26 November 2002 – 26 November 2004. These cases are discussed in more detail below.

[redacted] ***(Congestive cardiomyopathy, cardiac arrest, hepatitis acute, hepatic enzyme level abnormal, listless, dyspnoea, syncope, epistaxis, headache, nausea, vomiting, dehydration, abnormal behaviour, decreased appetite). Reported by a paediatrician.***
This case is that of a [redacted] with a history of ADHD, Asperger's syndrome, depression and anxiety. Phenytoin (for the treatment of febrile seizures) was discontinued 6 years prior. [redacted] had also previously received unspecified SSRIs for depression and anxiety.

Atomoxetine was started at 60mg daily. The dose was increased to 80mg daily 5 days later. The patient had been on venlafaxine for 6 months and carbamazepine for 2 years at the time of onset of the events. Thirteen days after starting treatment with atomoxetine [redacted]. The following day the patient presented with listlessness, panting, syncope, nosebleeds, headache, and loss of appetite. [redacted] experienced nausea and vomiting and attended the ER. On admission [redacted] liver enzymes and coagulation measures were elevated, and suggested severe acute hepatitis. The patient was hospitalised and required intubation with ventilation support and dialysis over the next 2 days. On the second hospital day the patient had a cardiac arrest and died. The cause of death was determined as massive

dilated cardiomyopathy and the liver congestion was consistent with the cardiomyopathy.

Assessor's comments:
It is unlikely that atomoxetine was responsible for this patient's 'massive' dilated cardiomyopathy given the short time to onset (13 days).

[redacted] ***(intentional overdose, cardiac failure, multiple drug overdose, convulsion, headache, dyspnoea, dizziness, abdominal distention, weight increased). Reported by a consumer with follow up from a physician.***
This case is that of a [redacted] patient with a history of ADHD, depression, anxiety, and seizures. [redacted] had an extensive history of [redacted] and numerous drug overdoses. [redacted] was concomitantly receiving clonazepam, amitriptyline, paroxetine and valproate.

The patient was hospitalised for a seizure event caused by an overdose of [redacted] having been on atomoxetine for 2 months. One month later the patient was dead. The consumer reported that the autopsy report states cardiac failure as the cause of death. The reporting psychiatrist felt that the death was a cardiac event relating to heroin overdose (the psychiatrist had not seen the autopsy report).

Assessor's comments:
The patient's cardiac death was most likely due to [redacted] overdose.

[redacted] ***(myocarditis, upper respiratory tract infection, nausea). Reported by a physician.***
A [redacted] patient received atomoxetine 40mg twice daily. Concomitant medications were unknown although [redacted] had previously received methylphenidate and amphetamine/dextroamphetamine. Atomoxetine was discontinued due to nausea approximately 5 months after starting treatment. The patient developed an upper respiratory tract infection. Three days after discontinuing atomoxetine the patient received diphenhydramine 50mg. [redacted] was alone for 90 minutes and died the same day.

Autopsy showed lymphocytic myocarditis consistent with viral origin, cardiomegaly with panchamber dilation, and pulmonary oedema with perioral "foam cone".

Assessor's comments:
The cause of death in this case was determined as viral myocarditis.

[redacted] ***(prescribed overdose, drug ineffective, death, hepatic cirrhosis, cardiomegaly, constipation, irritability, wound). Reported by a psychiatrist.***
This [redacted] patient has a history of cardiovascular disease, hypertension, diabetes mellitus, kidney problems, mood problems, congestive heart failure, venous stasis, back pain, irritable bowel syndrome, and sleep apnoea, raised liver enzymes and alcohol use. [redacted] was concomitantly receiving lisinopril, furosemide, cyclobenzaprine and acetaminophen/codeine.

The patient took atomoxetine 80mg daily titrated up to 120mg daily over a three month period. [redacted] experienced constipation on 120mg and atomoxetine was not having desired effect. After 3 months of treatment the patients blood pressure was

130/60, pulse 72 and [redacted] had no chest pain or palpitations. [redacted] was reportedly very irritable after each dose increase. After approximately four months on treatment with atomoxetine the patient died in [redacted] sleep. [redacted] had been drinking heavily that night.

Autopsy showed liver cirrhosis and some dilatation of the heart. Toxicological tests showed amitriptyline which the patient was not prescribed. [redacted] also had a significant wound which was not healing well due to [redacted] diabetes. The cause of death was listed as complications of alcoholism, cardiomegaly, degeneration of the mitral valve, morbid obesity, IDDM and venous stasis.

Assessor's comments;
This case is heavily confounded by the patients pre-existing cardiovascular disorders and current alcohol use.

[redacted] ***(myocardial infarction). Reported by a physician.***
A [redacted] patient with a medical history of arthritis and thyroid disorder, drug and alcohol abuse (although [redacted] had been sober for 6 years). [redacted] had no prior history of heart problems or diabetes and had no prior ECG done. [redacted] was concomitantly receiving levothyroxine, celecoxib, methotrexate, sertraline and tramadol. [redacted] had previously received fluoxetine for 3 months although this was discontinued prior to starting atomoxetine and [redacted] had previously received amphetamine/dextroamphetamine.

