Two 10 week, randomised, double-blind, placebo-controlled studies in adults:

18.1.1.1.1.4.1 LYAA **Atomoxetine (141) vs. placebo (139)**

18.1.1.1.1.4.2 LYAO **Atomoxetine (129) vs. placebo (127)**

An 18 week, double-blind, placebo-controlled study (LYAS) assessed non-inferiority between atomoxetine and placebo in tic severity in patients with ADHD and comorbid tic disorder:

LYAS Atomoxetine (76) vs. placebo (72)

A short term, randomised, double-blind, study in paediatric patients with ADHD comparing atomoxetine with placebo control and slow release methylphenidate (Concerta) was recently completed (LYBI).

18.1.1.1.1.4.2.1 Long term Placebo Controlled Studies

Two placebo-controlled long-term relapse prevention discontinuation study (following a 10 week open label atomoxetine period) in children and adolescents

LYAF Atomoxetine (292) vs. placebo (124)
HFBE Atomoxetine (59) vs. placebo (20)

In additional seven open-label studies are submitted. Studies HFBF, LYAI, and LYAR were open-label extension studies for eligible patients who had participated in a previous acute atomoxetine study.

18.2IV.2 Statistical Assessment of Efficacy

This assessment considers the evidence of efficacy for Strattera (atomoxetine - ATX), indicated for use in attention deficit / hyperactivity disorder (ADHD). The product is proposed for use in children over 6 years, adolescents and adults.
Data from the application are presented here in five sections, considering, in turn, short-term efficacy of twice daily dosing in paediatrics, short-term efficacy of once daily dosing in paediatrics, long-term efficacy in paediatrics, efficacy in adults and efficacy in subgroups. Following these are comments on methodology.

18.2.1 A. Short-Term Efficacy of Twice Daily Dosing in Paediatrics

Three trials are of pivotal importance for the acute efficacy of twice daily dosing. There is a dose-finding study (LYAC) and two applicant-nominated pivotal studies of efficacy. LYAC included 4 treatment groups (ATX 0.5, 1.2, 1.8 mg/kg/day and placebo) while HFBD and HFBK included three treatment groups (flexible ATX, placebo and methlyphenidate - MPH)

18.2.1.1 LYAC

LYAC was a multicentre, randomised, double-blind, placebo-controlled dose-response study that enrolled 297 US children and adolescents between 8 and 18 years of age. The study consisted of five study periods: a washout and screening period (Study Period I); an acute, randomised, double-blind, placebo-controlled treatment period for up to 8 weeks (Study Period II); a non-responder assessment period (Study Period III); a long-term, double-blind, responder extension period (Study Period IV); and a discontinuation period (Study Period V).

In the acute treatment phase, patients were randomised to one of four fixed-dose treatment groups: low-dose ATX (target dose 0.5 mg/kg/day), intermediate-dose ATX (target dose 1.2 mg/kg/day), high-dose ATX (target dose 1.8 mg/kg/day), or placebo in a 1:2:2:2 ratio, respectively. Randomisation was stratified by CYP2D6 and, for extensive metabolisers only, by whether or not patients had a history of prior stimulant treatment. Treatment was administered as a divided dose on a twice-daily basis and was titrated from 0.5 mg/kg/day in the higher dose groups.

The primary objective was to test the hypothesis that acute treatment with either ATX 1.2 or 1.8 mg/kg/day would be statistically significantly more effective in reducing the severity of ADHD symptoms as compared with placebo in paediatric patients who met the DSM-IV criteria for ADHD. Efficacy was assessed by comparing mean change from baseline to endpoint on the ADHDRS-IV-Parent:Inv Total score on the ITT population. This is an 18-item scale. Each item is marked from 0=never or rarely to 3=very often. The primary statistical model was ANCOVA based including terms for baseline, treatment, centre, visit, metabolism status, treatment-by-visit interaction and used an unstructured within-patient covariance matrix. Statistical tests were two-sided at the 5% level though primary comparisons were adjusted using Dunnett's test.

ATX (1.2 and 1.8 mg/kg/day) achieved clinically and statistically significantly greater mean improvement compared with placebo in ADHD symptoms on the ADHDRS-IV-Parent:Inv Total score, whether change was analysed using MMRM ($p<.01$) or change from baseline to endpoint using the LOCF approach (adjusted $p<.001$). ATX (1.2 and 1.8 mg/kg/day) achieved statistically significantly greater mean improvement compared with placebo on the Inattention ($p<.001$) and Hyperactivity-Impulsivity ($p = .001$) subscales of the ADHDRS-IV-Parent:Inv.

This study used three *a priori* definitions of response: a 25% decrease in ADHDRS-IV-Parent:Inv Total score; an endpoint CGI—ADHD-S score of at most 2; and an endpoint Clinical Global Impressions-Efficacy Index (CGI-EI) score of 1, 2, 5, or 6. The proportions of ATX-treated (1.2 and 1.8 mg/kg/day) patients meeting the first and last definitions of response were statistically significantly greater than the proportions of placebo-treated patients ($p<.001$).

The lowest ATX dose (0.5 mg/kg/day) was not statistically significantly different from placebo as assessed by the ADHDRS-IV-Parent:Inv, CGI-ADHD-S, response rate, and other secondary measures.

Patients who did not meet response criteria while on placebo or ATX 0.5 mg/kg/day showed a significant reduction in their ADHD symptoms by increasing their ATX dosage to 1.2 mg/kg/day during Study Period IV.

When ATX was discontinued (Study Period V), a statistically significant worsening in ADHD symptoms was observed in patients whose treatment was tapered ($p = .004$) and patients whose treatment was abruptly stopped ($p<.001$), as assessed by change in baseline to endpoint ADHDRS-IV-Parent:Inv Total Score. Scores at the end of Study Period V were still less than those at baseline for the entire study (from 56% to 61% less).

The two applicant-defined 'pivotal' studies were conducted prior to this dose-response study. They were identical to each other in design and had broadly similar patient populations, endpoints and methods of statistical analysis to LYAC, though the maximum permissible dose of ATX was 2.0 mg/kg/day. The results of these studies confirmed the statistically significant effect of ATX relative to placebo.

B. Short-Term Efficacy of Once Daily Dosing in Paediatrics

There were three short-term once-daily dosing trials (LYAT, LYGB and LYAW). There would generally be concerns over reduced efficacy in the latter part of the 24-hour dosing interval when switching from once to twice daily dosing. Therefore, trial LYBG is of greatest interest to this assessor as it assessed both morning and evening efficacy. LYAW is also of interest as it considers efficacy in the school setting.

18.2.1.2 LYBG

This is a multicentre, randomised study in 197 enrolled US children aged 6 to 12 years. The study consists of three study periods: a diagnostic assessment period; an acute, double-blind, placebo-controlled treatment period for up to 8 weeks; and an open-label extension period for approximately 6 months.

Approximately 160 patients were randomised between ATX and placebo in a 2:1 ratio. Dose was initially determined by weight and was increased or decreased based on clinical response and tolerability. The dose range for ATX was 0.8 - 1.8 mg/kg/day. Dose was administered once daily in the morning.

The primary objective of the study was to test the hypothesis that acute treatment for approximately 8 weeks with ATX provided superior efficacy compared with placebo in children with ADHD. The primary efficacy variable was analysed using a REML-based MMRM technique. This analysis included the fixed categorical effects of treatment, investigator, visit, cytochrome P450 2D6 (CYP2D6) metabolism status, and treatment-by-visit interaction. The analysis also included the continuous, fixed covariate of baseline (last of scores at Visit 1 and Visit 2) the ADHDRS-IV-Parent:Inv total score, the baseline ADHDRS-IV-Parent:Inv total score by-visit interaction score, and a random patient effect (where applicable, based on covariance structure). The unstructured, compound

symmetric, autoregressive of order one, and the heterogeneous versions of each were considered to model the within-patient variance and the covariance structure that produced the largest Akaike's Information Criteria score selected for this analysis. The primary analysis compared atomoxetine and placebo at the final post baseline visit using a contrast from the MMRM. A Satterthwaite approximation was used for the denominator degrees of freedom in the t-test at the final visit. This analysis was performed using PROC MIXED on the SAS software system.

In addition to the primary objective, this study was also powered to test the hypothesis that ATX provided superior efficacy on evening ADHD behaviours compared with placebo. Efficacy was measured using the Evening subscore of the DPREMB-Revised.

ATX achieved clinically and statistically significantly greater mean improvement compared with placebo in ADHD symptoms on the ADHDRS-IV-Parent:Inv Total score and both the inattention and hyperactivity subscale scores ($p<.001$). Results were robust to the method of statistical analysis used.

ATX achieved statistically significantly greater mean improvement compared with placebo on morning and evening ADHD symptoms as assessed by the DPREMB-Revised Morning / Evening subscore.

The results of LYBG were supported by the other trials of once-daily dosing, which were very similar in methodology, though doses and settings differed to some extent. The efficacy of ATX appears to be transferable to the school setting.

Acute Efficacy – Pooled Analysis
The six above-mentioned short-term studies were pooled for an overall assessment of short-term efficacy.

C. Long-Term Efficacy in Paediatrics
LYAF and HFBE were both relapse prevention trials.

LYAF

LYAF is being conducted in children and adolescents aged 6-15 in 11 European countries, Australia, South Africa, and Israel. The study consists of four study periods: a screening and washout period (Study Period I); a 10-week open-label, dose-titration period to determine ATX responders (Study Period II); a randomised, double-blind, placebo-controlled, continuation therapy period for patients who met the Study Period II response criteria (Study Period III); and a discontinuation period (Study Period IV).

Study Period III included two randomisations in which the initial randomisation visit was blinded to the patient and the investigator. The first randomisation was unbalanced with approximately 70% of patients assigned to ATX and approximately 30% of patients assigned to placebo. After approximately 1 year of treatment with ATX, patients assigned to ATX at the beginning of Study Period III were randomised a second time to continued

treatment with ATX or placebo in a 1:1 ratio. The study is ongoing, and continuing patients are past the second randomisation in Study Period III or have entered Study Period IV.

Patients had to meet the following response criteria at the end of open-label treatment before moving into double-blind, placebo-controlled treatment: a CGI-ADHD-S score □2 and a reduction of at least 25% from baseline in ADHDRS-IV-Parent:Inv Total score at both Visits 9 and 10.

ATX was titrated to a target dose (minimum of 1.2 mg/kg/day to a maximum of 1.8 mg/kg/day), based on efficacy and tolerability. Two equally divided doses were administered one in the morning and one late afternoon or early evening.

The primary objective of this study was to test the hypothesis that among paediatric patients who achieved a satisfactory initial response to acute (approximately 10 weeks) treatment with ATX, continued treatment with ATX is superior to placebo as measured by the number of days until relapse. Two definitions of relapse were used: 1) the per-protocol definition was a CGI-ADHD-S score (at two consecutive visits) that increased by 2 categories from the score at the end of Visit 10 **and** an ADHDRS-IV-Parent:Inv Total score that returned to □90% of the Study Period II baseline score; and 2) the *a priori* definition was a 50% increase in ADHDRS-IVParent:Inv Total score and an increase in CGI-ADHD-S of 2 points from the score at the end of Visit 10 at two consecutive visits. The distribution of the number of days to relapse was estimated for each treatment group (ATX and placebo) using the Kaplan-Meier product limit estimator. Treatment differences in the distributions were assessed with the Wilcoxon test using a 2-sided, 0.05 alpha level. Secondary efficacy was assessed by comparing mean change from baseline to endpoint (LOCF) using an ANOVA model with terms for treatment and investigator.

A total of 416 of the 604 treated patients responded and were randomised. The majority of withdrawals were due to lack of efficacy or adverse event. A number of withdrawals were noted during the randomised phase, but these withdrawals are not expected to introduce bias to the statistical comparisons. The difference in the time to symptomatic relapse statistically significantly favoured ATX ($p = .013$) on the Kaplan-Meier curves using the protocol-specified definition of relapse for all qualified patients (as defined in the protocol). Mean time-to-relapse in days (SD) for ATX-treated patients (227.65 [5.88]) was substantially longer than for placebo-treated patients (158.11 [7.92]). Similar results were also obtained for all randomised patients. The difference in the time to symptomatic relapse also statistically significantly favoured ATX ($p<.001$) on the Kaplan-Meier curves using the *a priori* definition of relapse for all qualified patients. Mean time-to-relapse in days (SD) for ATX-treated patients (208.67 [7.06]) was substantially longer than for placebo-treated patients (154.37 [12.22]). Similar results were also obtained for all randomised patients.

HFBE was similar in design in that ATX responders were randomised to continue on ATX or transfer to placebo. However, this was a failed study. The applicant attributes

this failure to confounding factors and problems with the study design. In particular they consider that all patients had a positive incentive to withdraw from the double-blind relapse prevention period, as they would then have been assured to receive open-label ATX in one of the extension studies. The small number of randomised patients (79) and the transition from open-label active treatment to double-blind (active or placebo) treatment is also mentioned.

D. Efficacy in Adults

Trials LYAA and LYAO are of pivotal importance for establishing short-term adult evidence of efficacy. The two trials were identical in design and were conducted concurrently. A combined total of 536 adults were enrolled to three study periods: a medication washout, screening, and assessment period of 15 to 46 days; a 10-week acute double-blind treatment period; and a 4-week, double-blind, discontinuation period. Patients were randomised between ATX and placebo in a 1:1 ratio. The initial dose of ATX was 30 mg administered twice daily: in the morning and in the late afternoon or early evening. The maximum dose was 60 mg twice daily. Dose was titrated (increased or decreased) based on response and tolerability. Following acute treatment, patients who entered Study Period III were re-randomised to one of two study drug discontinuation groups: abrupt discontinuation, or tapered discontinuation over a 4-week period.

The primary objective was to test the hypothesis that ATX at total daily doses of 60 to 120 mg for up to 10 weeks would have a statistically significantly greater reduction in ADHD symptoms compared with placebo. Primary efficacy was assessed by comparing the CAARS-Inv:SV Total ADHD Symptoms score at the final Study Period II visit using a contrast from MMRM. Secondary efficacy was assessed by comparing mean change from baseline to endpoint (LOCF) on the CAARS-Inv:SV Total ADHD Symptoms score and on other secondary measures using an ANOVA model with terms for CYP2D6 metabolic status, treatment, and investigator.

In both studies, ATX achieved a statistically significantly greater mean improvement compared with placebo in ADHD symptoms on the CAARS-Inv:SV Total score, whether change was analysed using MMRM (LYAA $p = 0.004$; LYAO $p<0.001$) or change from baseline to endpoint using the LOCF approach (LYAA $p = 0.006$; LYAO $p = 0.002$). In both studies, ATX achieved statistically significantly greater mean improvement compared with placebo on the Inattention (p□.01) and Hyperactivity-Impulsivity subscales ($p<0.02$) of the CAARSInv:SV.

18.2.2 Comments on Methodology and Results

The acute trials were very similar in terms of design, endpoints and statistical analysis. They are therefore reviewed together. In general the trials appear to be of a very high standard. There are no major methodological concerns. In particular the statistical analyses presented provide compelling evidence of efficacy and are supported by sensible sensitivity analyses confirming the robustness of the findings.

There are two outstanding issues:

Firstly, there is no trial of long-term efficacy in adults. The applicant extrapolates this evidence from the trials in children and adolescents. The validity of this extrapolation requires clinical consideration. The fact that the adult data is from short-term trials should be mentioned in the SPC if a licence is granted in this population.

Secondly, the question of dose requires further consideration. Only one trial LYAC was designed to compare different fixed dose levels. This trial was for short-term twice-daily treatment in paediatrics. There was no dose finding study for once daily dosing or in adults. Other trials compared flexible dose levels with placebo. Flexible dose trials, while able to demonstrate the efficacy of a proposed posology, are unable to verify that a dose increase is worthwhile for patients with inadequate response to a lower dose.

Considering the proposed posology, LYAC did not establish the absolute efficacy of the 0.5 mg/kg/day, though 1.2 mg/kg/day and 1.8 mg/kg/day were shown to be effective. Period III of the trial was to assess the efficacy of increased doses in non-responders. However, the applicant's claim that patients failing on 0.5 mg/kg/day responded better to 1.2 mg/kg/day is based on a comparison to the Period III baseline, not to a concurrent control group. Patients were not re-randomised. Consequently, this is considered weaker evidence, though the greater evidence of the 1.2 mg/kg/day dose is accepted. Clinical judgement should consider whether the SPC should allow 0.5 mg/kg/day as a therapeutic dose or whether the SPC should include a stronger recommendation to reach 1.2 mg/kg/day, regardless of whether a clinically significant effect is observed on the lower dose.
There is insufficient evidence that patients responding inadequately to 1.2 mg/kg/day will benefit from a dose increase to 1.8 mg/kg/day. This needs further elucidation.

The validity of all extrapolations on dose, i.e. to once-daily dosing, long-term treatment and treatment of adults (short and long-term) will have to be considered clinically.

Some minor comments are further described below:

- *Clinical judgement is required to establish the validity of the primary endpoint. The applicant claims that the endpoint was validated by the pivotal studies in this indication. Given that the data from the pivotal studies proved that a difference between active control and placebo could be detected using this scale in a repeated fashion, its use seems reasonable.*

- *Patients required both a baseline and a follow-up measure for inclusion to the ITT population. This is not in line with ICH E9. Patient withdrawals were more frequently due to AE on ATX and due to lack of efficacy on placebo. However, the number of exclusions and withdrawals during the treatment period along with the consistent efficacy results give rise to no concerns over the introduction of important bias.*

- *There was some evidence of a treatment by centre interaction in LYAC, but this appears to have been quantitative in nature. There was also evidence of a quantitative interaction in the different metaboliser subgroups and a potentially qualitative interaction for ADHD subtypes, with a large effect being observed for the combined subtype and a smaller effect being observed for the inattentive subtype (see below). This finding did not replicate the results of HFBD or HFBK and the applicant considers it to be an anomaly.*

- *In a number of studies some sponsor personnel were permitted to view the randomisation schedule before the acute phase portion of the study. The trial reports do not specify which personnel were allowed access to unblinded data or randomisation schedules, though is at least one study, sponsor personnel, who had contact with investigational sites, were given access to summary data by treatment group. It is not clear why even this level of unblinding was necessary.*

- *There are minor methodological concerns with the primary analysis in some studies. The primary analysis included a large number of covariates in a MMRM model. The lack of pre-specification of the precise covariance structure to be used and the absence of an unadjusted sensitivity analysis are of no great concern. The sensitivity analyses supplied support the primary analysis.*

Pooling the acute data is considered appropriate, and an investigation of heterogeneity of effect sizes between once and twice daily dosing found in Table CTD 2.7.3.7. The results of the pooled analysis confirm the effects observed in the individual studies. The pooled analysis is not considered pivotal for evidence of efficacy.

Randomised-withdrawal trials have been used to provide evidence of long-term efficacy. The applicant is commended for conducting this type of trial. The present trial demonstrates that treatment for longer than 10 weeks is appropriate. Phase III will aim to generate data to show that treatment beyond 52 weeks is appropriate and the results of this Phase of the trial will be of great interest.

E. Efficacy in Subgroups

Data were combined to increase the sample size and the statistical power to detect treatment effects. Three separate pools of data were combined: data from the acute, randomised, double-blind, placebo-controlled paediatric studies; data from the acute, randomised, double-blind, placebo-controlled adult studies; and data from the two open-label studies that included patients with a CYP2D6 PM and EM genotype (LYAB and LYBB). In pooling these data, the consistency of treatment effects across sub-populations was assessed by the therapy-by-subgroup interaction term in an ANCOVA model with terms for protocol, therapy, subgroup (age, sex, origin, CYP2D6 metabolic status, ADHD subtype, and prior stimulant use), and therapy-by-subgroup interaction.