Patient was switched to 80mg daily atomoxetine for the treatment of ADHD. Patient died of a heart attack [redacted] four months after starting treatment with atomoxetine. No autopsy was performed.

Assessor's comments:
It is unlikely that atomoxetine played a role in this patient's death. The patient's previous drug and alcohol abuse, concomitant celecoxib and methotrexate are other possible explanations.

[redacted] ***(anoxic encephalopathy, cardiac arrest, brain death, anxiety, agitation). Reported by a physician.***
This [redacted] patient had a history of ADHD, depression, restless leg syndrome, and mitral valve prolapse which was reportedly asymptomatic. [redacted] was concomitantly receiving olanzapine, citalopram and mirapex. Vital signs were normal 10-14 days prior to the event.

After approximately 3 months of treatment with atomoxetine 80mg daily the patient experienced a full cardiac arrest at the office where [redacted] worked. There was a reported delay of 15 minutes before CPR was commenced. [redacted] was shocked 4-5 times and was transported to the hospital in sinus rhythm, but unconscious. The patient was on life support and never regained consciousness. Autopsy revealed anoxic encephalopathy secondary to cardiac arrest. Autopsy also revealed severe congenital mitral valve prolapse. According to the MAH the manner of death was determined as natural.

Assessor's comments:
This case is confounded by the patient's severe congenital mitral valve prolapse and concomitant medication.

[redacted] ***(sudden death, cardiorespiratory arrest, bronchitis, cough, aspiration, urinary incontinence, faecal incontinence). Reported by a paediatrician.***
This [redacted] patient had no family history of cardiovascular disorder or sudden death. No baseline ECG was done. [redacted] was reportedly taking no concomitant medications.

The MAH states that atomoxetine was titrated slowly by 10mg every week for 6 weeks to a final dose of 40mg daily (1.2mg/kg). [redacted]. CPR was started. The patient aspirated, there was incontinence of the bowel and bladder and [redacted] felt that the heart was not beating. Patient was pronounced dead on arrival at hospital. [redacted] was pulseless, apneic and asystolic. ER diagnosis was cardio-respiratory arrest.

Autopsy failed to reveal a reveal a specific cause of death and the manner of death was undetermined. Pathological diagnoses: sudden unexplained death in childhood and peribronchiolar chronic inflammation.

Assessor's comments:
This case is difficult to assess given the autopsy was inconclusive and thus the cause of death unknown.

[redacted] ***(arteriosclerosis, chest pain). Reported by a physician.***
This [redacted] patient had a history of heart disease and high blood pressure. [redacted] also had a family history of coronary artery disease. [redacted] concomitantly received methylphenidate and atorvastatin. After 4 months of treatment with methylphenidate the patient started atomoxetine 25mg which was titrated to 50mg then to 75mg daily. Patient had no complaints of chest pain, palpitations, insomnia or fatigue about 48 days after starting atomoxetine. Twelve days later the patient awoke and complained of "funniness" in [redacted] chest and chest pains. Patient collapsed in hospital and died after an unspecified amount of time. Autopsy stated cause of death to be ateriosclerotic cardiovascular disease and natural causes. [redacted] had coronary artery disease with two major arteries showing significant blockage by plaque. An area of scarring was present in the heart muscle, showing evidence of past myocardial infarction.

Assessor's comments:
This patient had pre-existing coronary artery disease which had been confirmed by the autopsy results.

5. Summary of Spontaneous Adverse Events Reports of Cardiac Disorders associated with Atomoxetine (27 November 2004 – 30 September 2005)

At the request of the MHRA the MAH has submitted a line listing of all reports of cardiac disorders associated with atomoxetine since the cut-off date of the previous cumulative review (26 November 2004) discussed in Section 4 above. Table 14 below provides an overview of the number of cases of each cardiac disorder reported for atomoxetine during the period 27 November 2004 – 30 September 2005).

Table 14. Reports of cardiac disorders for atomoxetine (27 November 2004 – 30 September 2005)

MedDRA Preferred Term	Number of reactions	Serious Report	Assessor's Notes
Supraventricular Arrhythmias			
Sinus arrhythmia	1	1	
Supraventricular extrasystoles	1	1	
Total			
Ventricular arrhythmias			
Cardiac arrest	1	1	1 Fatal
Cardio-respiratory arrest	1	1	1 Fatal
Ventricular extrasystoles	1	1	
Total			
Arrhythmias unclassified			
Arrhythmia	7	3	
Bradycardia	1		
Cardiac flutter	1		
Extrasystoles	2	1	
Gallop Rhythm Present	1		
Heart rate abnormal	2		
Heart rate irregular	7	2	
Palpitations	49	5	
Pulse abnormal	1		
Total			
Tachycardia			
Heart rate increased	112	12	
Tachycardia	60	17	
Sinus tachycardia	2		
Total			
Cardiac Conduction Disorders			
Atrioventricular block first degree	2	1	
Bundle Branch Block	1	1	
Conduction Disorder	1		
Total			
ECG QT Prolongation			
Electrocardiogram QT prolonged	2	2	
Electrocardiogram QT corrected prolonged	4	4	
Total			
Other ECG abnormality			
Electrocardiogram abnormal	4		
Electrocardiogram T wave inversion	1	1	
Total			

Mycocardial Disorders			
Cardiomegaly	1	1	
Cardiomyopathy	1	1	
Congestive cardiomyopathy	1	1	1 Fatal
Dilatation ventricular	1	1	1 Fatal
Viral myocarditis	1	1	
Total			
Cardiac Valve Disorders			
Mitral valve incompetence	1	1	
Mitral valve prolapse	1	1	
Tricuspid valve incompetence	1	1	
Cardiac valve disease	1	1	1 Fatal
Total			
Other Cardiac Disorders			
Ateriospasm coronary	1	1	
Cardiac disorder	1		
Cardiovascular disorder	3		
Cardiac Murmur	1	1	
Cyanosis	1		
Myocardial infarction	2	2	1 Fatal
Pulse Pressure Decreased	1		
Total			
Total (all cardiac disorders)			**6 fatal reactions (corresponding to 3 patients)**

NB the fatal congestive cardiomyopathy, dilatation ventricular, cardiac valve disease and cardiac arrest were reported in the same patient.
In many cases one or more different cardiac disorders were reported in the same case, thus the table corresponds to the number of reported reactions and not the number of patients/cases.
The 'Serious Report' column refers to the seriousness of the report and does not necessarily mean that the reported cardiac disorder itself was considered serious. Some reports may be considered serious due to other reported adverse events however it is difficult to determine the serious event in the reports from the line listing provided by the MAH.

The vast majority of cardiac disorders reported during the period 27 November 2004 – 30 September 2005 were cases of heart rate increased (n=112), tachycardia (n=60), and palpitations (n=49). Sinus tachycardia and palpitations are recognised adverse effects of atomoxetine and are listed in section 4.8 'Side Effects' section of the current SPC.

Since the data covering this period (27 November 2004 – 30 September 2005) has been provided as a line listing, only the cardiac disorders which were of particular concern in the review of the previous period (26 November 2002 – 26 November 2004) are reviewed in detail in this section. The MAH has been requested to provide a full review of the new data relating to cardiac adverse events. Adverse event reports of cardiac disorders with a fatal outcome, reports of QT/QTc interval prolongation and other ECG abnormalities, and reports of myocardial infarction are discussed in more detail below.

5.1 Fatal Cases

There were three fatal cases reported during the period 27 November 2004 – 30 September 2005. These cases are described as follows.

[redacted] *(Cardio-respiratory Arrest)*
This case involves an [redacted] with a history of suicidal ideation, depression and ADHD, tonsillectomy and premature birth (4lbs, 10oz). There was no family history of sudden death. An ECG a few years ago was normal whilst receiving methylphenidate and bupropion. The patient had previously taken amphetamine mixed salts. At the time of [redacted] death [redacted] was taking atomoxetine 40mg daily and bupropion. One month into atomoxetine treatment, amphetamine mixed salts was discontinued. [redacted] did not have a pulse. The patient died of cardiopulmonary arrest. The autopsy had no abnormal findings, toxicology screen was negative and bupropion levels were therapeutic.

[redacted] *(Myocardial Infarction)*
Very few details were available for this case. The case is that of a [redacted] patient who had unspecified pre-existing heart conditions. The patient experienced a heart attack and died. No further details are available.

[redacted] *(Cardiac arrest, Congestive cardiomyopathy, Cardiac Valve Disease, Dilatation Ventricular)*
This [redacted] had a medical history of Poland's syndrome (underdevelopment or absence of the chest muscle on one side of the body and webbing of the fingers of the hand on the same side) and ADHD. The patient started atomoxetine 18mg daily to be increased to 25mg daily after 3 days. The patient had stopped clonidine when atomoxetine was started and was concomitantly receiving risperidone. On the third day of atomoxetine treatment the patient was found unresponsive having suffered a cardiac arrest. The patient survived transfer to hospital and an echocardiogram revealed dilated cardiomyopathy and significant valvular disease. The patient died. Autopsy of the heart revealed cardiomegaly and left ventricular dilatation, no acute viral aetiology, hypertrophy of the myocytes, findings consistent with chronic changes.