- HFBD and HFBK were excluded from the subgroup analysis by CYP2D6 metabolic status as these studies excluded PM patients.
- LYAW was excluded from all of the subgroup analyses because this study used a different primary efficacy measure.

Studies using once-daily dosing were pooled with studies that used twice-daily dosing because the results of the individual studies indicated no difference in treatment effects between these two dosing regimens.

18.2.3 Comments on Results and Methodology

Given that overall evidence of efficacy has been established this pooling of data is considered reasonable to investigate effects in various subgroups.
Two statistically significant interactions were discovered. There was evidence that the effects of ATX differed between extensive metabolisers (EM) and poor metabolisers (PM), and between the different ADHD subtypes. This latter interaction is considered to be of little consequence. It is a quantitative interaction and, as such, it is the magnitude only of the treatment effect that differs, its direction still indicates a beneficial effect in both subgroups. This is also true for metaboliser type, though the estimated effect of ATX treatment is greater in PM. However, this interaction is complicated by whether dosing was once or twice daily. Statistically significantly greater response was achieved in PM patients on twice-daily compared to once-daily dosing. This difference was not observed for EM patients, of which there were markedly more. Given that these subgroups are based on only 16 patients, the applicant suggests that they might be viewed as preliminary findings. This seems reasonable unless there is an overwhelming biological plausibility that PM might do better with twice-daily dosing, in which case this might be reflected in the SPC.

18.3 Overall Conclusions (Statistical)

Evidence of efficacy for Strattera has been clearly established. The applicant has conducted a large number of trials using once-daily and twice-daily dosing, has used randomised withdrawal designs to establish evidence of long term efficacy and has tested ATX in each relevant age group. There is a paucity of evidence of long-term efficacy in adults and the validity of the extrapolation from paediatric data requires clinical consideration.

The trials were generally without methodological concerns. Statements around unblinding of some sponsor personnel prior to database lock are of some concern, but appropriate statistical tests have been conducted and missing data has been appropriately handled.

The proposed posology requires further consideration. In paediatrics there is a benefit of 1.2 mg/kg/day over 0.5 mg/kg/day. However, there is no evidence of an additional benefit for the 1.8 mg/kg/day dose (either as a once-daily dose or as two divided doses). The risk:benefit of the higher dose should be considered. In adults the two pivotal trials were conducted using daily doses of 60 to 120 mg. However, the SPC proposes a start dose of 40mg. This discrepancy should also be considered. The validity of extrapolating the paediatric dose-finding work to adults should also be considered.

18.3.1 Outstanding Statistical Issue

According to the relevant trial reports sponsor personnel had unblinded access to the randomisation schedule and to interim data in a number of the pivotal studies. The

reasons for and extent of this access should be clarified and implications for trial conduct and results should be discussed.

Company's Response (Summary)

The clinical data package submitted to the MHRA assessing the efficacy of atomoxetine for the treatment of paediatric ADHD includes 6 double-blind, placebo controlled studies ranging from 6 to 9 weeks, as well as a relapse prevention study. Additionally, Study LYBI is now complete and the results have been provided in response to Question 7. All of these trials demonstrated statistically significantly greater symptom reductions for Strattera as compared with placebo, and all with similar treatment effect sizes. Among these studies, only 2 (proof-of –concept Study HFBD and Study HFBK) had interim data analyses conducted, and both studies utilised the same Data Monitoring Board (DMB). The DMBs for these interim analyses included Lilly employees, though not anyone with direct responsibilities for the conduct of the study. None of the other studies had interim analyses. Given the consistency of Study HFBD and Study HFBK results with the other studies, we are confident that the results are meaningful and unbiased. Even if the results of Study HFBD and Study HFBK were excluded from consideration, the remaining studies provide a large and convincing body of evidence supporting atomoxetine's efficacy. Therefore, as discussed and agreed with the MHRA in December 2003, the interim analyses in Study HFBD and Study HFBK do not affect the final judgment of the safety and efficacy of atomoxetine.

We appreciate the MHRA's position that DMBs for interim analyses be composed of individuals independent of the sponsor. As discussed with the MHRA in December 2003, Lilly agrees with this position, and has changed its policy since the late 1990s when Study HFBD and Study HFBK were conducted: membership of DMBs for interim analyses of studies that are planned as pivotal registration studies are now, under usual circumstances, composed of individuals external to Lilly.

Assessor's Comment

The applicant argues that the unblinding of certain sponsor personnel had no detrimental effect on the outcomes of the affected trials. This cannot be confirmed, but it is accepted that the results of these trials are reasonably consistent with results of other trials in the programme.

Point cleared.

18.4 IV.3 General Medical Aspects of Short Term Paediatric Efficacy Studies

This section will consider clinical aspects of the studies in children and adolescents, in particular the patient populations studied and the rating scales used as the major efficacy endpoints. Repetition of points made by the statistical assessor will be avoided and hence the reports of the two assessors should be considered together. The individual studies are described in section IV.4-8 of this report. The adult studies differed in many ways from the paediatric and they are considered in section IV.12.

18.4.1 IV.3.1 Study Populations and Diagnostic Criteria

Studies were conducted at various centres in Europe, Canada, Australia, Israel, South Africa, and the United States (US). Studies HFBD, HFBK, LYAW, and LYBG primarily studied children aged 6 to 12 years whilst all other paediatric studies included both children and adolescents.

Diagnoses of ADHD according to DSM-IV criteria and the presence or absence of comorbid disorders were confirmed by a standardised, semistructured interview, the Kiddie Schedule. For studies using the ADHDRS-IV-Parent: Inv scoring system (HFBD, HFBK, HFBE, LYAC, LYBG, LYAT, and LYAF) patients were required to score at least 1.5 standard deviations (SD) above age and sex norms at baseline.

In Study LYAW, which used the ADHDRS-IV- Teacher: Inv scoring system, patients were required to score at least 1.0 SD above age and sex norms at baseline and to have a mean Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) ADHD Index score at least 1.5 SD above age and sex norms.

The applicant states that these requirements correspond with ADHD symptoms of greater than moderate severity at baseline. This appears valid.

18.4.1.1.1.1.1 Exclusion Criteria

Patients with a history of bipolar or psychotic disorder were excluded.

Comorbid conditions including depression and anxiety disorders (including generalised anxiety disorder, panic disorder, and social phobia) were not exclusion criteria in the paediatric studies. This is considered appropriate given that it is representative of the population likely to receive atomoxetine in clinical practice. Nevertheless, the proportion of patients with depression or anxiety in most studies was low (typically less than 5%) and suggests that this did not confound efficacy assessments.

Studies HFBD, HFBK, and LYAC excluded patients who were previously unresponsive to methylphenidate.

Patients with motor tic or Tourette's syndrome were excluded only in the earlier Phase II studies.

18.4.2 IV.3.2 Treatment Regimens

Atomoxetine was initiated at doses between 0.29 and 0.89 mg/kg/day and (except in the fixed dose-response study) was increased to a target dose. In most studies the target dose was 1.2 mg/kg/day and the maximum total daily dose was 1.8 mg/kg/day. Study medication was administered once daily in the morning in the Phase III acute, double-blind, placebo-controlled studies (LYAT, LYAW, and LYBG). In the earlier Phase II studies, the fixed dose-response study, the tic study and the long term studies, study medication was administered as a twice daily divided dose in the morning and late afternoon/early evening.

18.4.3 IV.3.3 Primary Efficacy Measure

The primary efficacy measures administered in all of the short term paediatric clinical studies was the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHDRS-

IV). In one study (LYAW) the teacher reported version of the scale was used (ADHDRS-IV-Teacher:Inv) and in all others the parent reported version (ADHDRS-IV-Parent:Inv) was used. The primary efficacy analysis was the mean change from baseline to endpoint on this measure in the ITT population. In the long-term studies, LYAF and HFBE, the ADHDRS-IV-Parent:Inv and CGI-ADHD-S were the primary measures and number of days to symptom relapse was the primary endpoint.

ADHDRS-IV is an 18-item scale used to assess ADHD symptom severity in children and adolescents using the same 18 items that are used to define a diagnosis of ADHD in the DSM-IV. A qualified researcher scored the instrument during an interview with the parent/teacher, who assessed the symptom severity of the child's symptoms over the previous week. Each item is marked by the researcher from 0=never or rarely to 3=very often. The total score therefore ranges from a score of 0 to 54.

In addition to the total score, subscale scores for Inattention features and for Hyperactivity-Impulsivity features were computed from the 18 items. The Inattention subscale is the sum of the scores on the odd-numbered items and the Hyperactivity-Impulsivity subscale is the sum of the scores on the even-numbered items.

The psychometric properties of the ADHDRS-IV have been documented in published studies
(Murphy and Barkley 1996; DuPaul et al. 1998) and the reliability and validity of the instrument has been reviewed by the applicant and the clinical expert. Age and sex norms have been established based on a sample of 2000 children in the US. The results of validation analyses conducted by the sponsor indicate that the ADHDRS-IV-Parent:Inv has acceptable reliability (inter-rater, test-retest), internal consistency, validity (convergent and discriminant), and responsiveness when investigator administered and scored.

Assessor's Comment
The applicant has presented sufficient evidence to demonstrate that this instrument is adequately validated and that it is applicable to non-US populations as demonstrated by the additional assessment of the scale's psychometric properties in a predominantly European population in study LYAF.

18.4.4 IV.3.4 Definition of Response to Treatment

All paediatric studies included several categorical assessments of improvement (response). The *a priori* definitions of response were stringent in some studies (patients with complete symptom remission) and more sensitive in other studies (patients with at least some benefit).
Because the *a priori* definitions of response varied across studies, a post hoc definition was developed primarily to compare the response rates from the acute placebo-controlled paediatric studies. The post hoc definition of response was a mean change from baseline to endpoint decrease in ADHDRS-IV-Parent:Inv Total T-score of at least 10 points.

Analysis showed that a decrease from baseline to endpoint of 10 points in the ADHDRS-IV-Parent:Inv total T-score corresponded with a decrease of one point in the CGI-ADHD-S score. Similar correlation was found with the CGI-ADHD-S score.

Assessor's Comment
This definition of response represents on average a change of one point on a 0-3 range in 13 of the 18 items of the ADHDRS-IV scale. It is considered clinically meaningful.

18.4.5 IV.3.5 Secondary Efficacy and Quality of Life Measures

The following secondary efficacy measures were used:

- Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S)
- Clinical Global Impressions-ADHD-Improvement (CGI-ADHD-I)
- Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S)
- Daily Parent Ratings of Evening and Morning Behaviour-Revised (DPREMB-Revised)
- Quality of Life Measure in Pediatric Studies - Child Health Questionnaire (CHQ)

CGI-ADHD-S is a single-item rating of the clinician's assessment of the severity of ADHD symptoms in relation to the clinician's total experience with ADHD rated on a 7-point scale (1 = normal, not at all ill; 7 = among the most extremely ill patients). A higher score indicates greater severity of ADHD symptoms.

The CGI-ADHD-I measures the total improvement (or worsening) of a patient's ADHD symptoms from the beginning of treatment, regardless of whether or not improvement (or worsening) was thought to be due entirely to drug treatment. Improvement is rated on a 7-point scale (1 = very much improved; 7 = very much worsened).
The psychometric properties and sensitivity of the CGI scales have been well documented. They are generally regarded as reliable, accurate, and relevant in studies in psychiatric conditions.

The CPRS-R:S is a 27-item rating scale completed by the parent to assess problem behaviours related to ADHD (Conners 1997). It was administered in Studies HFBD, HFBK, HFBE, LYAB, LYBB, LYAT, and LYAW. The psychometric properties of the scale appear to be adequately validated.

The DPREMB-Revised scale is a short instrument that was developed by the sponsor and was administered in Study LYBG. It measures the level of difficulty with 11 specific common morning or evening behaviours (for example, getting up and out of bed, doing or completing homework, sitting through dinner). Possible scores for each item range from 0 (no difficulty) to 3 (a lot of difficulty). The psychometric properties of this instrument have not been established although it was used in a pilot form in a previous study (LYAT) and appeared to perform satisfactorily. Although it cannot be considered to be fully validated as yet it appears to be an appropriate tool.

The CHQ is a broad-based health outcomes measure designed to assess the physical and psychosocial well being of children 5 years of age and older. It was administered in Studies LYAB, LYAC, LYAF, LYAW, and LYBG.

18.5IV.4 Dose-Response Studies and Data Supporting Posology

A single dose response study is submitted. In addition the applicant claims that two open-label studies (LYAB and LYBB) and the doses to which patients were titrated in the pivotal short term studies support the proposed posology. As pointed out by the statistical assessor it is considered that while able to demonstrate the efficacy of a proposed posology, these data are unable to verify that a dose increase is worthwhile for patients with inadequate response to a lower dose, and therefore add very little information on dose-response. The justification for the proposed posology must therefore depend on the data from study LYAC.

18.5.1 IV.4.1 Paediatric Fixed Dose Response Study (LYAC)

Study LYAC was a multicentre, randomised, double-blind, placebo-controlled parallel fixed dose response study conducted in the US in 297 children and adolescents aged 8 - 18 years who met the DSM-IV criteria for ADHD. The acute, randomised, 8 week main study period (II) was followed by a non-responder assessment period (Study Period III); a double-blind responder extension period (IV); and a discontinuation period (V).
Patients were randomised to one of four fixed target dose treatment groups: 0.5, 1.2 or 1.8 mg/kg/day, or placebo in a 1:2:2:2 ratio, respectively. Doses were administered as a twice daily divided dose. Primary efficacy endpoint results from the acute treatment period were as follows:

		Baseline	Endpoint	Change	p-val* vs Placebo	
Treatment	n	Mean (SD)	Mean (SD)	Mean (SD)	Adjusted	(Unadjusted)
Placebo	83	38.3 (8.9)	32.5 13.8	-5.8 10.9		
ATX 0.5	43	40.2 (9.6)	30.3 15.2	-9.9 14.6		(0.155)
ATX 1.2	84	39.2 (9.2)	25.5 13.8	-13.6 14.0	<0.001	(<0.001)
ATX 1.8	82	39.7 (8.7)	26.2 14.8	-13.5 14.5	<0.001	(<0.001)

18.5.1.1.1.1.1 Assessor's Comment

Atomoxetine 1.2 and 1.8 mg/kg/day were both clinically and statistically significantly superior to placebo in the primary efficacy analysis (ADHDRS-IV-Parent:Inv score), on both the inattention (p<.001) and hyperactivity-Impulsivity (p=0.001) subscales, and on a number of the secondary endpoints including responder analyses. However there was no evidence of any additional benefit from increasing the dose from 1.2 to 1.8 mg/kg/day. The lower 0.5 mg/kg/day dose was not statistically significantly superior to placebo and is considered to be sub-therapeutic.
In the extended non-responder assessment period, patients who did not meet response criteria in the 8 week main study period showed a significant reduction in their ADHDRS-IV-Parent:Inv score by increasing their dose to 1.2 mg/kg/day. This provides

some evidence of a significant treatment effect of an adequate dose of atomoxetine beyond 8 weeks.
When atomoxetine was discontinued (Study Period V), a statistically significant worsening in ADHDRS-IV-Parent:Inv Total Score was observed whether treatment was tapered (p = .004) or abruptly stopped (p<.001). There was no evidence of symptom rebound (i.e. ADHDRS score worse than baseline) with either discontinuation method. Again this shows evidence of long term maintenance of efficacy.
This study is considered to show satisfactory evidence of dose-response. The steep part of the curve is around 0.5 mg/kg/day and response plateaus after 1.2mg/kg/day.

18.5.2 IV.4.2 Justification for Once Daily Dosing

The only parallel fixed dose response study employed twice daily divided dosing. However the applicant now proposes once daily dosing in the SPC. The pharmacokinetic data do not support once daily dosing as the elimination half life of atomoxetine is only 3.5 hours in extensive metabolisers and no non-clinical pharmacodynamic data are available. Therefore a justification for once daily dosing must depend on clinical studies employing this posology.

18.6 IV.5 Pivotal Short Term Paediatric Efficacy Studies

Three Phase III randomised, double-blind, placebo-controlled studies in children/adolescents are presented. In all three studies, medication was administered once-daily in the morning. Two studies (LYAT and LYBG) were conducted in the home setting and hence the ADHDRS-IV parent version (investigator administered and scored) was the primary efficacy measure. Study LYAW was conducted in the school setting and the ADHDRS-IV teacher version (investigator administered and scored) was the primary efficacy measure.

Only the results for the primary efficacy analyses are presented here for each individual study. Secondary analyses are presented later for the combined data set of the five short term paediatric efficacy studies that used ADHDRS-IV-Parent:Inv Total score as the primary endpoint. Safety data are considered separately.

18.6.1 IV.5.1 LYAT

171 children and adolescents aged 6 to 16 years who met the DSM-IV criteria for ADHD at nine study sites in the US were randomised to receive atomoxetine (85 subjects) vs. placebo (86 subjects) over a 6 week treatment period. The dose was titrated from a starting dose of 0.5mg/kg/day, based on clinical response, safety and tolerability, to a maximum dose of 1.5mg/kg/day.
This study also looked at evening symptoms, as measured by the Daily Parent Ratings of Evening and Morning Behaviour - Revised (DPREMB-R). This is important as the PK profile raises concerns over reduced efficacy in the latter part of a 24-hour dosing interval with once daily dosing.
Results for the primary efficacy endpoint (ADHDRS-IV-Parent:Inv Total score):

Treatment	N	Baseline Mean (SD)	Mean Change	Difference vs. placebo and 90% CI **	P value
Atomoxetine Placebo	84 83	37.6 (9.4) 36.7 (8.8)	-15.8 -5.0	-10.8 (-11.2 , -4.4)	<0.001

Assessor's Comment

Atomoxetine showed clinically and statistically significant superiority to placebo in the primary endpoint, ADHD symptoms on the ADHDRS-IV-Parent:Inv Total score and also on the Inattention and Hyperactivity-Impulsivity subscales. Maximal efficacy was seen after 2 weeks. Atomoxetine was also statistically significantly superior to placebo in late afternoon and evening symptoms (inattentive and easily distracted [p = .003], and settling down and getting ready for bed [p = .023])

18.6.2 IV.5.2 LYBG

197 children and adolescents aged 6 to 12 years who met the DSM-IV criteria for ADHD at 12 study sites in the US were randomised to receive atomoxetine (133 subjects) vs. placebo (64 subjects) over an 8 week treatment period. The dose was titrated from a starting dose of 0.8 mg/kg/day, based on clinical response, safety and tolerability, to a maximum dose of 1.8 mg/kg/day.

The study also included an assessment of evening behaviour using the evening sub-score of the DPREMB-Revised.

Following the acute double-blind treatment period continuing patients entered an open-label extension period of the study.

Results for the primary efficacy endpoint (ADHDRS-IV-Parent:Inv Total score):

Treatment	N	Baseline Mean (SD)	Mean Change	Difference vs. placebo and 90% CI **	P value
Atomoxetine Placebo	126 60	42.1 (9.2) 42.3 (7.1)	-16.8 -7.0	-9.8 (-13.8, -5.9)	<0.001

Assessor's Comment

Atomoxetine showed clinically and statistically (p<0.001) significant superiority to placebo in the primary endpoint, ADHD symptoms on the ADHDRS-IV-Parent:Inv Total score and also on the Inattention and Hyperactivity-Impulsivity subscales. Efficacy was evident as early as 1 week after the start of treatment with atomoxetine and continued at each visit until the endpoint of the acute treatment phase.

This study used three a priori definitions of responders: a 25% decrease from baseline to endpoint in ADHDRS-IV-Parent:Inv Total score; an endpoint CGI-ADHD-S score of 1 or 2; and an endpoint ADHDRS-IV-Parent:Inv Total T-score of 65. The proportion of atomoxetine-treated patients meeting the definition for response was statistically significantly greater compared with the proportion of placebo-treated patients (p<0.001) using each of the three individual definitions for response.