Assessor's Comments:
The first fatal case this period of cardiopulmonary arrest in an [redacted] is difficult to assess given the autopsy revealed no abnormal findings. This is the second case in which a cause of death could not be established in a child who was taking atomoxetine at the time of death. The first ([redacted]) is discussed in section 4.7 above. The MAH has not included cases of sudden death/sudden unexplained death in these reviews of cardiac disorders associated with atomoxetine. The MAH has been requested to perform a search of their post marketing safety surveillance database in order to identify any further cases of sudden unexplained death in patients receiving atomoxetine. These cases will be reviewed prior to the discussion at the January 2006 PhVWP meeting.

The fatal case of myocardial infarction is confounded by the patient's age and pre-existing cardiovascular disorders. This is the fourth case (second fatal) of myocardial infarction reported for atomoxetine. Three of the reports occurred in adult patients

and the issue of cardiac safety of atomoxetine in adult patients with pre-existing cardiovascular disease is currently under surveillance in the MAH Cardiovascular and Cerebrovacsular Outcome study. The MAH should continue to monitor spontaneous reports of myocardial infarction associated with atomoxetine.

The third and final fatal case in confounded by the patient's medical history and a causal association between the cause of death (cardiomegaly, dilated cardiomyopathy and valvular disease) and atomoxetine is unlikely given the time to onset (3 days).

5.2 ECG Abnormalities

Electrocardiogram QT Interval Prolonged

Reports of QT/QTc interval prolongation, were of some concern in the review for the period 26 November 2002 – 25 November 2004. A further two cases of 'Electrocardiogram QT interval prolonged' and four cases of 'Electrocardiogram QTc interval prolonged' were reported during the period 27 November 2004 – 30 September 2005. All 6 reports were considered to be serious. These cases are reviewed in further detail below along with reported cases of other ECG abnormalities reported during this period.

Table 15. Reports of Electrocardiogram QT interval prolonged and Electrocardiogram QTc Interval prolonged reported for atomoxetine during the period 27 November 2004 – 30 September 2005.

Case	Patient Details	Dose/ Duration	Adverse Events	Comments
[redacted]	[redacted]	Overdose (1800mg)	Non-accidental overdose, Electrocardiogram QT corrected interval prolonged, Tachycardia	Overdose of 30 60mg capsules of atomoxetine.
[redacted]	[redacted]	Unknown Unknown	Electrocardiogram QT corrected interval prolonged	Concomitant albuterol inhaler intermittently. Atomoxetine was discontinued the QTc interval prolongation recovered.
[redacted]	[redacted]	40mg daily unknown	Electrocardiogram QT corrected interval prolonged, Sinus arrhythmia	Medical history of ADHD, anxiety and Tourette's syndrome. No previous history of cardiac disorders. Patient was not receiving any concomitant medication. QTc interval 450-470msec (unclear as to which formula used), ventricular rare = 93 bpm. Atomoxetine was discontinued and the QT interval was normal (404msec) approx 3 weeks later.
[redacted]	[redacted]	18mg daily	Electrocardiogram QT prolonged, Dizziness,	Medical history: congenital HIV infection.

		1 week	Convulsion.	Concomitant medication: methylphenidate, abacavir, didanosine, sulfamethoxazole, albuterol, cromoglicic acid and ritonovri/lopinavir. ECG showed long QT interval. Diagnosed presyncopal episode due to atomoxetine. Atomoxetine was discontinued
[redacted]	[redacted]	10mg daily 5 days	Electrocardiogram QTc interval prolonged	Performed baseline ECG. ECG at 5 days showed a prolongation of 20 (units unknown). Atomoxetine is continuing. QT prolongation is continuing.
[redacted]	[redacted]	10mg-20mg-25mg daily 4 weeks	Electrocardiogram QT interval prolonged, Tachycardia, Abdominal pain upper, malaise, hyperhidrosis	Medical history: left ventricular hypertrophy. Dose increased to 20mg. QT interval prolongation of 126% (considered not pathological by cardiologist). Dose increased to 25mg, further ECG showed QT interval prolongation of 120%. QT interval 430msec (within upper normal range) 2 weeks later. Atomoxetine was ongoing. The patient recovered.

Assessor's comments:
The values of QTc interval were reported in only one of the six cases (450-470msec) and it is unclear which correction method was used (Bazetts would over correct with faster heart rates). A positive dechallenge was observed in this case and the patient had no relevant history and was not receiving any concomitant medication.

There are two cases in which there are no apparent confounding factors, although values for the QTc interval are not provided. A QT interval prolongation of 20 (units unknown) from baseline was reported 5 days after starting atomoxetine 10mg in a [redacted]. Treatment with atomoxetine is continuing as is the QT prolongation. The second case involves an [redacted] who developed QTc interval prolongation an unknown time after starting atomoxetine. [redacted] recovered on withdrawing treatment with atomoxetine. Concomitant medication was intermittent albuterol inhaler.

One patient was HIV positive and was receiving multiple concomitant medications at the time of onset of dizziness, convulsion and long QT interval. However a pre-syncopal episode due to atomoxetine was diagnosed 1 week after starting atomoxetine. Whilst the patient was receiving other medications, the pre-syncopal episode appeared to be temporally related to starting atomoxetine.

One of the cases involved an overdose of 30 x 60mg atomoxetine. No further information regarding this case is available. It is unclear if the overdose involved other medication or was an overdose of atomoxetine alone.

In the final case, QT interval prolongation was observed 4 weeks after starting atomoxetine. However the QT interval normalised whilst atomoxetine was continued and the case is also possibly confounded due to pre-existing left ventricular hypertrophy.

These reports combined with the 27 serious reports of QT/QTc interval prolongation reported during the period 26 November 2002 – 26 November 2004 (discussed in section 4.4 above) make a cumulative total of 33 worldwide spontaneous cases of QT/QTc interval prolongation for atomoxetine since first launch. Whilst the lack of detail with regard to QTc values makes these reports difficult to assess, there are three cases in which a causal relationship with atomoxetine can not be ruled out. The MAH should make every effort to follow up these reports in order that a full assessment can take place.

Other ECG Abnormalities

A total of four reports of electrocardiogram abnormal and one report of electrocardiogram T wave inversion were reported during the period 27 November 2004 – 30 September 2005. Table 16 below provides further details of these cases.

Table 16. Reports of other ECG abnormalities reported for atomoxetine during the period 27 November 2004- 30 September 2005.

Case	Patient Details	Dose/ Duration	Adverse Events	Comments
[redacted]	[redacted]	25mg daily unknown	Electrocardiogram abnormal, tachycardia	Medical history of ADHD, generalised anxiety disorder and pervasive developmental disorder. Concomitant medications: mirtazapine, aripiprazole and clonidine Atomoxetine was discontinued and the ECG was normal
[redacted]	[redacted]	40mg daily	Lack of drug effect, Electrocardiogram abnormal, Heart rate increased, Increased blood pressure, Blood pressure decreased, Upper respiratory tract infection, Chest pain, Bronchial infection	Medical history: Adult ADD, afternoon drowsiness. Concomitant medication: modafinil, unspecified acid reducer. Events occurred after increasing dose of atomoxetine to 60mg. Atomoxetine was discontinued during bronchial infection and was restarted after 3 days. The events resolved.
[redacted]	[redacted]	60mg/day Approx 1.5 years	Blood pressure increased, Electrocardiogram abnormal	Medical history: hypertension, family history of cardiac problems, aggression, mood disorders, tics. No arrhythmia, no alcohol, caffeine or illicit drug use. Concomitant medication: guanfacine.

				Patient was asymptomatic. Follow up ECG by cardiologist was normal. Atomoxetine was discontinued. BP remained high, HR<100bpm, sinus rhythm, QT/QTc interval normal, ventricular rate = 65.
[redacted]	[redacted]	60mg/day	Chest pain, dyspnoea, Electrocardiogram abnormal, potassium low, drug screen positive.	Medical history: asthma, very active. Severe chest pain, ECG was abnormal. Bloods showed low potassium. Drug screen was 'slightly' positive for barbiturates. Outcome unknown.
[redacted]	[redacted]	40mg - 60mg daily 4 days	Electrocardiogram T wave inversion, tiredness	History: cannabis abuse, hyperkinetic disorder of social conduct, learning disability. Concomitant medication: methylphenidate (discontinued due to cannabis abuse). ECGs prior to atomoxetine were without pathological findings. Atomoxetine was discontinued. The patient has not yet recovered.

Assessor's Comments:
There were four reported cases of 'electrocardiogram abnormal' and one case of 'electrocardiogram T wave inversion' reported during the period 27 November 2004 – 30 September 2005.

One of the cases of electrocardiogram abnormal is confounded by concurrent low potassium. The remaining three cases of electrocardiogram abnormal could possibly be confounded by concomitant medication however follow up ECGs were normal in two cases in which atomoxetine was discontinued and in the third case the abnormal ECG was observed after an increase in dose of atomoxetine. In this third case atomoxetine was discontinued during a bronchial infection and was restarted after 3 days. The events had resolved. These four cases of electrocardiogram abnormal, together with the four cases reported during the previous 2 year period make a total of eight cases of unspecified electrocardiogram abnormalities reported for atomoxetine.

The case of T-wave inversion is the second case to be reported for atomoxetine (1 case reported during the previous period).

5.3 Myocardial Infarction

There were 2 further cases of myocardial infarction reported during the period 27 November 2004 – 30 September 2005. This makes a total of 4 cases of myocardial infarction reported for atomoxetine, two of which were fatal. The new fatal case involved a [redacted]. The previous case was in a [redacted]. Both fatal cases are likely to be confounded by the patients underlying cardiovascular disorders. In addition, there is an ongoing study (Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults) which will further evaluate the cardiovascular effects of atomoxetine in adult patients with pre-existing cardiovascular disease.