Atomoxetine was statistically significantly superior to placebo on evening and morning ADHD symptoms as assessed by the DPREMB-Revised evening subscore ($p<0.001$) and morning subscore ($p = .018$). The fact that efficacy was well maintained during the 24 hour dosing interval with once daily dosing in the morning, despite plasma levels being very low by the evening indicates that therapeutic activity during the course of the dosing interval does not directly correlate with plasma levels. This is in contrast to the stimulants, for which an "on-off" effect is often seen, corresponding with fluctuations in plasma levels. Clinical experience shows that many subjects treated with methylphenidate often require an evening dose for this reason.

18.6.3 IV.5.3 LYAW

Study LYAW was a school outcome study and the primary efficacy measure was a teacher report measure, the ADHDRS-IV-Teacher: Inv. 153 children and adolescents aged 8 to 12 years who met the DSM-IV criteria for ADHD at 11 study sites in the US, Puerto Rico, and Canada were randomised to receive atomoxetine (101 subjects) vs. placebo (52 subjects) over a 6 week treatment period. The dose was titrated from a starting dose of 0.8 mg/kg/day, based on clinical response, safety and tolerability, to a maximum dose of 1.8 mg/kg/day. Following the acute double-blind treatment period continuing patients entered an open-label extension period of the study. Results for the primary efficacy endpoint:

Treatment	N	Baseline Mean (SD)	Mean Change	Difference vs. placebo and 90% CI **	P value
Atomoxetine	101	38.7 (7.7)	-14.3	-7.3 (-10.9 , -3.0)	<0.001
Placebo	51	36.7 (8.4)	-7.2		

Assessor's Comment

Atomoxetine showed clinically and statistically ($p<0.001$) significant superiority to placebo in the primary endpoint, ADHD symptoms on the ADHDRS-IV- Teacher:Inv Total score and also on the Inattention and Hyperactivity-Impulsivity subscales. Atomoxetine is shown to be effective in short term treatment in the school setting.

18.7 IV.6 Supportive Short Term Efficacy Studies

18.7.1.1.1 HFBD and HFBK

These Phase II exploratory 9 week, randomised, double-blind, placebo-controlled studies in stimulant-naïve children/adolescents (aged at least 7 years) in the home setting in the US were of identical design. They included an active comparator (methylphenidate) in addition to placebo in order to validate the study design. The numbers randomised were as follows:

HFBD	Atomoxetine (65) vs. placebo (62) vs. methylphenidate (20)
HFBK	Atomoxetine (64) vs. placebo (62) vs. methylphenidate (18)

Poor metabolisers were excluded due to the lack of safety data at the time of these studies. Study medication was titrated up to atomoxetine 2.0 mg/kg/day and

methylphenidate 1.5 mg/kg/day, based on clinical response. The 9 week placebo-controlled treatment period was followed by a single-blind discontinuation period. The primary efficacy endpoint was atomoxetine vs. placebo mean change from baseline to endpoint on the ADHDRS-IV-Parent:Inv Total score. Results for the primary efficacy endpoint are as follows:

	Treatment	N	Baseline Mean (SD)	Mean Change	Upper, lower 90% CI mean difference vs. placebo **	P value
HFBD	Atomoxetine Placebo	64 61	41.2 (8.9) 41.4 (7.9)	-15.6 -5.5	-14.1 , -5.2	<0.001
HFBK	Atomoxetine Placebo	63 60	37.8 (7.9) 37.6 (8.0)	-14.4 -5.9	-12.4 , -3.5	<0.001

18.7.1.1.1.1.1.1 Assessor's Comment

In both studies, atomoxetine was clinically and statistically significantly superior to placebo in the analysis of the primary efficacy endpoint, the responder analysis and also on some but not all of the secondary endpoints. Following abrupt discontinuation of study medication there was no evidence of rebound effects.

18.8IV.7 Clinical Studies in Special Populations

18.8.1 IV.7.1 Co-morbid Tic Disorder Study (LYAS)

This was an acute, double-blind, placebo-controlled study in patients with ADHD and co-morbid tic disorder conducted in 148 children and adolescents aged 7 to 17 at 15 study sites in the US. Patients met the DSM-IV diagnostic criteria for ADHD and also had concurrent Tourette's Disorder or chronic motor tic disorder. The primary objective of the study was to demonstrate non-inferiority of atomoxetine compared with placebo in terms of tic severity.

The Yale Global Tic Severity Scale (YGTSS) was the primary efficacy measure. It was designed to measure tic severity and degree of impairment in patients with Tourette's syndrome and other tic disorders. It is administered and scored by the clinician during a semi-structured interview with the patient and/or parent and evaluates the number, frequency, intensity, complexity, and interference of motor and phonic (vocal) tic symptoms. Each symptom and overall level of impairment are rated on a 6-point scale (0 = none/absent to 5 = severe/always) giving Total and Overall Impairment scores, and Motor and Phonic Tic Subscale scores. Satisfactory literature references are provided to confirm that the scale is a valid instrument for this purpose, that data generated by it correlate well with other tic rating scales, that it is sensitive to treatment effects and that it is widely used by academics in this field. The clinical expert also supports the use of this scale.

Following a screening and washout period, patients were randomised to receive atomoxetine or placebo for the main 18 week treatment period. Beginning at 0.5

mg/kg/day the dose was titrated using a standard schedule according to clinical response and safety and tolerability up to a maximum of 1.5 mg/kg/day.

18.8.1.1.1.1.1.1 Assessor's Comment

Formal non-inferiority of atomoxetine compared with placebo in terms of tic severity was demonstrated. When only the data from patients with Tourette's syndrome were analysed, atomoxetine was statistically significantly superior to placebo (p = 0.027). As this was a secondary analysis without multiplicity correction it should be interpreted with caution. Nevertheless this clearly contrasts with the stimulants (e.g. methylphenidate), which are contraindicated in Tourette's syndrome because they are known to exacerbate tics.

18.9 IV.8 Active Comparator Phase III Study LYBI

A three way acute treatment study with both placebo and active comparators (study LYBI) was nearing completion at the time of the initial submission. The completed safety and efficacy results are now included in the updated dossier (Clinical Summary Addendum). The only other active comparator data are from the Phase II studies HFBD and HFBK, which did not include sufficient numbers of patients treated with the active comparator (methylphenidate) to provide any confirmatory evidence of relative efficacy.

LYBI is not of pivotal importance to the demonstration of efficacy in this application. It is not a regulatory requirement to show efficacy relative to an established product. The study re-affirms the efficacy of atomoxetine relative to placebo and its failure to demonstrate non-inferiority to methylphenidate (Concerta™) is not considered crucial. A summary of the results is presented below:

Percentage of Patients Classified as Responders* During Study Period II

	Atomoxetine		Methylphenidate		Placebo		ATX vs MPH
	N/N	%	N/N	%	N/N	%	p-Value
All Patients	95/213	44.6	119/211	56.4	16/68	23.5	0.016
Prior Stimulant Users	50/134	37.3	65/127	51.2	9/40	22.5	0.026
Stimulant Naïve Patients	45/79	57.0	54/84	64.3	7/28	25.0	0.423

Abbreviations: ATX=atomoxetine, MPH=methylphenidate.
* P-values are based on the Fisher's exact test.

The applicant argues that the results in the subgroup of stimulant naïve patients might better represent the relative efficacy of atomoxetine and methylphenidate. This is because some prior stimulant users, those expected to perform poorly on methylphenidate, were excluded from the study. It is considered reasonable to conclude that this would cause a bias in favour of methylphenidate. However, the proportion of patients likely to be affected by these exclusions has not been provided and the magnitude of this bias cannot be ascertained. It can certainly not be verified that the bias is of sufficient magnitude that atomoxetine would otherwise have been shown to be non-inferior. Indeed, even in the sub-population of stimulant-naïve patients, the data are consistent with the response to atomoxetine being lower. The applicant's conclusion that

differences in response rates are 'modest' and of 'uncertain clinical relevance' appear to be based primarily on differences in point estimates, which is at best an incomplete interpretation of data from a non-inferiority trial, and is questionable given the choice of non-inferiority margin, which is supposed to define those differences of clinical relevance.

The study also contained a second, double-blind, randomised, extension phase in which:

1. non-responders to atomoxetine who were CYP2D6 extensive metaboliser (EM) patients were randomised to continue at the same dose or to high-dose atomoxetine (up to 3.0 mg/kg/day);
2. responders to atomoxetine continued at the same dose or on a lower dose (approximately 0.5 mg/kg/day)
3. patients who were initially treated with methylphenidate were switched to atomoxetine for a 6-week treatment trial, and then were randomised to continuation therapy in the same manner as described above based on their response to atomoxetine.

These are all reasonable extensions of the initial acute treatment phase. In particular, parts 1 and 2 above are interesting given that they involve re-randomisation and not simply an uncontrolled switch of treatments (as in3).

There was no confirmatory evidence that increasing the dose of atomoxetine (to 3.0 mg/kg/day) in non-responders would lead to an increased effect compared to continued dosing at the same dose level. This is in line with recommendations made during the original CSM consideration of this application that doses above 1.2mg/kg had not demonstrated additional benefit.

Similarly there was no confirmatory evidence as to whether patients should be maintained at the same dose on which they responded or switched to a lower dose.

There was some evidence that patients who did not respond to methylphenidate might respond to atomoxetine, but, as described above, in an uncontrolled dataset, it is not possible to distinguish between the effect of atomoxetine and the duration of treatment.

In summary, there is evidence to hypothesise that the efficacy of atomoxetine might be less than the efficacy of methylphenidate. This is not considered crucial to the overall evidence of efficacy for atomoxetine. The extension phases are of interest but provide little or no confirmatory data that should impact on the licensing decision.

18.10IV.9 Combined Results of Short term Paediatric Efficacy Studies

The applicant has presented analyses of the combined efficacy data set from all short term (6 to 9 week) efficacy studies in children and adolescents, i.e. studies HFBD, HFBK, LYAC, LYAT, LYBG, and LYAW. All studies except LYAC employed flexible (titrated) dosing regimens. Since the atomoxetine 1.2 and 1.8mg/kg/day dose arms in Study LYAC gave similar results these doses were combined in the combined efficacy

analyses. As 0.5mg/kg/day was sub-therapeutic this dose was excluded. This is reasonable. A wide range of patients from many European as well as American centres were studied but all were required to meet the same DSM-IV diagnostic criteria. All of these studies used similar methods (placebo-controlled, double-blinded) although there were significant design differences between some of the studies and hence number of the analysis criteria were defined post hoc. Overall it is considered that the studies are sufficiently similar in both their design and the characteristics of the study populations for the combined analyses to be valid.

The table below summarises the mean change from baseline to endpoint analysis for the primary efficacy endpoints using a LOCF approach to missing data. These data are displayed graphically on page 30 of the clinical overview.

	Treatment	N	Baseline Mean (SD)	Mean Change	Difference vs. placebo and 90% CI **	P value
HFBD	Atomoxetine Placebo	64 61	41.2 (8.9) 41.4 (7.9)	-15.6 -5.5	-10.1 (-14.1 , -5.2)	<0.001
HFBK	Atomoxetine Placebo	63 60	37.8 (7.9) 37.6 (8.0)	-14.4 -5.9	-8.5 (-12.4 , -3.5)	<0.001
LYAC	Atomoxetine 1.2 Atomoxetine 1.8 Placebo	84 82 83	39.2 (9.2) 39.7 (8.7) 38.3 (8.9)	-13.7 -13.5 -5.8	-7.9 (-12.0 , -3.1) -7.7 (-11.7 , -2.8)	<0.001
LYAT	Atomoxetine Placebo	84 83	37.6 (9.4) 36.7 (8.8)	-15.8 -5.0	-10.8 (-11.2 , -4.4)	<0.001
LYBG	Atomoxetine Placebo	126 60	42.1 (9.2) 42.3 (7.1)	-16.8 -7.0	-9.8 (-13.8, -5.9)	<0.001
LYAW	Atomoxetine Placebo	101 51	38.7 (7.7) 36.7 (8.4)	-14.3 -7.2	-7.3 (-10.9 , -3.0)	<0.001

** 95% CI: 2- sided confidence interval of LS means difference in change score between atomoxetine and placebo.

18.10.1.1.1.1.1.1 Assessor's Comment

Baseline mean symptom severity was fairly consistent, both across the studies and between active and placebo in each study. The magnitude of response to placebo and to active atomoxetine was also generally very consistent at 5-7 and 14-16 respectively on the ADHDRS- IV scale primary endpoint. Atomoxetine was superior to placebo with a high degree of statistical significance in each study.

The point estimates for the superiority of atomoxetine compared with placebo ranged from 7.3 to 10.8 points on the ADHDRS- IV scale. Particularly since none of these studies employed an established active comparator the clinical significance of this net treatment effect requires critical examination. The mean change from baseline to endpoint in ADHDRS-IV-Parent:Inv total score was approximately 9 points greater than placebo in the combined analysis. This represents on average a change of one point on a score of 0-3 in half of the items of the ADHDRS-IV scale (18 symptoms rated 0=never or

rarely to 3=very often). The superiority of atomoxetine over placebo is therefore considered to be clinically meaningful.

18.11IV.10 Subgroup Analyses from the Combined Paediatric Efficacy Data Set

For the purpose of subgroup analyses data were combined from the acute placebo-controlled paediatric and adult studies and from the two open-label studies that included both extensive and poor metabolisers (LYAB and LYBB). This is considered a reasonable approach.

Statistically significant interactions on the effects of atomoxetine were identified for the different ADHD subtypes and between extensive metabolisers and poor metabolisers.

18.11.1 IV.10.1 ADHD Subtypes

In atomoxetine treated patients a statistically significantly greater ($p = 0.001$) mean improvement in ADHD symptoms was seen in Combined subtype of patients compared with either Hyperactive/Impulsive or Inattentive subtypes. However a beneficial effect was seen in all subgroups and it was only the magnitude of the treatment effect that differed. This interaction is considered to be of little consequence.

18.11.2 IV.10.2 Extensive versus Poor Metabolisers

In atomoxetine treated patients a statistically significantly greater ($p = 0.001$) mean improvement in ADHD symptoms was seen in the poor metaboliser subgroup (mean change from baseline 22.6) compared with extensive metabolisers (mean change from baseline 14.1). As only 16 patients were included in this analysis this result should be interpreted with caution. Nevertheless it might add some support to the contention that doses higher than 1.2mg/kg/day might be justified despite the lack of dose-response evidence (study LYAC).

18.11.3 IV.10.3 Dosing Frequency

In the poor metaboliser subgroup statistically significantly greater response was seen with twice-daily compared to once-daily dosing. This difference was not observed for extensive metabolisers, the numbers of which were much greater. As only 16 poor metaboliser patients were included in the analysis this result should be interpreted with caution.

18.11.4 IV.10.4 Other Subgroup Analyses

Subgroup analyses revealed no effect on efficacy in atomoxetine treated patients of age <12 and ≥12), gender, race, previous stimulant exposure, co-morbid Oppositional Defiant Disorder.

18.12IV.11 Long Term Paediatric Efficacy Studies

Two long-term, placebo-controlled relapse prevention studies in paediatric patients (LYAF and HFBE) are presented. They are supported by three open-label and other safety studies (HFBF, LYAI, and LYAR) and long-term, double-blind efficacy data from the paediatric dose-response study LYAC (study period IV).

18.12.1 IV.11.1 Paediatric Relapse Prevention Study LYAF

This relapse prevention study was conducted in 604 children and adolescents aged 6 to 15 years in 11 European countries, Australia, South Africa, and Israel. Following a screening and washout period and a 10-week open-label dose-titration period (to a target dose of 1.2 - 1.8 mg/kg/day in twice daily divided doses), patients who met the defined response criteria (CGI-ADHD-S score □2 **and** a reduction of at least 25% from baseline in ADHDRS-IV-Parent:Inv score) were randomised to receive atomoxetine or placebo in the double-blind study period III. Approximately 70% of patients were assigned to atomoxetine and 30% to placebo. After 1 year of treatment with study medication, patients in the atomoxetine group were randomised a second time to continued treatment with atomoxetine or placebo in a 1:1 ratio. The primary efficacy endpoint of the study was the number of days until relapse. Two definitions of relapse were used:

1) CGI-ADHD-S score increased by □2 points **and** an ADHDRS-IV-Parent:Inv Total score that returned to □90% of the baseline score
2) 50% increase in ADHDRS-IV-Parent: Inv Total score and an increase in CGI-ADHD-S of □2 points

From a total of 604 treated patients 416 responded and were randomised. Key results of this study up to the second randomisation in Study Period III are as follows.

The time to symptomatic relapse statistically significantly favoured atomoxetine (p = 0.013) on the Kaplan-Meier curves. Mean time-to-relapse for atomoxetine-treated patients 227.65 days, substantially longer than for placebo-treated patients (158 days). After 9 months of post-randomisation treatment, statistically significantly more atomoxetine-treated patients maintaining their response compared with placebo-treated patients (atomoxetine:126 [43.2%] versus placebo: 35 [28.2%]; p = .004).

No significant differences in treatment effects across nations (country) were apparent.

A total of 163 patients continuing to respond to 1 year of treatment with atomoxetine were included in the second randomisation. Of these, 10 placebo-treated patients and 2 atomoxetine-treated patients in the ITT population relapsed based on the protocolled criteria. This difference reached the conventional 5% level of statistical significance. Supportive analyses were broadly consistent with these findings.

The applicant is commended for conducting a relapse-prevention study of this duration and with multiple randomisations of responders. These data provide particularly compelling evidence of efficacy for long-term treatment. The 52-week relapse-prevention data demonstrate that after 1 year of atomoxetine treatment, patients continuing for a further 6 months with treatment rather than switching to placebo were statistically significantly less likely to relapse or experience partial symptom return. The low relapse rate on placebo (approximately 12%) in this extension phase raises a further issue for consideration. As the majority of patients continuing on placebo did not experience a relapse in the 6 months following the second randomisation, it is credible that a number of patients might be able to discontinue treatment at some point.

Appropriate information on the proportion of patients relapsing at 1 year (active and placebo) has been added to Section 5.1 of the SPC and section 4.4 includes suitable advice on monitoring patients who require long term treatment.

18.12.2 IV.11.2 Paediatric Relapse Prevention Study HFBE

This relapse prevention study was conducted in 228 children and adolescents aged 7 to 15 years at 23 study sites in the US. Following a screening and washout period, patients were randomised to receive open-label treatment with atomoxetine or methylphenidate in a 4:1 ratio. Patients in the atomoxetine group who met the pre-defined response criteria (as for Study LYAF) were then randomised to receive atomoxetine or placebo in an up to 48-week randomised, double-blind, placebo-controlled, variable discontinuation period. The final phase was a double-blind, placebo-controlled, variable taper and treatment discontinuation period (Study Period IV). The definitions of relapse were as for study LYAF.

18.12.2.1.1.1.1.1 Results

This was essentially a failed study. The primary efficacy endpoint showed no difference from placebo. The applicant states that "because of a number of potentially confounding factors and problems with the study design that were not identified before implementation, the results of this study cannot be definitively interpreted with respect to the efficacy". The clinical expert report discusses possible reasons for the failure to show superior efficacy in maintenance treatment compared with placebo. The key issue is the high relapse rate in both study groups. There appears to be some validity to some of the clinical expert's arguments, in particular the possibility that parents were motivated to report that their child had relapsed because they would then be given open label atomoxetine instead of study medication that could be placebo.

18.12.2.1.1.1.1.2 Assessor's Comment on Long Term Relapse Prevention Efficacy Data

HFBE was a relatively small exploratory Phase II study conducted prior to finalising the design of the larger Phase III study LYAF. It is recognised that sometimes studies such as this fail for reasons other than the efficacy of the product being tested. The Phase III study LYAF showed clear evidence of efficacy of atomoxetine for relapse prevention in the medium to long term. It is considered that there is adequate evidence of long term efficacy despite the failure of study HFBE.

18.13IV.12 Adult Efficacy Studies

Two short-term adult efficacy studies are presented, LYAA, and LYAO. These were both 10 week randomised, double-blind, placebo-controlled studies in adult patients with ADHD. No long term studies in adults have been conducted.

Diagnoses were confirmed by structured clinical interview. Confirmation (by a significant other, friend, or family member) of childhood as well as current ADHD

symptoms was an inclusion criterion. This is important since ADHS is a condition of onset in childhood.

The 18-Item Total ADHD Symptoms score of the Connors' Adult ADHD Rating Scale, Investigator rated, Screening Version (CAARS-Inv:SV Total score), was the primary efficacy measure. It was administered and scored by experienced blinded raters. It includes inattention and hyperactivity-impulsivity subscales and the range of possible scores is 0 to 54. Patients were required to score at least 20 on this measure at baseline, corresponding to at least moderate ADHD symptoms.

Literature references on the psychometric properties of the scale are presented. In addition to validation as a self- and observer-rated instrument, the sponsor assessed the reliability and validity of the measure as a clinician-administered and clinician-scored instrument during an interview with a patient. Acceptable reliability and validity correlations were observed. A copy of the analyses is included in the Summary of Clinical Efficacy appendix. It supports the applicant's contention that the measure is sensitive to treatment effects and is gaining wide acceptance in the field. This has also been confirmed in the External Expert Opinion provided by [redacted]

The two adult studies, LYAA and LYAO, were identical concurrent studies conducted in a total of 536 adults aged 18 and older with DSM-IV ADHD at study sites in the US and Canada. The starting dose of atomoxetine was 60 mg/day, with subsequent increases to 90 and 120 mg/day as indicated by clinical response. Following the main 10-week double-blind acute treatment period patients were re-randomised to either abrupt discontinuation, or tapered discontinuation over a 4-week period. The results for the primary efficacy endpoint of the studies are presented in the tables below and are also displayed graphically in the bar chart (fig 2.5.3) on page 32 of the Clinical Overview.

18.13.1 IV.12.1 Study LYAA

At Visit 8 (the last Study Period II visit), atomoxetine-treated patients experienced a significantly greater reduction in CAARS-Inv:SV Total ADHD Symptom scores as compared to placebo (p=0.004). Numerical differences favouring atomoxetine over placebo were seen at every visit, with statistical significance noted at all except Visit 5. The general pattern showed an increased treatment difference between atomoxetine and placebo over time. The following table shows the changes from baseline at the efficacy evaluation visits.

	Atomoxetine		Placebo		Treatment Difference	
Visit	LS Mean (SE)	p-value	LS Mean (SE)	p-value	LS Mean (SE)	p-value
4	28.82 (0.90)	<0.001	30.76 (0.93)	<0.001	-1.94 (0.82)	0.020
5	27.67 (0.99)	<0.001	28.62 (1.02)	<0.001	-0.95 (1.00)	0.342
6	25.23 (1.00)	<0.001	28.18 (1.03)	<0.001	-2.94 (1.02)	0.004
7	23.90 (1.10)	<0.001	27.44 (1.12)	<0.001	-3.54 (1.21)	0.004
8	23.88 (1.13)	<0.001	27.60 (1.15)	<0.001	-3.72 (1.26)	0.004

The 95% Confidence Interval on Change from Baseline to Visit 8 were (-12.04, -7.57) for atomoxetine and (-8.35, -3.81) for placebo. The net treatment effect of atomoxetine is

estimated at 3.7 points on the CAARS-Inv:SV Total ADHD Symptom score. This is of questionable clinical significance given that the range of possible scores is 0 to 54, and it is smaller than the placebo response.

18.13.2 IV.12.1 Study LYAO

At Visit 8 (the last Study Period II visit), atomoxetine-treated patients experienced a significantly greater reduction in CAARS-Inv:SV Total ADHD Symptom scores as compared to placebo ($p<0.001$). Numerical differences favouring atomoxetine over placebo were seen at every visit, with statistical significance noted at all except (again!) Visit 5. As in study LYAA the treatment difference between atomoxetine and placebo generally increased over time. The following table shows the changes from baseline at the efficacy evaluation visits.

	Atomoxetine		Placebo		Treatment Difference	
Visit	LS Mean (SE)	p-value	LS Mean (SE)	p-value	LS Mean (SE)	p-value
4	28.81 (1.17)	<0.001	31.43 (1.14)	<0.001	-2.62 (0.95)	0.006
5	26.61 (1.24)	<0.001	28.80 (1.22)	<0.001	-2.19 (1.12)	0.052
6	24.87 (1.29)	<0.001	28.74 (1.27)	<0.001	-3.87 (1.23)	0.002
7	23.88 (1.34)	<0.001	27.89 (1.31)	<0.001	-4.01 (1.32)	0.003
8	22.63 (1.37)	<0.001	27.23 (1.33)	<0.001	-4.60 (1.37)	<0.001

The 95% Confidence Interval on Change from Baseline to Visit 8 were (-14.57, -9.18) for atomoxetine and (-9.90, -4.65) for placebo. The net treatment effect of atomoxetine is estimated at 4.6 points on the CAARS-Inv:SV Total ADHD Symptom score. This is a little more convincing than study LYAA but is still of questionable clinical significance in the context of a range of possible scores of 0 to 54, and is again smaller than the placebo response.

18.14 Efficacy Conclusions

Evidence of efficacy for atomoxetine in both once-daily and twice-daily dosing has been clearly established both in short-term and long-term treatment of children and adolescents over the age range proposed in the SPC (over 6 years). The randomised-withdrawal trials provide robust evidence of long-term efficacy; the 52 week re-randomisation data from LYAF will be of considerable additional interest. The primary endpoint in the pivotal studies is considered to be satisfactory as the basis for proof of efficacy in the requested indication. Statistically significant superiority to placebo was consistently shown (except in one failed Phase IIb long term study). The net treatment effect of atomoxetine is considered to be clinically highly significant.

There were initial concerns about the pharmacokinetic suitability of atomoxetine for once daily dosing because of its short half life of 3.5 hours. However the clinical data indicate that efficacy is maintained with once daily dosing, presumably because therapeutic activity (and receptor binding) does not fluctuate in parallel with plasma levels. In addition the extrapolation of dose-response data from study LYAC (in which doses were divided twice daily) to once-daily dosing has been satisfactorily justified. The SPC states that "Strattera can be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening". This is

generally satisfactory although it would be helpful to indicate that divided dosing might be preferable where patients either experience adverse effects in the first few hours following dosing or experience worsening ADHD symptoms in the evenings or early morning.

There are however a number of areas of difficulty. These are highlighted below and are discussed more fully in the overall discussion and conclusions at the end of this report.

18.14.1.1 Paediatric Posology

Two aspects of the proposed posology in children and adolescents require consideration.

Study LYAC, the only study that provides reliable dose-response data, showed that for full therapeutic efficacy 0.5mg/kg/day was insufficient and that a dose increase to 1.2mg/kg/day is necessary. The proposed SPC recommends an initial daily dose of 0.5mg/kg/day, maintained for a minimum of 7 days, following which the dose should be increased to a target of 1.2mg/kg/day if the patient has not experienced clinically significant symptom response. As 0.5 mg/kg/day was not shown to be superior to placebo, and is clearly inferior to 1.2mg/kg/day, titration to 1.2mg/kg/day, regardless of the therapeutic response to the lower dose would be preferable.

Study LYAC showed no evidence of an additional benefit for the 1.8mg/kg/day dose. Nevertheless the dose was generally titrated up to 1.8 to 2mg/kg/day in the flexible dose studies. These however add little information on dose response as they do not demonstrate that that increasing the dose to 1.8mg/kg/day produces any additional efficacy in patients with an inadequate response to 1.2mg/kg/day. The data provide little justification for doses higher than 1.2mg/kg/day.

18.14.2 Evidence of Efficacy in Adults

No product is currently approved for the treatment of ADHD in adults. The efficacy studies conducted by the company in this population were all placebo controlled. This is appropriate.

There is reasonable evidence of efficacy in adults in two short-term studies. This is statistically robust. However the magnitude of the net treatment effect in the short term pivotal adult studies was relatively small (smaller than the placebo response) and of questionable clinical significance.

Of greater concern is that there are no long-term efficacy data in adults. Limiting the indication in adults to short term treatment is not an option because ADHD in adults is not a short term condition and treatment is likely to be required for years. This was also the opinion of the CPMP in their advice of 18 October 2002 (question 3c). The applicant is therefore relying on extrapolation from the paediatric long term data and adult short term data but this can only provide supporting evidence. ADHD in adults is not necessarily the same clinical entity as ADHD in children, even though the diagnosis in adults requires onset of the condition in childhood. Co-morbid psychopathologies are also

rather different between the paediatric and adult groups. Long-term data showing maintenance of efficacy in adults will be required before an indication can be approved in this population.

The exclusion of adult patients with co-morbid anxiety or depression is considered to be appropriate, as the requirement of the studies was to show an ADHD-specific treatment effect. However many patients fulfilling the diagnostic criteria for ADHD are likely to have co-morbid anxiety or depression and the applicant should discuss the implications for the applicability of these studies to the general adult ADHD population.

Notwithstanding these concerns, atomoxetine does appear to have some efficacy in adults in the short term and there is an unmet clinical need. If a licence is granted in adults, the SPC (section 5) should indicate that the adult data are exclusively from short-term studies and show evidence of modest efficacy only.

18.14.3 Adult Posology

If a licence is granted for an indication in adults the proposed posology in this population require consideration. The adult dose range proposed in the SPC (40-120mg) is not consistent with the dose range employed in the two pivotal trials (60-120mg). A lower starting dose of 40mg might be desirable on safety grounds but this is not likely to be fully efficacious (it is approximately equivalent to 0.5mg/kg/day which was sub-therapeutic in paediatric patients). The SPC should be amended accordingly.

The second issue is that no dose-response data in adults are available, in either the short or long-term. The applicant has shown that the pharmacokinetics are similar in children and adults and the use of a fixed dose rather than on a mg/kg basis is justified. Nevertheless the validity of extrapolating the short term paediatric dose-finding data to adults is questionable for the same reasons that extrapolation of the paediatric long term data to adults is questionable. It is very possible that there could be important differences between childhood ADHD and adult ADHD that might necessitate different (weight adjusted) doses in the two populations. The lack of any dose-response information in adults is of concern.

18.14.4 Outstanding Issues - Efficacy

(Following the initial assessment of these applications the following outstanding issues and questions relating to efficacy were addressed to the company. They are followed by the company's summary of response and then the MHRA's assessment of the response).

2. **The applicant should justify the lack of evidence of long-term efficacy in adults. Extrapolation of the paediatric long term data to adults is of questionable validity because there may be important differences between childhood ADHD and adult ADHD, even though the diagnosis in adults requires onset of the condition in childhood. Co-morbid psychopathologies are also likely to be different between the paediatric and adult groups.**

3. **The applicant should justify the lack of dose-response data in adults, in either short or long-term treatment. Although the pharmacokinetics are similar in children and adults and the use of a fixed dose rather than on a mg/kg basis is justified, the validity of extrapolating the short term paediatric dose-finding data to adults is questionable. It is possible that there could be important differences between childhood ADHD and adult ADHD that might necessitate different (weight adjusted) doses in the two populations. The dose advice in the SPC should properly reflect the data provided.**

Company's Response (Summary)

As questions 2 and 3 both concern ADHD in adults they are considered together

Lilly has provided an overall summary of the disorder in this subpopulation addressing the topics raised in both questions on continuity from childhood ADHD, comorbidities, and validity of extrapolation of paediatric data, as well as the clinical significance of atomoxetine's pharmacological effect. Additionally an external expert opinion on these topics, "ADHD in adults in Europe and the need for licensed pharmacotherapeutic treatment", [redacted] is provided. Finally, new atomoxetine clinical trial data on long-term efficacy and dose-response are given.

ADHD in adults is, by definition, an ongoing disorder present from early childhood, and characterised by a symptom profile (inattention and hyperactivity/impulsivity) that is consistent across the lifespan, as described in the literature and as confirmed by clinicians specialising in this field (see expert opinion in Annex 2). Many children with ADHD followed longitudinally continue to experience symptoms, and the symptoms continue to be in the areas of inattention and hyperactivity/impulsivity, with inattention tending to become more prominent as patients grow older. Additionally, the overall patterns of comorbidity in adult ADHD patients are very similar to those in paediatric patients, as described in the literature and confirmed by clinicians specialising in this field (see expert opinion in Annex 2). These facts support the validity of extrapolation of some paediatric data to the adult subpopulation, as also concluded in the expert opinion.

Atomoxetine's long-term efficacy is supported by new data from study LYAR, a 3-year open-label extension study in which all patients that participated in the two acute studies (LYAA and LYAO, initial MAA, 5.3.5.1.9, 5.3.5.1.10) could enrol. Analyses of 97 weeks' treatment in 384 patients demonstrate statistically significant improvement in ADHD symptoms as assessed by mean reduction in symptom severity scores on all measures of ADHD symptoms, with mean CAARS-Inv Total ADHD Symptom scores decreasing 33.2% from 29.2 at baseline of open-label therapy to 19.5 at the end of open-

label therapy (p<.001). Statistically significant results were also seen on functional outcomes, the Clinical Global Impression-Severity (CGI-ADHD-S) scale, and on other relevant secondary measures (see Table 2.3). Forty-seven percent of patients had at least a 30% improvement on the CAARS-Inv Total ADHD Symptom scores (see Table 2.4). These results, though not double-blind, strongly suggest that response to atomoxetine is maintained during long-term treatment. Indeed, most patients experienced continued improvement with longer duration of treatment.

Concerning dose, several factors make it unlikely that adults with ADHD would have a markedly different dose response to atomoxetine than children and adolescents. Paediatric and adult ADHD is a single disorder. Atomoxetine pharmacokinetics do not vary significantly with age as noted by the MHRA and CSM. Atomoxetine's mechanism of action is through the norepinephrine transporter (NET) in all patients. Preclinical studies suggest that expression of NET does not change markedly through the lifespan. Additionally, at doses similar to those used in the paediatric trials (on a weight-adjusted basis assuming an average 70kg adult), there was a marked treatment effect in adults in acute studies LYAA and LYAO. Finally, new analysis of symptom reduction by final dose in adults in study LYAR using weight-adjusted dose suggests a dose response that mirrors that in paediatric patients (Figure 3.2). All these factors support the validity of consistent dosing recommendations for paediatric and adult patients.

With regard to clinical significance of pharmacological effects, acute studies LYAA and LYAO demonstrate, using rigorous methodologies, that atomoxetine has a specific effect greater than placebo in reducing symptoms of ADHD in adults as evaluated by the primary outcome measure (CAARS-Inv Total ADHD Symptom scores). This scale maps directly to each of the symptoms in DSM-IV, thus providing a direct measure of clinical relevance. As stated in the expert opinion, " a change in these 18 items [...] reflects an improvement in core ADHD symptoms" [...] and "thus the primary outcome measure has in itself great clinical and practical validity, not the least because of the association of ADHD symptoms and measures of impairment of functioning". Further, when commenting on the effect sizes in studies LYAA and LYAO, the experts stated that these are nearly identical to the effect size obtained with methylphenidate in their controlled trial in adults with ADHD in the Netherlands (Kooij et al. 2004, in press). Finally, the expert opinion authors, based on their own clinical trials and review of the paediatric and adult atomoxetine data presented in these responses, concluded that "treatment effects reported of atomoxetine in adults with ADHD are real, trustworthy, clinically significant, and not transient, and quite comparable to those that were obtained with psychostimulants".

Against the efficacy benefits illustrated above, atomoxetine is well tolerated in the adult subpopulation and has demonstrated an acceptable safety profile in clinical trials and after one year of broad clinical use. Therefore, we believe that all available data on atomoxetine in adult ADHD patients demonstrate a favourable risk-benefit assessment that supports the therapeutic indication in this subpopulation.

Assessor's Comment

Question 2 - Evidence of Long-Term Efficacy in Adults - Study LYAR

Some new clinical trial data have been presented in response to this point.

Patients who participated in the two 10-week double-blind randomised placebo-controlled studies in adults (LYAA and LYAO – for details see the original assessment report in the Pink Sheets) could enrol into the uncontrolled extension study LYAR. Patients re-started treatment on a dose of 50mg/day and could be titrated to a maximum of 160mg/day based on clinical response. Data from 384 patients with up to 97 weeks of exposure to atomoxetine in study LYAR are now available.

The table below gives information on the number of patients continuing treatment and the reasons for withdrawal for those patients having discontinued treatment.

Summary of Patient Disposition and Primary Reason for Study Discontinuation all Enrolled Patients Study B4Z-MC-LYAR

Characteristic	Number
Patients entering open-label study	385
Patients receiving atomoxetine	384
Number continuing open-label study	125 (32.6%)
Reason for Discontinuation	
Lack of efficacy	96 (25.0%)
Adverse event	42 (10.9%)
Protocol violation	11 (2.9%)
Other (lost to follow-up, etc.)	110 (28.6%)

The table below presents data on CAARS-Inv Total ADHD Symptom scores, the primary endpoint from the acute studies, and other endpoints measured in the uncontrolled extension period. In the table, baseline refers to the score at the start of uncontrolled treatment.

	N**	Baseline Mean (SD)	Endpoint Mean (SD)	Change Mean (SD)	*p*-Value
CAARS-Inv Total ADHD Symptom score	372	29.2 (11.5)	19.5 (10.6)	-9.7 (12.5)	<.001
CAARS-Inv Inattentive subscale	372	16.4 (6.5)	11.4 (6.5)	-4.9 (6.9)	<.001
CAARS-Inv Hyp/Impulsive subscale	372	12.8 (6.4)	8.1 (5.1)	-4.7 (6.3)	<.001
CGI-Severity	372	4.3 (1.1)	3.2 (1.3)	-1.1 (1.3)	<.001
CAARS-Self Total ADHD Symptom score	327	29.3 (10.8)	21.0 (10.8)	-8.2 (10.6)	<.001
CAARS-Self Inattentive subscale	327	16.5 (6.2)	12.2 (6.5)	-4.4 (5.9)	<.001
CAARS-Self Hyp/Impulsive subscale	329	12.8 (6.0)	8.9 (5.4)	-3.8 (5.3)	<.001
WRAADDS Total	335	14.9 (6.2)	10.0 (6.2)	-4.9 (6.4)	<.001
Hamilton Anxiety (HAMA)	340	6.2 (4.6)	6.5 (5.4)	0.3 (5.1)	.343
Hamilton 17-item Depression (HAMD-17)	338	4.8 (3.9)	5.4 (4.8)	0.6 (4.6)	.018
Sheehan Disability Total Score	333	15.0 (7.2)	11.1 (7.8)	-3.9 (7.9)	<.001
Sheehan Work subscale	333	5.2 (2.8)	3.8 (2.9)	-1.3 (3.1)	<.001
Sheehan Family subscale	333	5.4 (2.7)	4.0 (2.8)	-1.4 (2.9)	<.001
Sheehan Social subscale	333	4.5 (2.7)	3.3 (2.8)	-1.2 (2.9)	<.001

* Based on data from baseline of open-label study through endpoint of open-label study. Lower scores indicate improvement on all scales.

** N = the number of patients with a baseline and at least one post-baseline measure.

There are significant improvements from baseline to end of treatment on all variables except HAMA and HAMD-17. On HAMD-17 the patients were significantly worse at the end of open-label treatment compared with baseline.