The two non-fatal cases of myocardial infarction involve younger patients – the previously reported case in a [redacted] and a new case in a [redacted]. There were very few details available in the case of the [redacted] and the MAH were unable to obtain medical confirmation of this report. The [redacted] patient received atomoxetine 80mg/day but the time to onset was unknown. The patient developed 'arteriospasm coronary' and 'myocardial infarction' and fully recovered from the events. The patient had a history of using body building supplements and sporadic cigarette smoking.

Assessor's comments:
The MAH should continue to closely monitor spontaneous reports of myocardial infarction reported for atomoxetine given the two cases in young patients.

6. Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults - Interim Report (October 28 2005).

The results of clinical trials of atomoxetine in both children and adults revealed consistent increases in heart rate and blood pressure. Whilst at the time of licensing these cardiovascular effects were considered to be of little clinical significance in paediatric patients, they were considered to pose a potential safety issue for adults with pre-existing cardiovascular disease. As a result of these findings the MAH have commissioned a study to further investigate this potential safety issue post marketing.

The 'Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults' is a propensity score matched retrospective cohort study which uses automated medical and pharmacy claims data from the Ingenix Research Database. The aim of the study is to estimate the incidence of potential cardiovascular and cerebrovascular outcomes among adult patients who initiate therapy with atomoxetine compared to similar patients who initiate other drug treatments for ADHD and an age and gender-matched general population cohort.

This interim report (attached at Appendix A) describes the identification of the two study cohorts; patients with a first dispensing of atomoxetine and patients with a first dispensing of stimulant ADHD medication. The matching algorithm using the propensity score is described and demographic details for both cohorts are presented both before and after matching.

3,719 (23.5%) atomoxetine patients were not matched to a comparable initiator of stimulant medication. The baseline demographics following matching are similar

between the two groups. This suggests that the analyses will not be confounded by any of the known/identified variables used for the matching algorithm. However, any unidentified confounders may not be adjusted for; therefore the potential for residual confounding remains.

Future reports will include the identification of cardiovascular and cerebrovascular claims events among the matched cohorts and comparators.

Assessor's Comments:
Nearly one quarter of eligible atomoxetine patients were excluded from the study because no matched stimulant initiator could be found. A clear presentation of the difference in demographics, diagnoses and medications between the matched and unmatched initiators should be provided with diagnostic and therapy terms rather than codes to expand the information available from tables 4 to 6.

7. Analysis of Adverse Reaction Reports in the WHO database November 2005 (SIGNAL article 'Serious Cardiac effects of atomoxetine?')

The November 2005 issue of the WHO drug safety bulletin 'SIGNAL' includes an article by Dr Emilio Sanz (Spain) which considers serious cardiac effects of atomoxetine.

According to the article, the WHO centre has received 26 cases of cardiac arrest (3), ventricular tachycardia (4), and "QT prolonged" (19) associated with the use of atomoxetine (2004;4; IC 1.64, IC025 0.63). The majority of these cases concerned children and young people under the age of 16 years (18 cases). Other side effects most frequently reported in these cases include tachycardia (10 cases), extrasystoles (4 cases), chest pain (5 cases) and atrial fibrillation (3 cases).

A more recent review of the WHO data has revealed an increase in the IC values from 1.64 (IC025 0.63) in 2004:4 to IC 2.10 (IC025 1.59) in 2005:2. As of 7 September 2005, there have been 38 cases of QT prolonged, seven cases of cardiac arrest and five cases of ventricular tachycardia. A re-calculation of IC values based on the sub-dataset of reports in children (as opposed to the whole database) is to be performed in the near future.

The article discusses the possible role of both pharmacokinetic and pharamcodynamic interactions between atomoxetine and SSRIs as 'co-adjuvant' reasons for a possible increase in the activity of atomoxetine. The interaction between atomoxetine and SSRIs is listed in the EU SPC for atomoxetine and states that "In CYP2D6 extensive metaboliser patients, selective inhibitors of CYP2D6 may increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metaboliser patients". Nine patients were reportedly using at least one SSRI concomitantly. The concomitant use of fluoxetine and venlafaxine (which are metabolised by CYP 2D6) have been reported in this case series (one case with

fluoxetine, 3 cases with venlafaxine) and also three cases in which sertraline was used concomitantly.

The article states that from the available data it is not possible to determine whether it is the effect of atomoxetine or the SSRI alone, or a synergy between the two which is responsible for the observed QT interval prolongation. The article further discusses the possibility that the adrenergic stimulation caused by the increase in NA levels at the sympathetic synapses could also be linked to the arrhythmogenic effects of atomoxetine, because it is related to an increase in the magnitude of the Ca^{2+} current, an increase in the repolarizing K^+ and Cl^- currents, increases the sinus rate and facilitates the passage through the AV node.

The author concludes that the current data suggests that cardiac effects associated with atomoxetine treatment should be carefully and specifically studied, and the prevalence of QT prolongation in treated patients is to be confirmed by other studies with special attention to the concomitant use of SSRIs. It is concluded that a warning should be added to the product information for atomoxetine.