There are methodological difficulties relating to the reliable interpretation of these data. The data are uncontrolled and it cannot be verified that the effects observed are due to treatment and not to another confounding factor, such as the underlying course of disease following successful acute treatment or the open-label subjective assessment of response. A randomised withdrawal study would have been of greater worth in establishing the benefits of long-term treatment and. As such a study is available in paediatrics, and as the adult patients had already been recruited to LYAA and LYAO, it is unclear why such a study could not have been conducted. A related concern is that the p-values generated compare within-group changes over time and not between-group changes. They should be interpreted with caution.

This study cannot on its own definitively prove that long-term treatment with atomoxetine is efficacious. The evidence of long-term efficacy relies upon the facts that these data are fully consistent with long-term treatment being beneficial and that long-term treatment was demonstrated to be beneficial in the randomised withdrawal studies

conducted in paediatric patients. It is considered that the overall body of evidence from the adult data supported by extrapolation of the paediatric data provides sufficient evidence of efficacy in adults.

Point cleared

Question 3 - Dose-Response in Adults

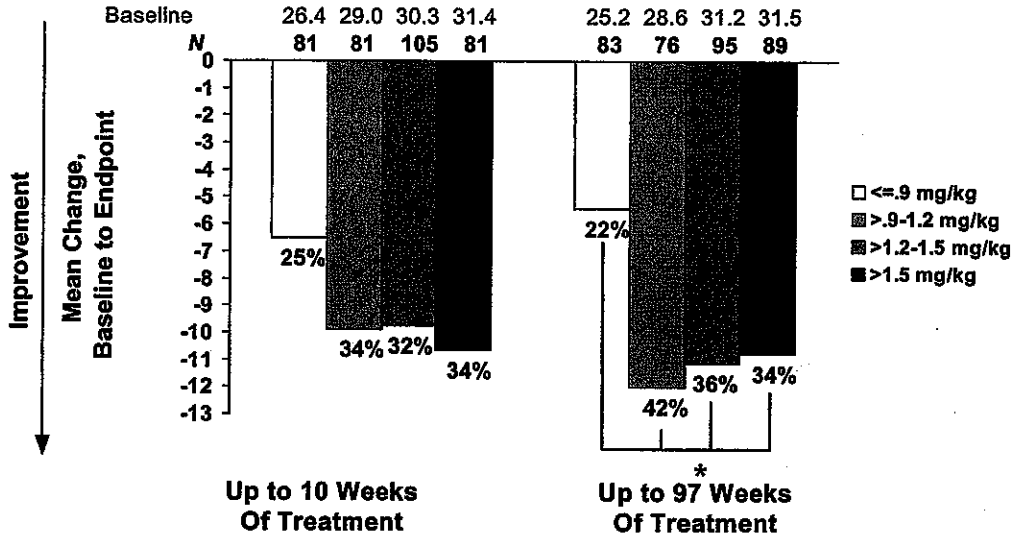
It remains the case that no dose-finding study has been conducted in adults. Some analyses on the effects weight-based dosing (≤0.90 mg/kg, >0.90-1.2 mg/kg, >1.2-1.5 mg/kg, >1.5 mg/kg) on clinical response have been presented. Adult patients from LYAR were divided into quartiles based on proposed dosing recommendations in the SPC, and allowing for broadly equal number of patients per group. These analyses were performed for data from LYAR but not LYAA/LYAO, the acute studies in adults.

Acute (10 week) and chronic (up to 97 week) outcomes were assessed in 384 patients. Endpoint symptom reduction as assessed by the primary outcome measure (CAARS) was measured against dose during the final visit interval. Other choices might have included average dose or average dose of last x visits etc. No sensitivity analyses have been conducted on this point.

Between dose group differences in mean change from baseline to endpoint (LOCF) scores were assessed using an analysis of covariance with terms for baseline, investigator, days on therapy, and dose group. Contrasts of least squares means across dose groups was computed using the ANCOVA model. The applicant appears to have investigated both linear and quadratic contrasts. In the paediatric dose-response acute study LYAC the test for linear dose response was based on an ACOVA model with terms for baseline, treatment, site, and CYP2D6 metaboliser status. Categorical data were compared across dose groups using a chi-square test. Poor metabolisers of atomoxetine (PMs, *N*=6) were excluded from analyses of efficacy (their dose in study LYAR was capped at 120 mg).

The figure below presents the results of analyses of two time periods: up to 10 weeks (selected to capture efficacy after the approximately the first 6 weeks, during which doses were being adjusted) and up to 97 weeks of treatment (the maximum duration of treatment).

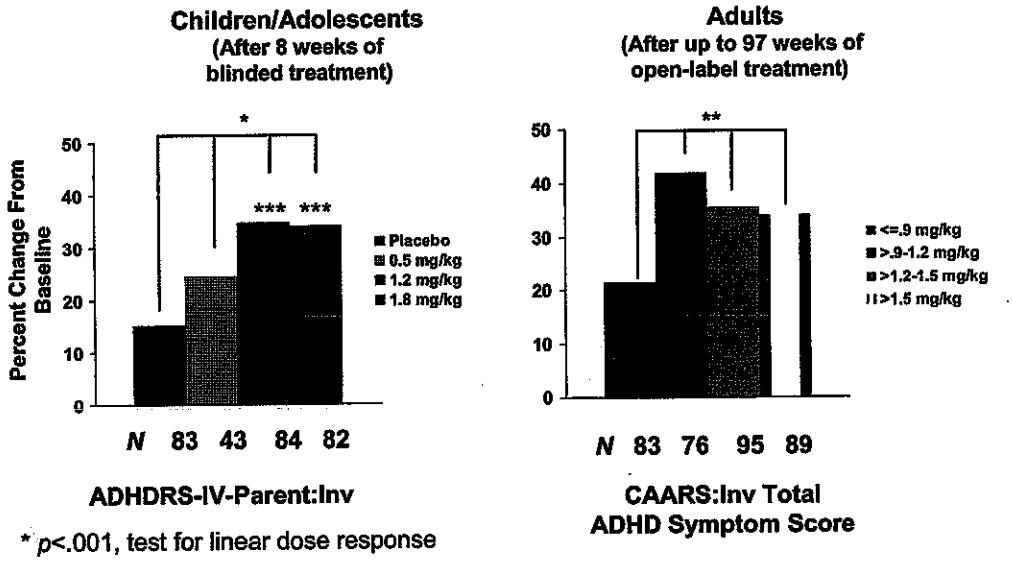
Study LYAR - CAARS:Inv Total ADHD Symptom Score after Acute and Long-Term Atomoxetine Treatment



*p<.05, test for quadratic dose response
All eight groups significantly improved from baseline (p<.001).
Percentages are percent change from baseline.

The applicant concludes the following:
"At endpoint the mean symptom reduction plotted against weight adjusted dose was examined. As shown in the figure below, the dose response was very similar to that observed in paediatric patients, with patients who received doses less than 0.9mg/kg/day having lesser mean symptom reductions than those in the higher dose groups, and no evidence of increased symptom reduction in doses above 1.2mg/kg/day. These results demonstrate a dose response that is virtually identical to that observed in children in the dose response study LYAC, providing further evidence of the consistency of dose response children and adults."

Effect of Dose on Treatment Efficacy in Children (STUDY LYAC) and Adults (Study LYAR)



* $p<.001$, test for linear dose response

*** $p<.001$, significant effect of dose (significantly different from placebo).

** $p<.05$, test for quadratic dose response.

There are a number of issues with these data presentations. Firstly, the adult patients in LYAR are a selective population comprising only patients who tolerated and responded to acute treatment (either active or placebo) prior to entering the extension. Secondly, the dosage groups being compared were not randomised, nor were investigators blinded to dose group. Thirdly, as all adult patients entering the extension phase commenced treatment with 50mg/day, those withdrawing prior to any titration for any reason (who consequently have little or no opportunity to mirror the improvement observed for the population as a whole) will have small change from baseline and will likely be included in the low dose group for the above data presentations. Twenty-five percent of patients withdrew from the study prior to 10 weeks. This might partially or fully explain the lower efficacy in the lowest dose group. Evidence for a dose response between doses above 0.9mg/kg/day is limited. There is, therefore, inconclusive evidence of a dose response. These analyses cannot be used in place of data from a randomised dose-response trial.

In the second data presentation comparing adults with children the same phenomenon is present. Also, the figure compares 8 weeks double-blind treatment with up to 97 weeks open-label treatment, the latter of which, as discussed above, is less reliable due to the subjective nature of the endpoint assessment. Furthermore, different endpoints are (necessarily) used.

It is considered that these analyses cannot prove that the dose response is similar in adults and children. Instead this must be demonstrated through pharmacokinetic and clinical arguments.

In this regard the applicant has made a reasonable case supporting the validity of broadly consistent dosing recommendations in terms of mg/kg for paediatric and adult patients. Pharmacokinetics have been shown to be comparable in adults and children and the applicant states that the pharmacodynamics (via the norepinephrine transporter) are also thought to be comparable. The high therapeutic index of atomoxetine and the high inter-individual variability of plasma levels are also relevant factors to consider. Despite the shortcomings of the adult clinical data, there is sufficient justification of the proposed posology in adults not to require further formal dose-response data in the adult population.

Point cleared

Assessors' Conclusions on Adult ADHD

The applicant, supported by the external expert opinion *"ADHD in adults in Europe and the need for licensed pharmacotherapeutic treatment"*, has adequately justified the clinical rationale for the use of atomoxetine for ADHD in adults. However the risk-benefit remains less clearly established than in the paediatric ADHD population. The main difficulties remain a lack of formal dose-response data and a lack of controlled long term clinical data in adults. The new uncontrolled data presented by the applicant are useful in that they are consistent with conclusions of efficacy and with the proposed dose advice. However despite the impressive looking p values these uncontrolled data are insufficient to fully address the original deficiencies. It is disappointing that a randomised withdrawal was not conducted as part of study LYAR.

The arguments on dose-response and long term efficacy therefore continue to rely quite heavily on extrapolating the paediatric data to adults. The arguments put forward regarding the validity of this extrapolation are reasonably persuasive however. The question of whether the applicant has done enough to justify the indication and posology in adults is not clear cut and comes down to a matter of clinical judgement.

The arguments in favour of an indication in adults include:

1. It can be argued that paediatric and adult ADHD is a single disorder. A proportion of children with ADHD continue to have the same problems well into (if not throughout) adult life. Adult ADHD is, by definition, an ongoing disorder present from early childhood and hence no clear distinction can be made between the two, even if the characteristics of the condition may change over time.
2. The two acute adult studies LYAA and LYAO were of good quality and showed statistically highly significant superiority of atomoxetine compared with placebo.
3. The new long term open label study LYAR, whilst uncontrolled and requiring caution in its interpretation, shows some evidence of (or is at least consistent with) maintenance of efficacy in long term treatment.

4. It might make little sense to withdraw an effective treatment from a patient who is still deriving benefit from it, because he/she has reached an arbitrary age cut-off. Because of this issue a pragmatic approach is required.

Therefore it is considered that an indication in adults has been justified.

4. **The applicant should justify the dose advice in the proposed SPC relating to the 0.5mg/kg/day dose. In study LYAC 0.5mg/kg/day was not significantly superior to placebo and was inferior to 1.2mg/kg/day. Titration to a target dose of 1.2mg/kg/day where tolerated would appear to be appropriate.**

Company's Response

We have amended the proposed SPC based on feedback from the MHRA at the meeting held on 02 December 2003 as follows:

"Dosing of Children and Adolescents up to 70kg Body Weight
Strattera should be initiated at a total daily dose of approximately 0.5 mg/kg. The initial dose should be maintained for a minimum of 7 days. After this time, the dose should be increased to a target total daily dose of approximately 1.2mg/kg, *unless patients have experienced clinically significant symptom response at the initial dose*."

We agree with the MHRA and CSM that the data from study LYAC suggest that most patients are likely to require a dose of 1.2 mg/kg/day, which is indeed specified as the target dose in the proposed SPC. However, as the proposed SPC does not recommend starting directly at the 1.2 mg/kg/day dose for any patient, we believe it is clinical good practice to reassess response after approximately a week on drug rather than automatically increasing the dose. The one-week timeframe for assessment of response is based on visit-wise analysis of clinical studies, which shows that this is the time elapsed when marked response to placebo is typically observed. The likelihood that some patients will respond adequately to the 0.5 mg/kg/day dose is supported by the clinical data, as summarised below.

1. The 0.5mg/kg/day arm in Study LYAC was not powered to demonstrate superiority to placebo.
2. Nonetheless, 0.5mg/kg/day superior to placebo on several important secondary measures including core ADHD symptoms.
3. Study LYAC results represent group mean data, with variability among individuals.
4. The pharmacokinetics of atomoxetine vary considerably from patient to patient. As a result of this variability, there is an overlap in expected plasma atomoxetine exposure between 1.2mg/kg/day and 0.5mg/kg/day. Thus, some patients would be expected to respond at 0.5mg/kg/day, and if they respond, no further dose increase would be clinically warranted.

Assessors' Comment

It is inappropriate to use inadequate trial design (lack of statistical power) as an explanation for an absence of evidence of efficacy. It is true however that there was some evidence of clinical efficacy for 0.5mg/kg based on secondary endpoints. This evidence is weaker than the evidence for 1.2mg/kg, which also appeared to have an effect of greater (mean) magnitude.

It is clear that the 0.5mg/kg/day dose should be more than sufficient in poor metabolisers, who represent a significant minority of the population. In these patients plasma levels at the 0.5mg/kg dose are already substantially higher than in extensive metabolisers receiving 1.2mg/kg and pushing the dose higher despite a good clinical response at the lower dose would not be appropriate.

Hence the company's proposal to allow patients to stay on the lower dose of 0.5mg/kg/day if they have responded well has merit. However the proposed wording *"unless patients have experienced clinically significant symptom response"* might deter dose escalations in those patients who respond to 0.5mg/kg but would respond further to 1.2mg/kg. These patients cannot be easily identified and the proportion of patients likely to respond in this way is unclear. It is clear, however, that if this proportion were large, a lack of upward titration would be undesirable. The following wording from the final approved SPC is preferable. Note that the possibility to maintain a patient on 0.5mg/kg is retained:

Dosing of Children and Adolescents up to 70kg Body Weight

Strattera should be initiated at a total daily dose of approximately 0.5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2 mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine). No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day.

In children and adolescents under 70 kg body weight, the safety of single doses over 1.8 mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated.

Point cleared

5. **The applicant should justify the use of doses greater than 1.2mg/kg/day. Study LYAC showed no evidence of an additional benefit for the 1.8mg/kg/day dose. The flexible dose studies add little information on dose response as they do not demonstrate that that increasing the dose to 1.8mg/kg/day produces any additional efficacy in patients with an inadequate response to 1.2mg/kg/day.**

Company's Response

We have amended the proposed SPC with regard to the recommended maximum daily dose based on feedback from the MHRA at the meeting held on 2 December 2003 as follows.

"Dosing of Children and Adolescents up to 70 kg Body Weight
Strattera should be initiated at a total daily dose of approximately 0.5mg/kg. The initial dose should be maintained for a minimum of 7 days. After this time, the dose should be increased to a target total daily dose of approximately 1.2mg/kg, unless patients have experienced clinically significant symptom response at the initial dose.

No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day. The recommended maximum total daily dose in children and adolescents is approximately 1.2mg/kg/day, which in practice typically corresponds to an actual administered dose of 1.0mg/kg/day - 1.4mg/kg/day, depending on the patient's exact weight and available dosage strengths of atomoxetine."

Assessor's Comment

The company has conceded that additional benefit has not been demonstrated for doses higher than 1.2 mg/kg/day. The wording was improved in the final approved SPC.

Point cleared

18.15V. CLINICAL SAFETY

18.16V.1 Introduction

Atomoxetine was originally studied in more than 1200 adults with Major Depressive Disorder (MDD) and in one urinary incontinence (UI) trial during the late 1980s and early 1990s. Efficacy of atomoxetine was not shown to be superior to placebo and therefore the product development for these indications was abandoned. The applicant states that no safety concerns were noted in these early studies.

Phase I studies were conducted in adults. In the light of the accumulating safety data in poor and extensive metaboliser adults, clinical studies enrolled both poor and extensive metaboliser paediatric patients. Cytochrome P450 2D6 genotype was performed on all patients studied but was maintained under double-blind conditions to assure that assessments of safety and efficacy would not be affected by expectation bias. Patients were therefore dosed regardless of CYP2D6 genotype.

Safety and tolerability data for three doses of atomoxetine (0.5, 1.2 and 1,8mg/kg/day) are provided by Study LYAC, and data for flexible once and twice daily dosing are provided by six placebo-controlled studies, three using twice-daily dosing and three using once-daily dosing. In addition to these efficacy studies, safety and tolerability data in children and adolescents are available from two large open-label studies, LYAB and LYBB and two extension studies (HFBF and LYAI) that provided long-term (up to 8 years) treatment with regular safety assessments.

Study LYAQ assessed safety in paediatric poor metabolisers, due both to CYP2D6 genotype and to CYP2D6 inhibition by concurrent fluoxetine.

The safety and tolerability of abrupt discontinuation of atomoxetine compared with placebo was assessed in three child and adolescent studies (HFBD, HFBK, and LYAC) and in the paediatric relapse-prevention Study LYAF.

Safety and tolerability (including abrupt discontinuation) were also assessed in two large acute placebo-controlled studies in adults (Studies LYAA and LYAO) plus the ongoing open-label extension Study LYAR.

Safety and tolerability analyses are presented below for the following safety populations:

The "Overall ADHD analysis group". This includes data from all clinical studies conducted in children and adolescents with ADHD, both acute and long-term. In addition the following subsets of this overall database were analysed:

Acute placebo-controlled studies (either once or twice daily dosing). This constitutes the primary placebo-controlled safety database. Median duration of treatment was 56 days.

Poor metaboliser ADHD group. To assess safety in patients with the highest presumed exposures, secondary analyses restricted to patients exposed to a maximum dose of greater than 1.2 mg/kg/day (high-dose patients) were also conducted.

18.17V.2 Patient Exposure

The safety of atomoxetine in patients with a DSM-IV diagnosis of ADHD was evaluated in 15 clinical studies in children and adolescents and in 3 clinical studies in adults. A total of 3262 children and adolescents were exposed to at least one dose of atomoxetine, 1704 for more than 6 months, 1236 for more than 1 year and 425 for more than 2 years. A total of 478 adults were exposed to atomoxetine, 236 for more than 6 months, and 173 for more than 1 year. The median duration of treatment with atomoxetine was 30 weeks (paediatric) and 41 weeks (adults). 70% of paediatric patients had a modal atomoxetine dose (the dose prescribed for the most number of days) of at least 1.2mg/kg/day and the average modal dose was 1.4mg/kg/day. The mean daily dose in adults was 95.5 mg/day.

A total of 238 poor metaboliser paediatric patients were studied, 7.3% of the total. This is comparable to the prevalence of the CYP2D6 poor metaboliser genotype in the general population (5-10%). 171 received doses of at least 1.2mg/kg/day, 145 were treated for

more than 6 months and 107 were treated for more than one year. The median duration of treatment of poor metaboliser paediatric patients with atomoxetine was 47 weeks. A total of 30 adult poor metabolisers were exposed to atomoxetine.

These data are supplemented by data from 17 clinical pharmacology studies involving more than 300 adults, 1 abuse-potential study, and 10 historical depression and urinary incontinence trials in more than 1200 adults.

18.17.1.1.1.1.1 Assessor's Comment

The numbers for short and long term patient exposure comfortably fulfil the requirements of ICH E1 and are satisfactory. The adequacy of the numbers for exposure of poor metaboliser paediatric patients is considered below.