Assessor's comments:
The WHO database contains a total of 38 cases of QT interval prolongation associated with the use of atomoxetine (cut off date 7 September 2005). In the review of spontaneous post-marketing reports, a total of 33 reports (27 + 6) were presented by the MAH for the period 26 November 2002 – 30 September 2005. The MAH should be requested to comment on the difference in number of reported cases of QT interval prolongation.

The article raises some interesting points and suggests that atomoxetine may cause QT interval prolongation in situations where steady-state plasma exposure to atomoxetine is increased, in particular in patients who are receiving concomitant medication (SSRIs) which inhibit CYP2D6.

8. Discussion

Pre-clinical and clinical trial data revealed effects of atomoxetine on heart rate and blood pressure. The effects of atomoxetine on heart rate are apparent in the review of the spontaneous reporting data in which the majority of reported cardiac disorders were tachycardia, heart rate increased and palpitations. In total there were 717 reactions of tachycardia and heart rate increased reported for atomoxetine during the period 26 November 2002 – 30 September 2005. Cases of palpitations were not discussed by the MAH in the first review of cardiac disorders. A total of 49 cases of palpitations were reported during the period 27 November 2004 – 30 September 2005. The MedDRA preferred term 'palpitations' codes to the cardiac disorders SOC and therefore should have been included in the MAHs first review covering the period 26 November 2002 – 26 November 2004. The MAH should be requested to comment on this omission.

During the period 26 November 2002 – 30 September 2005 there were a total of 11 case reports of cardiac disorders with a fatal outcome. These fatal cases involved 5 children and adolescents and 6 adults. Confounding factors or alternative causes of

the events leading to death were present in the majority of the reports however, in two of the fatal cases in children there were no obvious confounding factors. Attributing any causality to atomoxetine in these two deaths however is very difficult given that both patients appeared asymptomatic until immediately prior to death, the lack of detail regarding time to onset, and the fact that both autopsies failed to reveal a cause of death. The MAH did not include reports of sudden death in their review of cardiac disorders. The MAH has been requested to perform a search of their post marketing safety database for reports of sudden death/sudden unexplained death since sudden otherwise unexplained deaths may be indicative of fatal arrhythmias. A review of these reports will be presented at the January 2006 meeting of the CHMP PhVWP.

After reports of tachycardia, heart rate increased and palpitations, the most frequently reported cardiac disorders were QT/QTc interval prolongation – 33 cases were reported during the period 26 November 2002 – 30 September 2005. In those cases where actual QTc values were provided, 5 cases involved medically significant QTc interval prolongation (QTc>500msec or QTc change >60msec from baseline). However three of these reports were considered to be clearly or possibly confounded. The remaining two cases occurred following overdoses, one of which was a mixed overdose, the other involved an overdose of atomoxetine alone.

Both cases of overdose were excluded from further discussion by the MAH who states that this case does not represent the pharmacological actions of atomoxetine at therapeutic doses. However, in the case of overdose of atomoxetine alone does not rule out a causal association with the drug. This case may be indicative of a dose response and may warrant updating of the overdose section of the SPC. Two further cases may also indicate a dose response effect of atomoxetine on QT interval prolongation. In these two reports the MAH states that the events of QT interval prolongation occurred whilst the patients were receiving a prescribed daily dose of atomoxetine that exceeded the maximum recommended dose. These events were categorised as overdose cases by the MAH and were not considered to represent the properties of the drug at therapeutic doses and thus were not considered further. In both cases there was a positive dechallenge of atomoxetine and no possible risk or confounding factors are discussed/provided by the MAH. These cases would therefore seem to add some support to the possibility of QT interval prolongation at higher doses/overdoses of atomoxetine.

There are two cases in which the role of atomoxetine in QT prolongation can not be completely excluded at therapeutic doses. Two male children experienced borderline QTc prolongation (446msec and 462msec) less than 2 months after starting atomoxetine 25mg. Both continued on treatment and the events continued. These reports were from the same reporter who also reported 2 further similar cases involving young male patients who developed QTc intervals of 448 and 445msec less than 2 months after starting atomoxetine 25mg. The MAH have categorised these 2 further cases as possibly confounded due to concomitant medication (bupropion and fluoxetine), however neither bupropion nor fluoxetine are recognised to cause QT interval prolongation at therapeutic doses. The two latter cases are interesting given the WHO drug safety bulletin article (discussed in section 7 above, and attached at Appendix A) which discusses the possibility that pharmacokinetic and/or pharmacodynamic interactions between atomoxetine and inhibitors and substrates of CYP2D6 may be responsible for QT interval prolongation in a case series of nine

reports in the WHO database in patients taking SSRIs and atomoxetine. The current EU SPC for atomoxetine states that "In CYP2D6 extensive metaboliser patients, selective inhibitors of CYP2D6 may increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metaboliser patients". In the spontaneous reports of QT interval prolongation reported during the period 26 November 2002 – 26 November 2004 there are a further four cases in which concomitant SSRIs are listed as the only possible confounding factor (2 sertraline, 1 citalopram and 1 escitalopram). The times to onset were 3 months, 2 weeks, 5 months and unknown. QTc intervals were available in 3 cases (462, 445 and 440msec). All patients recovered after atomoxetine was discontinued although it is unknown (from the MAH report) whether sertraline, citalopram or escitalopram were continued in these cases.