18.18V.3 Common Adverse Events

18.18.1 V.3.1 Paediatric Population

In the acute efficacy studies (total N = 1065) treatment-emergent adverse events that were reported statistically significantly more frequently in atomoxetine-treated (N = 657) than in placebo-treated (N = 408) patients were:

Upper abdominal pain (18.1% versus 12.5%)
Decreased appetite (16.1% versus 5.6%)
Vomiting (11.4% versus 5.6%)
Somnolence (10.0% versus 4.2%)
Irritability (7.2% versus 4.2%)
Fatigue (6.5% versus 3.4%)
Dizziness (5.2 % versus 2.0%)
Dyspepsia (4.7% versus 1.2%)
Decreased weight (2.4% versus 0.0%)
Anorexia (2.1% versus 0.5%)
Mood swings (2.1% versus 0.5%)
Early morning awakening (1.2% versus 0%)
Mydriasis (1.2% versus 0%)

Additionally headache (21.2% versus 20.1%), nausea (8.5% versus 5.9%), cough (8.4% versus 8.1%), rhinorrhoea (3.7% versus 2.2%) and rash (3% versus 1.2%) were reported at an excess frequency over placebo and at a frequency >2% but the differences were not statistically significant. Nausea and rash are listed in the SPC but headache, cough and rhinorrhoea are not. This is acceptable as the excess over placebo was minimal for the latter three adverse events and a causal link to atomoxetine appears unlikely.

Pharyngitis was reported statistically significantly more frequently in placebo-treated patients than in atomoxetine-treated patients.

The most commonly reported treatment-emergent adverse events □10% incidence) for all atomoxetine-treated patients (the Overall ADHD Analysis Group) were headache, upper

abdominal pain, vomiting, decreased appetite, pharyngitis/nasopharyngitis, cough, nausea, pyrexia, upper respiratory tract infection, irritability, and fatigue.

Subgroups analyses of age (< and ≥ 12 years of age), sex, and racial origin did not reveal any differences in tolerability. The pattern of adverse events in poor metabolisers compared with extensive metabolisers is considered below. The few differences in AE reporting frequency between the once daily and twice daily dosing regimens were small in magnitude and did not suggest a differential pattern.

During long-term treatment, reporting rates for most adverse events declined markedly. The pattern of adverse events during long-term treatment did not suggest a different pattern from acute treatment, and there was no evidence of unexpected late-occurring events.

18.18.2 V.3.2 Poor Metabolisers

The following table shows the treatment-emergent AEs for which a statistically significant difference was observed between extensive and poor metabolisers (overall analysis group).

Event (MedDRA Preferred Term)	Extensive metabolisers	Poor metabolisers N = 107	P value
Appetite decreased	512 (17.0)	57 (24.1)	0.008
Insomnia	205 (6.8)	25 (10.5)	0.035
Multiple allergies	75 (2.5)	1 (0.4)	0.041
Abrasion	65 (2.2)	12 (5.1)	0.012
Sedation	51 (1.7)	10 (4.2)	0.012
Middle insomnia	46 (1.5)	9 (3.8)	0.016
Enuresis	35 (1.2)	7 (3.0)	0.030
Early morning waking	32 (1.1)	7 (3.0)	0.021
Tremor	32 (1.1)	12 (5.1)	<0.001
Depressed mood	30 (1.0)	7 (3.0)	0.016
Animal bite	23 (0.8)	5 (2.1)	0.049
Mydriasis	21 (0.7)	6 (2.5)	0.011
Syncope	21 (0.7)	5 (2.1)	0.037
Wound	6 (0.2)	3 (1.3)	0.023
Dyskinesia	3 (0.1)	2 (0.8)	0.046
Generalised anxiety disorder	3 (0.1)	3 (1.3)	0.006
Depression aggravated	2 (0.1)	3 (1.3)	0.003
Vasovagal attack	2 (0.1)	3 (1.3)	0.003
Cyst removal	1 (0.0)	2 (0.8)	0.015
Iron deficiency anaemia	1 (0.0)	2 (0.8)	0.015
Knee operation	1 (0.0)	2 (0.8)	0.015

The pattern of adverse events reported more frequently by poor metabolisers is generally similar to the overall pattern of AEs seen in the overall safety population, with miscellaneous gastrointestinal and CNS symptoms predominating.

The above table also considers those AEs occurring at low frequencies but which are possibly clinically relevant because their reported frequencies were more than twice as common in poor metabolisers than extensive metabolisers. They include depression (both newly reported and aggravation of existing depression) and generalised anxiety disorder,

as well as vasovagal attack and syncope. It is biologically plausible that these potentially more serious CNS and cardiovascular adverse effects are related to CYP 2D6 poor metaboliser status although the numbers are too small to draw definitive conclusions (the p values are not adjusted for multiplicity). Post-marketing safety data (over 1 million exposures) have not detected any signal for any particular adverse event, although the data collected in patients does not include genotype or phenotype for CYP2D6.

18.18.3 V.3.3 Psychiatric Adverse Events

In the acute efficacy studies decreased appetite, somnolence, irritability, fatigue, anorexia and mood swings were all reported more commonly in the active atomoxetine group than in placebo. In addition data in poor CYP 2D6 extensive metabolisers raise the possibility of drug exposure related depression and generalised anxiety disorder. However the numbers of reports are too small (single figures) to indicate a causal link to atomoxetine, particularly since these conditions are seen more frequently in patients with ADHD than in the general population. Nevertheless they are listed in the SPC as possible uncommon undesirable effects.

18.18.4 V.3.4 Cardiovascular Adverse Events

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 a 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.

In conclusion 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, although this should be kept under review in post-marketing surveillance.

18.18.5 V.3.5 Adult Population

The most commonly reported treatment-emergent adverse events with an excess incidence over placebo are listed below:

Adverse event	Atomoxetine	Placebo	P value
Dry mouth	56 (20.8)	17 (6.5)	<.001
Headache	47 (17.5)	45 (17.1)	1.000
Insomnia	35 (13.0)	17 (6.5)	013
Nausea	32 (11.9)	13 (4.9)	0.005
Appetite decreased	28 (10.4)	8 (3.0)	<.001
Constipation	26 (9.7)	10 (3.8)	0.009
Dizziness (exc vertigo)	17 (6.3)	5 (1.9)	0.015
Libido decreased	16 (5.9)	4 (1.5)	0.010
Dyspepsia	15 (5.6)	11(4.2)	0.548
Sinusitis	15 (5.6)	11(4.2)	0.548
Fatigue	14 (5.2)	7 (2.7)	0.181
Erectile disturbance	13 (7.5)	2 (1.2)	0.006
Sleep disorder	12 (4.5)	4 (1.5)	0.073
Sweating increased	12 (4.5)	2 (0.8)	0.012
Abnormal dreams	11 (4.1)	7 (2.7)	0.474
Middle insomnia	11 (4.1)	3 (1.1)	0.054
Palpitations	10 (3.7)	2 (0.8)	0.037
Paraesthesia	10 (3.7)	5 (1.9)	0.295
Myalgia	9 (3.3)	5 (1.9)	0.418
Pyrexia	9 (3.3)	5 (1.9)	0.418
Urinary hesitation	9 (3.3)	0 (0.0)	0.004
Hot flushes	8 (3.0)	2 (0.8)	0.106
Rigors	8 (3.0)	2 (0.8)	0.106
Sinus headache	8 (3.0)	3 (1.1)	0.222
Dysmenorrhoea	7 (7.4)	3 (3.3)	0.331
Urinary retention	7 (2.6)	0 (0.0)	0.015
Dermatitis	6 (2.2)	3 (1.1)	0.504
Difficulty in micturition	6 (2.2)	0 (0.0)	0.030
Ejaculation failure	6 (3.4)	3 (1.7)	0.502
Flatulence	6 (2.2)	2 (0.8)	0.286
Initial insomnia	6 (2.2)	3 (1.1)	0.504
Lethargy	6 (2.2)	3 (1.1)	0.504
Orgasm abnormal	6 (2.2)	2 (0.8)	0.286
Vision blurred	6 (2.2)	5 (1.9)	1.000
Weight decreased	6 (2.2)	2 (0.8)	0.286
Abdominal pain	5 (1.9)	1 (0.4)	0.216
Dysuria	5 (1.9)	1 (0.4)	0.216
Feeling jittery	5 (1.9)	0 (0.0)	0.061
Impotence	5 (1.9)	0 (0.0)	0.061
Pain NOS	5 (1.9)	0 (0.0)	0.061
Postnasal drip	5 (1.9)	1 (0.4)	0.216
Prostatitis	5 (2.9)	0 (0.0)	0.061
Somnolence	5 (1.9)	5 (1.9)	1.000

Assessor's Comment on Common Adverse Events

Miscellaneous gastrointestinal and CNS appear to be quite common in both children and adults but these are generally quite well tolerated, including in poor metabolisers. In addition a variety of genitourinary undesirable effects including erectile dysfunction were apparent. This pattern of undesirable effects reflects the pharmacological activity of atomoxetine on central and peripheral noradrenergic activity. No particular causes for concern were identified.

18.19V.4 Discontinuation Due to Adverse Events

18.19.1 V.4.1 Paediatric Population

The rate of discontinuations due to adverse events in atomoxetine-treated paediatric patients was 4.1% in the acute placebo-controlled studies (versus 1.2% for placebo, $p<0.05$) and 6.0% amongst all atomoxetine-treated patients. In contrast statistically significantly more placebo-treated patients discontinued due to lack of efficacy in these studies compared with atomoxetine-treated patients (8.0% versus 3.6%). Discontinuation due to adverse events were similar for twice (3.8%) and once daily (4.4%) dosing and for patients <12 years (5.9%) and □12 years of age (6.1%). The undesirable effects leading to discontinuation were in a similar pattern to the overall AE reporting and were predominantly gastrointestinal and CNS.

18.19.2 V.4.2 Poor Metabolisers

Among patients treated for a significant duration, statistically significantly more CYP 2D6 extensive metabolisers discontinued due to lack of efficacy compared with poor metabolisers (26.0% versus 17.3%). The difference between extensive and poor metabolisers in discontinuations due to adverse events approached but did not reach statistical significance (5.8% vs. 8.9% respectively, $p=0.063$). Overall, the reasons for discontinuation were similar for extensive and poor metabolisers. Similar results were observed in patients taking >1.2mg/kg/day, except that discontinuations for adverse events were similar for extensive and poor metabolisers in this high-dose group. During long-term treatment (>1 year), no significant differences were observed between extensive and poor metabolisers for any reason for discontinuation.

18.19.3 V.4.3 Adult Population

Overall 65 (13.6%) of adults discontinued due to an adverse event. The adverse events most frequently reported as the reason for discontinuation among atomoxetine-treated patients were erectile dysfunction and insomnia, both cited by 5 patients.

Assessor's Comment on Discontinuations

The rate of discontinuations was generally very low, which supports the contention that the balance between efficacy and undesirable effects is favourable. The pattern of adverse events leading to discontinuation does not indicate a safety concern.

18.20V.5 Deaths

No patient deaths were reported in any atomoxetine ADHD clinical trial.

18.21V.6 Serious Adverse Events

18.21.1 V.6.1 Children and Adolescents

In studies in children and adolescents 119 patients reported 168 serious adverse events. Of the events in patients with known treatment assignments, 148 occurred in atomoxetine-treated patients, and eight in patients taking placebo. Of atomoxetine treated patients with known CYP2D6 genotype, 9 were poor metabolisers (reporting 16 events) and 95 were extensive metabolisers (reporting 129 events). Hence there was no excess of serious adverse events in poor metabolisers (7.3% of patients studied were poor metabolisers).

Two patients, both extensive metabolisers, experienced syncope classified as serious. However both recovered rapidly and did not have an adverse outcome. As discussed elsewhere in this report, increased susceptibility to vasovagal syncope is probably a significant undesirable effect of atomoxetine in a minority of individuals. However it does not appear to represent a major safety concern.

39 serious psychiatric adverse events were reported of which all, with one exception (bipolar disorder "possibly" related) were considered by the investigator unrelated to study drug. There were 16 reported serious AEs relating to either depression, suicidal ideation, or deliberate self-harm (8 reports) occurring during atomoxetine treatment and 10 relating to aggression or agitation. Most had a previous history of impulsive behaviour, self-harm and/or depression. There were no reported suicide attempts.

A review of individual cases of serious psychiatric AEs shows that in most cases strong risk factors unrelated to atomoxetine treatment were present at the time of study entry. Only 3 patients who developed serious adverse events relating to depression, suicidal ideation, or self-injury did not have either a history of depression or an evident psychosocial precipitant. The majority of episodes were reported at only one or two visits, which the applicant argues is inconsistent with an ongoing drug effect. Also, the timing of the onsets of most of these adverse events was not consistent with an acute medication related event. In the acute placebo controlled analysis there was no difference between atomoxetine and placebo for depression (0.8% versus 1.0%, p=0.739) but a non-statistically significant trend towards more reports of aggression or agitation in atomoxetine treated patients compared with placebo (1.8% versus 0.7%, p=0.185). It is reasonable to conclude that there is no evidence that atomoxetine played a causal role in serious psychiatric adverse events although the possibility cannot be discounted. Due to the primary and concomitant psychiatric morbidity in an ADHD population the reported frequencies of serious psychiatric adverse events are probably in line with expectations.

Other categories of interest included Gastrointestinal Disorders (28), Nervous System Disorders (13), Cardiovascular Events (7), and Metabolism and Nutrition Disorders (7). The serious adverse events reported in these categories are all considered by the applicant to be unlikely to be related to atomoxetine. Examination of the individual case reports does not identify any cases for which atomoxetine might reasonably be implicated and there is no pattern that might indicate toxicity of atomoxetine. By far the commonest non-psychiatric serious AE was appendicitis (14 cases), the reported frequency of which is shown to be consistent with that which would be expected in the normal population.

18.21.2 V.6.2 Adults

In the adults studies 34 serious adverse events were reported in 12 atomoxetine-treated patients and in 3 patients taking placebo. No serious adverse events were related to study drug or protocol in the opinion of the investigator. Examination of the individual reports of serious adverse events again bears this out and does not identify any pattern that might indicate toxicity of atomoxetine. All serious adverse events reported in atomoxetine-treated adult were in extensive metabolisers.

Assessor's Comment on Serious Adverse Events

Other than two episodes of syncope no serious adverse events reported during the clinical trial programme appear likely to be attributable to atomoxetine. The major concern is the possibility of adverse psychiatric effects. Although there is at present no evidence of a safety issue in this respect the possibility cannot be excluded.

18.22V.7 Safety Related to Drug-Drug Interactions and Other Interactions

Coadministration with potent CYP2D6 inhibitors (e.g. fluoxetine) results in substantially increased exposure to atomoxetine (AUC), but not greater than that seen in patients with poor metaboliser genotype. The potential for interactions via cytochrome P450 (CYP) inhibition has been discussed in the PK section.

In clinical studies, certain medications were excluded including those with CNS activity that could confound interpretations of efficacy, monoamine oxidase inhibitors because of the known interaction with other monoamine reuptake inhibitors, and chronic (but not episodic) use of sympathomimetics, because of the potential for synergistic noradrenergic effects. No potential interactions with other concomitant medications have been identified. The data presented by the applicant in investigating possible interactions are adequate. The advice in the SPC is appropriate.

18.23V.8 Laboratory Findings

Clinical laboratory tests (serum chemistry, haematology, and urinalysis) were performed at baseline and endpoint and assayed by a central contract laboratory in all studies. The applicant has presented a comprehensive review of these data including many exploratory analyses. Analyses of clinical laboratory parameters were performed for baseline to endpoint change and for categorical analyses of treatment emergent high, low, or abnormal values.

Mean Changes from Baseline (Total Safety Population)

Data for patients who took at least one dose of atomoxetine are presented below.

Laboratory parameter	Units	Baseline	Endpoint	Mean change
AST	U/ L	27.8	26.8	-1.0
ALT	U/ L	18.8	17.6	-1.1
CREATINE PHOSPHOKINASE	U/ L	137	135	-2.6
ALKALINE PHOSPHATASE	U/ L	239	228	-11.6
GGT	U/ L	12.8	13.0	0.2
UREA NITROGEN	mmol/ L	4.74	4.68	0.06
CALCIUM	mmol/ L	2.44	2.46	0.02
INORGANIC PHOSPHORUS	mmol/ L	1.61	1.58	-0.03
SODIUM	mmol/ L	140.7	141.4	0.63
POTASSIUM	mmol/ L	4.24	4.26	0.02
CHLORIDE	mmol/ L	104	104	0
TOTAL PROTEIN	g/ L	72.9	72.8	-0.1
ALBUMIN	g/ L	43.3	43.8	0.5
GLUCOSE	mmol/ L	5.06	5.10	0.04
URIC ACID	umol/ L	241	247	6
CHOLESTEROL	mmol/ L	4.25	4.22	-0.03
BICARBONATE,	mmol/ L	23.7	23.3	0.4
CREATININE	umol/ L	47.6	51.4	3.8
BILIRUBIN	umol/ L	7.09	7.28	0.19
HAEMOGLOBIN	mmol/l Fe	8.28	8.36	0.08
WHITE CELL COUNT		6.96	6.95	-0.01
PLATELET COUNT		292	296	4

Atomoxetine was not associated with any clinically significant mean changes from baseline for clinical chemistry, haematology, or urinalysis compared with placebo.

18.23.1.1.1.1.1.1 Clinically Significant Treatment-Emergent Changes in Laboratory Parameters

Large changes in laboratory parameters were not common and were mostly related to other adverse events. No liver enzyme value (AST, ALT, Alk Phos, GGT) of more than twice the upper limit of normal was recorded in any patient. Other than cholesterol >5.7mmol/l no single laboratory parameter was clinically significantly elevated in more than 4 patients and no pattern (muscle, bone, renal etc) was apparent.

18.23.1.1.1.1.1.2 Comparisons with Placebo (Placebo Controlled Population)

In the analysis of baseline to endpoint changes in the acute placebo-controlled population more atomoxetine-treated patients developed treatment-emergent elevation of calcium ($p<0.05$ uncorrected for multiplicity). In contrast, statistically significantly more placebo-treated patients developed treatment-emergent low CPK and high inorganic phosphorus levels. The magnitude of the changes was small in each case and they were not associated with clinical findings. No other differences between the atomoxetine and placebo groups were apparent. Because a large number of atomoxetine versus placebo comparisons was made, a number of p values <0.05 is to be expected. No excess over placebo was observed for any clinically significant treatment-emergent changes in laboratory parameters. The pattern of abnormal laboratory values appear to be random and does not represent a safety concern.

18.24V.9 ECG and QTc

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. Data on the ECG and QTc are reviewed in detail in the supplement to the Clinical Overview provided by [redacted].

18.25V.10 Haemodynamic Effects

A comprehensive, well balanced and robust review of the cardiovascular was provided to the applicant by [redacted]

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. This is considered by [redacted] not to be of any serious consequence.

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. [redacted] considered this effect on blood pressure is clinically insignificant.

One might expect that modest tachycardia and elevation of blood pressure might be of more concern in an adult population because of the increasing prevalence of vascular disease with increasing age. However this issues is probably satisfactorily addressed by the SPC wording proposed by the applicant.

18.26V.11 Effects on Growth and Development in the Paediatric Population

As atomoxetine is proposed for medium to long term treatment of children and adolescents possible effects on height and weight and on sexual and intellectual development were investigated.

18.26.1 V.11.1 Height and Weight

Patients in the atomoxetine-treated group showed a mean [SD] decrease from baseline to endpoint in weight (-0.6 [1.4] kg) during acute treatment, compared with an increase of (1.2 [1.4] kg) in the placebo group. This difference is highly statistically significant ($p<0.001$). In a non-parametric analysis of effects on weight, weight loss of at least 3.5% of baseline weight at endpoint was seen in 174 (27.0%) of 645 patients treated with atomoxetine. This contrasts clearly with the 398 treated with placebo in whom weight loss was seen in only 4 (1.0%). This difference is also highly statistically significant ($p<0.001$).

Weight at baseline and endpoint for 418 patients treated with atomoxetine for at least 2 years was analysed. An absolute mean weight gain (10.7 kg) at endpoint was observed, but this corresponds to a slight decrease of -2.8 percentiles relative to the age adjusted

expected weight. The decrement at endpoint from the weight that would have been reached had the baseline normative weight been maintained was 0.9 kg. A plot of mean weight percentile against time for patients with at least 2 years of atomoxetine exposure showed that, relative to expected growth rates, growth velocity slowed during the first 6 months of treatment. After about 12 months mean weight percentiles began to increase again and at 24 months, the weight percentiles were back to the level they had been at 3 months of treatment and mean growth velocity had returned to expected rates.

Height gain during acute treatment was not significantly different between patients treated with atomoxetine (mean [SD] increase 0.83 [1.3] cm) and patients in the placebo group (mean [SD] increase 0.96 [1.3]) cm). However the duration of these studies (approximately 2 months) would probably be too short to detect an effect of atomoxetine on growth rate.

Although growth rates appear to recover after 24 months, the lost growth from the first 3 months of treatment was not recovered. However this appears to represent only a few percentiles on the age normalised height chart. No data are available on what might happen to rates of growth beyond 2 years, whether or not atomoxetine treatment was continued. The applicant concludes that "initiation of treatment with atomoxetine is associated with an initial weight loss and a transient slowing of growth velocity. During long-term treatment, growth velocity returns to normal rates; after 2 years, height and weight are close to values that would have been observed had baseline height and weight percentiles been maintained." This is probably a reasonable conclusion. The following advice in the SPC is satisfactory:

> *Growth should be monitored during treatment with atomoxetine. Patients requiring long-term therapy should be monitored and consideration should be given to interrupting therapy in patients who are not growing or gaining weight satisfactorily.*

18.26.2 V.11.2 Sexual Development

Atomoxetine did not appear to be associated with either a delay in onset of puberty as assessed by Tanner staging in the relapse prevention study LYAF or with observations of delayed sexual maturation in the overall peri-adolescent study population.

18.26.3 V.11.3 Intellectual Development

In the 1-2 year studies LYAF and LYAB atomoxetine was not associated with any adverse effects on intellectual ability (IQ) or educational achievement and there appear to be no concerns arising from the other short or long term studies.

18.27V.12 Safety in Other Special Groups and Situations

18.27.1 V.12.1 Pregnancy and Lactation

Women who were pregnant or breast-feeding and women of childbearing potential not using adequate contraception were excluded from all studies. No pregnancies were reported in patients exposed to atomoxetine during ADHD clinical studies but two were

reported during the adult depression studies conducted in the 1980s and 1990s. The outcome, a normal live baby, is known for only one of these cases.

18.27.2 V.12.2 Overdose

A total of 12 overdoses were reported. All were accidental, most were of less than twice the maximum dose allowed in the study, and the highest exposure seen was 6.8mg/kg/day. No clinically serious adverse events were associated with the incidents. No data are available on overdose in poor metabolisers.

18.27.3 V.12.3 Abuse Potential

Atomoxetine is not active at receptors known to be associated with abuse potential, (dopamine, opioid, and gamma-aminobutyric acid). In addition to a number of preclinical studies the potential for abuse and dependence was investigated in two abuse potential studies.

LYAD

Clinically relevant doses of atomoxetine, methylphenidate, and placebo were administered on separate days to healthy volunteers who had a history of recreational drug use.

Primary comparisons were between atomoxetine and placebo. Atomoxetine was perceived as unpleasurable compared with placebo and the profile of response for atomoxetine on the Addiction Research Centre Inventory scale was not consistent with that typically observed for euphoriants or amphetamines. Atomoxetine shows no significant potential for abuse.

Another study, LYBO, designed to assess the desirability of atomoxetine as an abusable drug in drug-abusing adults is ongoing.

18.27.3.1.1.1.1.1 LYBO

This study compared atomoxetine 180mg with methylphenidate, phentermine and desipramine in 46 experienced, stimulant-preferring drug abusers. The results confirmed that atomoxetine has significantly less abuse potential than methylphenidate or phentermine, and no greater than desipramine or placebo.

The applicant's claim that there is strong evidence of the lack of abuse potential for atomoxetine is justified. This gives it a clear advantage over methylphenidate and other amphetamines where there is a risk of substance abuse or drug diversion.

18.27.4 V.12.4 Withdrawal and Rebound

Withdrawal and rebound were investigated thoroughly in clinical studies with randomised withdrawal terminal phases. The data from these studies did not demonstrate any evidence of clinically important withdrawal effects or risks associated with abrupt or tapered discontinuation of atomoxetine in children, adolescents and adults. On discontinuation effects on pulse and blood pressure return toward baseline without evidence of a rebound effect. The SPC advice that treatment "can be discontinued without tapering the dose" is satisfactory.

18.27.5 V.12.5 Effects on Ability to Drive and Use Machines

The effects of atomoxetine on the ability to drive or operate machinery were not systematically studied. However atomoxetine was associated with increased rates of somnolence and fatigue relative to placebo. The wording in the SPC was amended to include this fact.

18.28V.13 Safety/Tolerability of Once Daily versus Twice Daily Dosing

The rates of discontinuations due to adverse events were similar in the two groups (3.8% in twice-daily dosing and 4.4% in once-daily dosing). The odds ratio for atomoxetine versus placebo was statistically significantly greater in patients dosed once daily than in patients dosed twice daily for treatment-emergent vomiting, nausea, and fatigue. However the magnitudes of the differences were modest and it is considered that these findings do not represent important difference in tolerability between the two groups. The final approved SPC wording is therefore adequate.

18.29V.14 Post Marketing Experience

The first worldwide marketing authorisation was in the USA in November 2002. The first PSUR including one year post-marketing safety data in over 1 million patients has not revealed any clinically significant issues resulting in label changes in any of the countries where Strattera is licensed.

18.30V.15 Safety and Tolerability Conclusions

Miscellaneous gastrointestinal and CNS undesirable effects appear to be quite common in both children and adults but are generally quite well tolerated. In addition a variety of genitourinary undesirable effects including erectile dysfunction were apparent. These undesirable effects were predictable based on atomoxetine's noradrenergic pharmacology and reflected the pattern seen in the clinical pharmacology studies. They were predominantly mild in severity and the withdrawal rates due to AEs were generally low (4.1% overall for atomoxetine treated patients).

In poor CYP 2D6 metabolisers atomoxetine was generally well tolerated although a modest but significant increased frequency of adverse events was seen. The difference in tolerability from extensive metabolisers is surprisingly small considering that plasma levels (AUC) are at least five times higher than normal. There is no evidence of a major safety issue in this population although the total number of poor metabolisers studied was less than 200. The SPC adequately reflects the adverse events that are more frequent in poor metabolisers.

Vasovagal attack and syncope represent a potential safety issue, especially poor metabolisers, although even in the latter group these events were usually not problematic. The first PSUR included a 12-month cumulative review of these topics without detection of a safety signal.

Psychiatric adverse events did not appear to occur more frequently in patients treated with atomoxetine compared with placebo. A detailed review of the case reports of

treatment emergent serious psychiatric morbidity gives the impression that these events are far more likely to be related to the underlying disorder than to treatment with atomoxetine. This impression is supported by the lack of significant differences from placebo in analyses of the controlled data. Depression and generalised anxiety disorder were however numerically more frequent in poor metabolisers although the number of reports is too small to draw firm conclusions. The SPC adequately reflects these 2 adverse events as being more frequent in poor metabolisers. The conclusion based on the data currently available is that there is no evidence of a causal link between atomoxetine and psychiatric adverse events. However this remains a possibility and should be the subject of close scrutiny in post-marketing surveillance.

In conclusion there is evidence that the frequency of adverse events is related to drug exposure, although the issue appears to be mainly one of tolerability rather than safety. There is currently no evidence of an important safety issue with CYP 2D6 polymorphism or inhibition by concomitant medication although this needs to be closely monitored. Although the incidence of undesirable effects appears to be higher and there are possible signals for depression, generalised anxiety disorder and vasovagal events that will require attention in post-marketing surveillance, the overall pattern of adverse events remains acceptable in poor metabolisers. The applicant's claim that "the adverse event profile in PM and EM patients is similar, regardless of dose" is not supported by the data however. Thus, section 4.8 of the SPC was revised to include concise information on the frequency of adverse events in poor metabolisers.

The pattern of adverse events during long-term treatment did not suggest a different pattern from acute treatment, and there was no evidence of unexpected late-occurring events.

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 this should be the subject of close scrutiny in post-marketing surveillance.

In growing children there was an initial modest weight loss. During longer-term treatment, rates of growth (height and weight) recovered although the initial losses were not fully recovered by 24 months. This issue is adequately addressed by the SPC warnings.

Atomoxetine was not associated with adverse effects on hepatic or other laboratory parameters or cardiac depolarisation (QT interval). No evidence of withdrawal reactions or abuse potential was observed. The safety and tolerability of atomoxetine was similar regardless of whether the total daily dose was given once daily or as a divided twice daily dose.

Data from the active comparator study LYBI showed no major differences in tolerability between atomoxetine and methylphenidate. Atomoxetine was associated with significantly higher rates of fatigue and somnolence while methylphenidate was associated with more insomnia, reflecting the non-stimulant nature of atomoxetine.

19 VI Risk – benefit conclusions

The risk-benefit in children and adolescents is clearly positive for both short term and long term treatment, including poor metabolisers. The posology in the final approved SPC is satisfactory and fully justified by the data. The data from the three way acute treatment study with active comparator as well as placebo (study LYBI) indicate that the efficacy of atomoxetine might be a little less than that of methylphenidate. This is not a serious deficiency in the overall evidence of efficacy for atomoxetine. Atomoxetine and methylphenidate were both well tolerated, with no evidence of serious safety concerns related to either drug and there was not a clinically significant difference between active treatments in effects on cardiovascular tone. The data clearly show that atomoxetine has important safety/abuse potential advantages over the stimulants currently used to treat ADHD, as well as a favourable profile in patients with co-morbid tics. Atomoxetine is therefore likely to have an important place in the treatment of ADHD.

Concerning the adult subpopulation, the applicant, supported by the external expert opinion *"ADHD in adults in Europe and the need for licensed pharmacotherapeutic treatment"*, has adequately justified the clinical rationale for the use of atomoxetine for ADHD in adults. Adult ADHD may differ in some ways from its paediatric counterpart and is perhaps associated with greater psychiatric co-morbidity and personality disorder. Paediatric data can therefore only provide supporting evidence of efficacy in adults. It would appear reasonable that individuals diagnosed as having ADHD in childhood might benefit from continuing treatment into adulthood if their symptoms persist. Since there is currently no medicinal product licensed for the treatment of adult ADHD it can be argued that there is an unmet clinical need. There is clear evidence of efficacy in short term treatment in adults although the magnitude of the treatment effect might be smaller than that seen in children. Despite the relative lack in adults of well controlled long term efficacy data and formal dose-response data, the available adult data supplemented by extrapolation of paediatric data are considered to be sufficient to support the indication.

20 VII CLINICAL OVERVIEW

The clinical overview (previously clinical expert report) is provided by [redacted] It is of excellent quality and presents a balanced review of the subject matter. It is supplemented by a comprehensive review of the cardiovascular provided to the applicant by [redacted]

21 VIII PRODUCT LITERATURE

21.1.1.1.1.1.1.1.1 VIII.1 SPC

The SPC is satisfactory (changes requested following initial assessment are not detailed here but were all satisfactorily resolved).

21.1.1.1.1.1.1.1.2 VIII.2 PIL

The PIL is satisfactory.

21.1.1.1.1.1.1.1.3 VIII.3 Labels

The labelling is satisfactory.

ANNEX 3

Overview of PSUR 04
(27 November 2004 – 26 May 2005)

Review of the most recent PSUR (27 November 2004 – 26 May 2005)

This report provides an overview of the spontaneous adverse event reports, studies and literature reports from the most recent PSUR for atomoxetine (covering the period 27 November 2004 to 26 May 2005). Due to time constraints this is not a full assessment of the PSUR data. Instead it provides an overview of the reports and will attempt to identify issues of concern which may require further assessment. The PSUR will be assessed in more detail in due course.

The key issues of suicidal behaviour, hepatotoxicity, seizure and cardiovascular disorders are discussed in the main body of the risk:benefit assessment report. In addition, separate reviews of suicidal behaviour, hepatotoxicity and seizure are provided in Annex 1&4 (suicidal behaviour), Annex 5 (hepatoxocity), and Annex 6 (seizure).

For the purpose of this PSUR, where reports of reactions affecting more than one system organ class (SOC) have been received, the MAH has assigned the report to the SOC of the most clinically significant serious reaction (primary reaction). The other reactions in the report have been listed in the SOC of the primary reaction so that cases only appear once in the line listing. A summary of all of the reported reactions for each SOC is also provided in which each reaction is listed in its relevant SOC independently of other reactions that may have been reported in the case.

A total of 1020 reports were received during the period covered by the report (estimated patient exposure for the same period is 1,272,000 patients). Of these 1020 reports, 1012 were spontaneous reports (24 from Regulatory Authorities), 7 reports from clinical trials and 1 report from a post-marketing study. There were no literature reports.

There were 7 fatal cases. According to System Organ Classes the fatal cases were: 2 Cardiac Disorders; 2 General Disorders and Administration Site Conditions; 1 Hepato-biliary Disorder; and 2 Psychiatric Disorder.

There were 187 serious cases reported during the period covered by the PSUR. The most frequently reported serious cases fell into the following SOCs: Cardiac Disorders (14), Gastrointestinal disorders (19), Hepato-biliary disorders (13), Investigations (21), Nervous System Disorders (38), Psychiatric Disorders (43).

Table 1 below summarises the number of cases in each System Organ Class (SOC) for the six month period covered by this PSUR and compares it to the six month period covered by the preceding PSUR.

Table 1. Reported cases for atomoxetine

System Organ Class	Current Period (27 Nov 2004 through 26 May 2005)					Previous Period (27 May 2004 through 26 Nov 2004)	
	Fatal Cases	Total Serious Cases	Non-Serious Cases	Total Cases Serious & Nonserious	Frequency (%)	Total Cases (Serious & Nonserious)	Frequency (%)
Blood and lymphatic system disorders	0	2	1	3	0.3%	2	0.2%
Cardiac disorders	2	14	29	43	4.2%	40	3.6%
Congenital and familial/genetic disorders	0	0	1	1	0.1%	3	0.3%
Ear and labyrinth disorders	0	0	2	2	0.2%	4	0.4%
Endocrine disorders	0	0	0	0	0%	0	0%
Eye disorders	0	3	28	31	3.0%	27	2.4%
Gastrointestinal disorders	0	19	114	133	13.0%	126	11.4%
General disorders and administration site conditions	2	9	43	52	5.1%	61	5.5%
Hepato-biliary disorders	1	13	4	17	1.7%	3	0.3%
Immune system disorders	0	0	1	1	0.1%	6	0.5%
Infections and infestations	0	1	6	7	0.7%	7	0.6%
Injury and poisoning	0	2	13	15	1.5%	15	1.4%
Investigations	0	21	165	186	18.2%	112	10.1%
Metabolism and nutrition disorders	0	2	3	5	0.5%	13	1.2%
Musculoskeletal, connective tissue and bone disorders	0	3	7	10	1.0%	9	0.8%
Neoplasms benign and malignant (including cysts and polyps)	0	0	0	0	0%	1	0.1%
Nervous system disorders	0	38	88	126	12.4%	139	12.6%

(continued)

System Organ Class	Current Period (27 Nov 2004 through 26 May 2005)					Previous Period (27 May 2004 through 26 Nov 2004)	
	Fatal Cases	Total Serious Cases	Non-Serious Cases	Total Cases Serious & Nonserious	Frequency (%)	Total Cases (Serious & Nonserious)	Frequency (%)
Pregnancy, puerperium and perinatal disorders	0	0	0	0	0%	0	0%
Psychiatric disorders	2	43	156	199	19.5%	274	24.8%
Renal and urinary disorders	0	4	47	51	5.0%	41	3.7%
Reproductive system and breast disorders	0	1	46	47	4.6%	60	5.4%
Respiratory, thoracic and mediastinal disorders	0	1	5	6	0.6%	24	2.2%
Skin and subcutaneous tissue disorders	0	5	46	51	5.0%	60	5.4%
Social circumstances	0	0	0	0	0%	0	0%
Surgical and medical procedures	0	0	2	2	0.2%	60	5.4%
Vascular disorders	0	6	26	32	3.1%	19	1.7%
Total	**7**	**187**	**833**	**1020**	**100%**	**1106**	**100%**

Fatal Cases

There were seven reported cases with a fatal outcome. These were:

[redacted] Cardiorespiratory arrest
Myocardial infarction
Death, drug level increased
Death
Hepatic failure, renal insufficiency, vomiting, prothrombin time prolonged
[redacted] Completed suicide
Completed suicide

These reports are discussed in more detail in the relevant System Organ Classes below.

Blood and Lymphatic System Disorders

There have been three case reports where the *primary* reaction was categorised to this SOC. These were: mononucleosis syndrome (non-serious), neutropenia aggravated (serious), and thrombocytopenia (serious). In both serious cases (neutropenia and thrombocytopenia) the patient was receiving concomitant medication which could confound the report (methylphenidate and risperidone). However, the pre-existing neutropenia worsened when atomoxetine was commenced and continued when

methylphenidate was withdrawn. Haematologist reported that the neutrophil drop was due to an immune disorder.

A total of 14 reactions were categorised in this SOC (6 serious, 8 non-serious). The 6 serious reactions are unlisted.

Cardiac Disorders

There were 43 case reports in which the primary reaction coded to the cardiac disorders SOC (14 serious, 27 non-serious). Two cases had a fatal outcome.

In total there have been 58 reactions categorised in this SOC. Of these 15 were serious (8 unlisted, 7 listed), and 43 were classed as non-serious (7 unlisted, 36 listed).

The first fatal case (cardio-respiratory arrest) in an [redacted] appears to have no obvious confounding factors. Autopsy showed no abnormal findings and no cause of death was certified. Heart, lungs and liver were normal and stomach was empty.

The fatal myocardial infarction occurred in a man in his 70's with unspecified pre-existing heart conditions.

There have been 8 serious, unlisted reactions during the reporting period in this SOC. In only six of these cases, the *primary* reaction coded to cardiac disorders SOC. These cases were 'arrhythmia'; 'atrioventricular block first degree'; 'bundle branch block' and 'chest pain'; 'cardiomegaly'; 'extrasystoles'; and 'mitral valve prolapse'.

It is clear from the line listing in the PSUR that these and previously reported cardiac events associated with atomoxetine require further more detailed assessment. The fatal case of cardio-respiratory arrest in an 11-year old with no apparent confounding factors is worrying. The autopsy would not have revealed an arrhythmia. Cumulatively there are 9 serious reports of conduction disorders and 17 serious reports of supraventricular arrhythmias and also cases of ventricular arrhythmias which warrant furthe. See also the Investigations SOC for reports of ECG abnormal and QTc interval prolongation.

Eye Disorders

There have been 31 case reports where the primary reaction was categorised into the eye disorders SOC (3 serious, 28 non-serious). In total there have been 48 reactions which coded to the Eye Disorders SOC (3 serious unlisted, 19 non-serious unlisted, 26 non-serious listed). The three serious unlisted reactions were 'eye disorder' (unspecified nerve damage in left eye); 'papilloedema', 'paralysis', 'headache', 'nausea' and 'vomiting'; 'visual acuity reduced'. Of note, the most frequently reported reaction (n=24) was mydriasis which is listed in the SPC.

Gastrointestinal Disorders

There have been 133 case reports (19 serious, 114 non-serious) where the primary reaction coded to Gastrointestinal Disorders SOC during the period 27 November 2004-26 May 2005.