Preclinical data which was assessed at the time of licensing (see section 2 above) concluded that atomoxetine is unlikely to cause QT interval prolongation at therapeutic doses and clinical trial data confirmed this. However, initial assessment of the pre-clinical data raised concerns with respect to the potential for QT interval prolongation in CYP2D6 poor metabolisers given the potential for N-Desmethyl-Atomoxetine to accumulate in CPY2D6 poor metabolisers and the fact that hERG K^+ channel inhibition predicted for atomoxetine would indicate concern. However, further assessment of the available data led to the conclusion that that there is no substantial clinical risk associated with atomoxetine and its primary metabolites at the recommended clinical doses.

The cases of QT prolongation associated with atomoxetine and SSRIs in the WHO report and the cases of QT prolongation associated with both intentional and prescribed overdose, together with the early pre-clinical concerns regarding concerns about QT interval prolongation in CYP2D6 poor metabolisers do not rule out the possibility that at the very least, atomoxetine may cause QT interval prolongation in situations where steady-state plasma exposure to atomoxetine is increased. The MAH should provide a summary of the cases of QT interval prolongation associated with atomoxetine and concomitant SSRIs with a view to strengthening the current warnings in the SPC about concomitant use of SSRIs.

The review of the present data concerning arrhythmias (supraventricular arrhythmias, ventricular arrhythmias and unclassified arrhythmias) did not establish a causal relationship between arrhythmias and atomoxetine. However the MAH should continue to closely monitor cases of atrial fibrillation, cardiac flutter and ventricular tachycardia. In addition, the MAH did not provide any details regarding the non-serious cases of 'arrhythmia unclassified' which prevented causality assessment in these cases. The MAH should be requested to provide a review of the case details for the 40 non-serious cases of unclassified arrhythmias reported for atomoxetine.

At present there is not enough evidence to suggest a causal relationship between atomoxetine and other ECG abnormalities, cardiac conduction disorders (including AV block or bundle branch block), or other cardiac disorders (including cardiac valve disorders, myocardial disorders and myocardial infarction). The MAH should continue to closely monitor such events.

The interim report of the 'Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults' (Appendix A) describes the identification of the two study cohorts; patients with a first dispensing of atomoxetine and patients with a first dispensing of stimulant ADHD medication. The matching algorithm using the propensity score is described and demographic details for both cohorts are presented both before and after matching.

Nearly one quarter of eligible atomoxetine patients were excluded from the study because no matched stimulant initiator could be found. A clear presentation of the difference in demographics, diagnoses and medications between the matched and unmatched initiators should be provided with diagnostic and therapy terms rather than codes to expand the information available from tables 4 to 6. Future reports of the study will include the identification of cardiovascular and cerebrovascular claims events among the matched cohorts and comparators.

The MAH review of cardiac disorders was limited to MedDRA preferred terms in the Cardiac Disorders SOC and the HLGT 'Cardiac and Vascular Investigations' in the Investigations SOC. Given the link between atomoxetine and peripheral ischaemia, the MAH should be requested to provide a line listing of all cases of adverse events relating to central ischaemia.

9. Conclusions

- The cases of QT prolongation associated with atomoxetine and SSRIs in the WHO report and the cases of QT prolongation associated with both intentional and prescribed overdose, together with the early pre-clinical concerns regarding concerns about QT interval prolongation in CYP2D6 poor metabolisers do not rule out the possibility that at the very least, atomoxetine may cause QT interval prolongation in situations where steady-state plasma exposure to atomoxetine is increased.

- The MAH should continue to closely monitor cases of atrial fibrillation, atrial/cardiac flutter, ventricular tachycardia and myocardial infarction.

- An addendum report which will assess the MAH responses to requests for further information will be provided before the January meeting of PhVWP. This report will consider the MAHs responses to a request for further information regarding omission of cases of palpitations from the first period of the cardiac review, reported cases of sudden death, review of the cases of QTc interval prolongation in which patients are receiving concomitant SSRIs, further details of the 40 cases of unclassified arrhythmias, and an overview of events related to central ischaemia. With respect to the Atomoxetine Cardiovascular and Cerebrovascular Outcome Study in Adults, the MAH is requested to provide a clear presentation of the difference in demographics, diagnoses and medications between the matched and unmatched initiators with diagnostic and therapy terms rather than codes to expand the information available from tables 4 to 6.

[redacted]

23 November 2005

APPENDIX A

Atomoxetine and Cardiovascular and Cerebrovascular Outcomes in Adults