In total there have been 350 reactions categorised in this SOC. Of these 303 were classified non-serious and 47 were considered serious (11 unlisted, 36 listed). The most frequently reported GI reactions were: nausea (93), vomiting (82), abdominal discomfort (37), abdominal pain (37), upper abdominal pain (22), constipation (18), diarrhoea (11) and stomach discomfort (11). All of these adverse reactions are recognised and are listed in the SPC.

There have been 11 serious unlisted reactions, 2 of which were primary reaction terms which coded to the GI SOC. These were 2 cases of pancreatitis. There are a cumulative total of 5 serious cases of pancreatitis and 1 pancreatitis acute. The MAH has provided a review of pancreatitis associated with atomoxetine.

Pancreatitis
The MAH identified a total of 12 case reports (15 adverse events) from the safety database (health professional and consumer reports since 01/01/1983). The reactions reported were: pancreatitis (6), pancreatitis acute (1), blood amylase increased (4) and lipase increased (4).

The MAHs analysis excludes 5 of the 12 reports since they did not have a MedDRA preferred term which coded to pancreatitis and did not have information that is supportive of a diagnosis of pancreatitis (pancreatic and renal transplant, lipase increased due to gastroenteritis, blood amylase increased - patient had gastrointenstinal bleed, and 2 cases in which there was insufficient information to determine the etiology of the raised lipase and/or amylase levels).

All of the 7 remaining cases were considered by the MAH to have clear confounding factors (gallbladder disease (2), alcohol abuse (1), gastric bypass surgery with pancreatic stents (1), viral infection & negative dechallenge (1), and no information on medical history/lack of other information (1)).

On review of the MAHs analysis, it can be concluded that there is no evidence of a causal relationship between atomoxetine and pancreatitis in the reported cases.

General Disorders and Administration Site Conditions
There have been 52 case reports where the primary reaction was categorised in this SOC (9 serious, 43 non-serious).

In total there have been 167 reactions categorised in this SOC (17 serious, unlisted and 150 non-serious).

There were 2 case reports with a fatal outcome (death, drug level increased; and death). It is difficult to establish causality in these two fatal cases. In the first case the patient was on multiple medications (all of which were found to be raised in in the blood). In the second case there are too few details to establish causality.

There have been a total of 167 reactions reported during the reporting period in this SOC. The most frequently reported reactions were fatigue (40), pyrexia (16), other temperature regulation disorders (hypothermia, chills, feeling cold, feeling hot) (11); malaise (13), feeling abnormal (16), influenza-like illness (10). Fatigue and cold/flu symptoms are recognised adverse effects of atomoxetine.

There have been 7 serious, unlisted primary reactions in this SOC. These are chest pain (1), drug interaction (5) and drug withdrawal syndrome (1). The drug interactions and drug withdrawal syndrome will be discussed in the 'Drug Interaction' section below and 'Drug Abuse and Drug Withdrawal' section in the main report.

Immune System Disorders

There has been 1 non-serious report where the primary reaction was categorised to Immune System Disorders SOC. This was 'seasonal allergy'.

There are a cumulative total of 11 serious immune system disorders. These are hypersensitivity (7), drug hypersensitivity (1), anaphylactic reaction (1), anaphylactic shock (2).

Allergic reactions are mentioned in section 4.4 of the SPC including angioneurotic oedema. The case of anaphylaxis and 2 cases of anaphylactic shock may warrant further assessment with a view to updating the SPC.

Infections and Infestations

There have been 7 cases where the primary reaction coded to Infections and Infestations SOC (1 serious).

In total there have been 24 reactions (3 serious, 21 non-serious) categorised in this SOC. All were unlisted. There is no real pattern to the reported reactions with the majority being single first cases. Those reactions reported more frequently than twice during the period are nasopharyngitis (3, non-serious), urinary tract infection (3, non-serious) and viral infection (3, non-serious).

There is 1 report in which the primary reaction was serious, unlisted and coded to this SOC. This is a case of pneumonia. Cumulatively there have been 3 serious reports of pneumonia.

Injury, Poisoning and Procedural Complications

There have been 15 case reports in which the primary reaction coded to this SOC (2 serious, 13 non-serious).

In total, there have been 23 reactions categorised in this SOC during the period 27 November 2004- 26 May 2005. Of these, 7 were classified as serious and 16 were non-serious. All reactions were unlisted. The most frequently reported reactions were: contusion (8), medication error (4) and fall (3).

There were 2 serious case reports in which the primary reaction coded to this SOC and was unlisted. These are a case of contusion and a case of foreign body trauma.

Based on the number of reports of contusion this could be an issue that is further assessed, however children (especially those with ADHD) tend to be more accident prone and therefore may bruise more frequently.

Investigations

There have been 186 case reports where the primary reaction SOC coded to Investigations (21 serious, 165 non-serious).

There have been a total of 336 reactions categorised in the Investigations SOC during the period covered by PSUR 4. The most frequently reported reactions were: weight decreased (48); alanine aminotransferase increased (48); aspartate aminotransferase increased (40); hepatic enzyme increased (29); heart rate increased (21); blood bilirubin increased (18); alkaline phosphatase increased (13), weight increased (12), drug screen false positive (12). Weight decreased, abnormal liver enzymes, jaundice, tachycardia are listed adverse effects of atomoxetine in the EU SPC.

There have been 6 serious case reports with an unlisted primary reaction which coded to investigations. These are: blood sodium decreased (1); blood urine present (1); QTc interval prolonged (2); ECG T-wave inversion (1); weight increased (1).

Of note, there are a cumulative total of 25 serious cases of QTc prolongation (13) and QT-prolonged (12). Questions were raised at the time of licensing of atomoxetine with regards to its QT interval prolonging potential and these issues were resolved at that time (see pages 20-23 and 37-38 of the repeat MRP assessment report, Annex 2). Also clinical trial data showed no effect of atomoxetine on ECG recordings and atomoxetine did not significantly affect QTc in either CYP2D6 PMs or EMs. However, it is felt that the number of spontaneous reports warrant further review of its potential to cause arrhythmias.

As discussed in the Cardiac Disorders SOC, the reports of cardiac arrhythmias and ECG abnormalities including QT interval prolongation should be further assessed.

Metabolism and Nutrition Disorders

There have been 5 cases in which the primary reaction coded to this SOC (2 serious).

In total there have been 51 reaction categorised in this SOC during the period covered by PSUR4. Of these reactions 5 were serious (3 unlisted, 2 listed) and 46 were non-serious (5 unlisted, 41 listed). The most frequently reported reactions were decreased appetite (29) and anorexia (14). Both anorexia and decreased appetite are listed in the EU SPC for atomoxetine.

There have been 2 serious reports with unlisted primary reactions which coded to this SOC. They are dehydration (associated with non-stop vomiting) and insulin-dependent diabetes mellitus.

Musculoskeletal and Connective Tissue Disorders

There have been 10 case reports in which the primary reaction coded to the musculoskeletal and connective tissue disorders SOC (3 serious, 7 non-serious).

In total there have been 29 reactions categorised in this SOC. Three of these 29 reactions were serious and 26 were non-serious. All reported reactions were unlisted. The most commonly reported reactions were: muscle spasms (6), myalgia (5), arthralgia (5), muscle twitching (4).

The three serious, unlisted reactions which coded primarily to this SOC were: arthralgia, erythema and urticaria; myositis, hepatic failure, pain in extremity and pyrexia; and rhabdomyolysis, nasopharyngitis abdominal pain, peripheral oedema and myalgia.

These are the first reported serious cases of myositis and rhabdomyolysis for atomoxetine. The number of cases of myalgia and arthralgia warrant further assessment of these cases with a view to updating the SPC.

Nervous System Disorders

There have been 126 case reports in which the primary reaction coded to the Nervous System Disorder SOC (38 serious, 88 non-serious).

There have been a total of 281 reactions categorised in the nervous system disorders SOC. Of these, 77 were serious (66 unlisted, 11 listed) and 204 were non-serious (132 unlisted, 72 listed). The most frequently reported reactions were: dizziness (48); headache (46); somnolence (46); convulsion (20) (plus 3 petit mal epilepsy, 1 grand mal convulsion, 2 epilepsy, 1 partial seizures); disturbance in attention (13); psychomotor hyperactivity (13) and syncope (11). Dizziness, somnolence, headache and syncope are recognised adverse effects of atomoxetine and are listed in section 4.8 of the EU SPC.

There have been 36 serious cases with an unlisted reaction as a primary reaction in this SOC.

The serious case reports were (excluding convulsions – see below): cerebrovascular accident; extrapyramidal disorder; headache, Gilbert's syndrome, malaise, epistaxis and pyrexia; headache, dizziness and hot flush; hypotonic-hyporesponsive episode, lethargy, dizziness, coordination abnormal, feeling abnormal, tachycardia, hypertension, dizziness, cold sweat, livedo reticularis, and blood glucose increased; migraine and vomiting; myoclonus; loss of consciousness and memory impairment; syncope and blood glucose decreased; syncope, hallucination, fatigue and nausea; syncope, dizziness, heart rate increased, and blood pressure decreased; syncope, dizziness, heart rate increased and hypotension; syncope, palpitation, tachycardia and arrhythmia; and syncope. Orthostatic hypotension is a recognised adverse effect of atomoxetine. Cases of syncope and loss of consciousness are discussed with cardiac disorders in the main risk:benefit report.

Other reactions of note which warrant further assessment are: hypoaesthesia (6) /paraesthesia (4); speech disorder (1)/dysarthria (1) (plus two cumulative serious cases of each); movement disorders (dyskinesia, dystonia, extrapyramidal disorder); and tremor.

There were a total of 21 serious case reports with the primary reaction of convulsion (16), epilepsy (1), grand mal convulsion (1), partial seizures (1) or petit mal epilepsy. The MAH has conducted a cumulative review of all reported cases of seizure (26 November 2002 – 26 November 2004) with an additional review of subsequent cases reported 27 November 2004 - 26 May 2005. An overview of these reviews is provided below. The full assessment of the MAH review can be found at Annex 7 of the main risk benefit assessment report.

Seizures

A total of 19 possible seizure events (15 patients) were identified from the atomoxetine clinical trial database. There were a total of 183 case reports of seizure related adverse events identified from spontaneous data during the period 26 November 2002 – 26 November 2004. An additional 37 spontaneous case reports were identified for the six month period 27 November 2004 – 26 May 2005. Of the spontaneous reports of seizure, there were 4 reports in patients with no prior history of seizures in which a causal relationship with atomoxetine could not be excluded.

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 aggravating the patients' underlying seizure disorder can not be ruled out.

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.

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 events since US launch. The SPC should be updated to include seizure events in section 4.4, 4.8 and 4.9.

Psychiatric disorders
During the six-month period covered by this PSUR there were a total of 199 case reports (43 serious) in which the primary reported reaction coded to the 'Psychiatric disorders' SOC. Two of the case reports had a fatal outcome and both were reports of completed suicide involving young adults with previous psychiatric history (schizotypal personality disorder; depression and substance abuse).

In total there have been 430 reactions categorized in the "Psychiatric disorders" SOC during the period covered by this PSUR assessment and of these 77 were classified as serious. Due to the large number of psychiatric reactions reported (the majority of which are unlisted), in September 2005 the MHRA requested the MAH to perform a cumulative review of all psychiatric disorders reported for atomoxetine. The MAH is currently performing the review and it is anticipated that it will be available during the first quarter of 2006. In the mean time the MAH has provided a summary of the total number of psychiatric adverse events reported for atomoxetine since first launch. A discussion of these events together with a cumulative review of all spontaneous reports of suicidal behaviour reported for atomoxetine can be found in Annex 4 of the main risk:benefit assessment report.

Renal and Urinary Disorders
There have been 51 case reports where the primary reaction coded to the renal and urinary disorders SOC (4 serious, 47 non-serious).

In total there have been 83 reactions which coded to this SOC. Of these, 8 were serious (87 unlisted, 1 listed) and 75 were classified non-serious (37 unlisted and 38 listed). The most frequently reported reactions were: urinary retention (22); urinary hesitation (20); chromaturia (10) and dysuria (8). Urinary retention and urinary hesitation are listed in the EU SPC for atomoxetine for adults (adult clinical trial data).

There have been 4 serious case reports with an unlisted primary reaction which coded to this SOC. These were: haemorrhage urinary tract (2); nephrolothiasis and cholelithiasis; urinary retention (1). Urinary tract haemorrhage should be further assessed as in both cases a positive dechallenge was observed.

Reproductive System and Breast Disorders

There have been 47 case reports where the primary reaction coded to the reproductive system disorders SOC (1 serious, 46 non-serious).

A total of 79 reactions have been reported that are categorised to this SOC. Of these, 1 was serious (unlisted) and 78 were classified non-serious (51 unlisted, 27 listed). The most commonly reported reactions were: ejaculation failure (18); sexual dysfunction (15); and testicular pain (9). Ejaculation failure and sexual dysfunction are listed (adult clinical trial data) in section 4.8 of the atomoxetine SPC.

There has been one serious unlisted reaction which was benign prostatic hyperplasia. There were two non-serious cases of priapism and one of painful erection. The MAH comment that considering the pharmacological properties of atomoxetine, the events of priapism are unlikely to be related.

Respiratory, Thoracic, and Mediastinal Disorders
There were 6 cases in which the primary reported reaction coded to this SOC (1 serious, 5 non serious).

A total of 24 reactions were categorised to this SOC. The most frequently reported reactions were: dyspnoea (6); pharyngolaryngeal pain (4); throat irritation (3); epistaxis (3); and cough (3). All of the reactions were unlisted.

There was 1 serious case in which the primary reaction which coded to this SOC was unlisted. This was a case of dyspnoea with chest pain and rash which is a likely allergic reaction. Allergic reactions are listed in 4.4 of the SPC but not 4.8 (pruritus and rash are listed but not angioneurotic oedema). These should be added to 4.8 also (see immune system disorders for other relevant reported cases).

Skin and Subcutaneous Tissue Disorders
There have been 51 case reports where the primary reaction coded to this SOC (5 serious, 46 non-serious).

There is a total of 100 reaction categorised in the Skin SOC during the period covered by this PSUR. Seven of these were considered serious (1 unlisted, 6 listed) and 93 were classified as non-serious (17 unlisted and 76 listed). The most commonly reported reactions were: rash (25); pruritus (17); urticaria (13) and hyperhydrosis (7). Allergic reactions including pruritus, rash and urticaria are listed in section 4.4 of the SPC for atomoxetine.

There has been one serious unlisted reaction which coded to this SOC. This was a case of Henoch-Schonlein purpura with haemorrhagic shock. This is the first serious case of Henoch-Schonlein purpura reported for atomoxetine.

Of note, cumulatively there are 3 serious cases of erythema multiforme and 2 cases of Stevens Johnson syndrome. These serious skin disorders should be further assessed.

Social Circumstances
There have been no case reports where the primary reaction coded to the Social Circumstances SOC.

In total, there have been 2 reported reactions which code to this SOC. Both reactions were considered serious and were unlisted. These were 'physical assault' and 'social problem'. Aggression and hostility have just been added to the EU SPC for atomoxetine.

Vascular Disorders
There have been 32 case reports in which the primary reported reaction coded to the Vascular Disorders SOC (6 serious, 26 non-serious).

A total of 57 reactions were reported during this six month period which coded to the Vascular Disorders SOC. Eleven of these reports were serious (5 unlisted, 6 listed) and 46 were classified as non-serious (17 unlisted, 29 listed). The most frequently reported reactions were: hypertension (18); peripheral coldness (6); hot flush (6); pallor (6); Raynaud's phenomenon (4); hypotension (4); orthostatic hypotension (4); and flushing (4). Increase in blood pressure is mentioned in section 4.8 of the SPC for atomoxetine (children and adults) and peripheral coldness is listed in section 4.8 of the atomoxetine SPC in the adult clinical trial section.

In total there have been 3 serious reports with an unlisted reaction which coded to the Vascular Disorders SOC. These were: 'malignant hypertension'; 'Raynaud's Phenomenon', 'difficulty in walking', 'dysmennorhoea' and 'fatigue'; and a case of 'vasoconstriction' with 'abdominal pain', 'dizziness', 'disturbance in attention', 'dissociation' and 'fatigue'.

Raynaud's phenomenon
The MAH has conducted a cumulative review of spontaneous adverse reports of Raynaud's phenomenon for the period 26 November 2002 – 26 May 2005.

The MAH atomoxetine safety database was searched for consumer and healthcare professional reports using the following MedDRA preferred terms:

Raynaud's phenomenon, skin discolouration, peripheral coldness, livedo reticularis, nail discolouration, peripheral vascular disorder, poor peripheral circulation, and cyanosis.

The retrieved case reports were categorised as follows:

Category 1: Raynaud's phenomenon

Any case coded to the MedDRA preferred term of *Raynaud's phenomenon*. The clinical content did not dictate inclusion in this category. Case information did not need to match a clinical definition.

Category 2: Peripheral Vascular Instability with Peripheral Coldness
Any case that combined aspects of vascular changes in the periphery, skin color changes, and peripheral coldness. The case information did not allow a distinction between coldness and vascular changes, but clearly suggested peripheral vascular instability. In addition, the case was not coded to the preferred term of *Raynaud's phenomenon.*

Category 3: Peripheral Vascular Instability
Any case that described vascular changes in the periphery and skin colour changes. The definition of Raynaud's phenomenon found in the background section of the MAH's report was utilized. The clinical content in the case matched the general definition of Raynaud's syndrome. In addition, the case was not coded to the preferred term of *Raynaud's phenomenon.*

Category 4: Peripheral coldness
Any case that described cold extremities could not be differentiated from peripheral vascular instability events or the impact of a cold environment.

Category 5: Not relevant
Cases that are not relevant to the review. Any case that did not fit the first four categories. Any case without peripheral vascular instability or peripheral coldness. For example, a case coded to *skin discoloration* whereby the term was used to describe dark circles under the eyes.

A total of 142 case reports (of 154 adverse events) were retrieved using the search. Eighty (56%) of the reports were consumer reports and the rest were from healthcare professionals. Four of the 154 adverse events were considered serious. The following table provides an overview of the cases.

Table 2

MedDRA Preferred Term	No. of Events	No. Serious Events
Raynaud's phenomenon	16	1
Peripheral Vascular disorder	1	0
Peripheral coldness	58	0
Poor peripheral circulation	8	1
Skin discoloration	57	1
Nail discoloration	1	0
Livedo reticularis	1	0
Cyanosis	12	1
Total Events	**154**	**4**

The following table displays the results of the categorisation by the MAH.

Table 3

Categories	No. of cases	% of total
Category 1 Raynaud's phenomenon	16	11.3
Category 2 Peripheral vascular instability with peripheral coldness	17	11.9
Category 3 Peripheral vascular instability	30	21.1
Category 4 Peripheral coldness	40	28.2
Category 5 Not relevant	39	27.5
TOTAL cases	**142**	**100**

The MAH considered cases in category 1-3 (n=63) to be of the most clinical relevance with category 4 being potentially relevant to the topic (n=40). There were 3 serious cases out of the 103 cases. None of the 142 cases led to serious outcomes such as gangrene or surgical intervention.

Following review of the cases, the MAH concludes that atomoxetine has the potential to exacerbate pre-existing Raynaud's phenomenon with 7 cases that described a worsening of symptoms. The MAH also state that whilst these 'cases are not compelling that atomoxetine causes the development of peripheral vascular instability and/or Raynaud's phenomenon in a patient without risk factors, the known pharmacology of atomoxetine makes it plausible that atomoxetine may be associated with the symptoms of Raynaud's phenomenon'.

Raynaud's phenomenon should be added to section 4.8 of the SPC for atomoxetine.

Late Breaking Information.
During the one month period after the data lock for this PSUR (27 May 2005 – 26 June 2005), a total of 151 case reports of 303 reactions were received by the MAH.

A total of 16 of the 151 case reports were considered to be serious (135 non-serious). Twenty-four of the 303 reported reactions were considered to be serious (13 unlisted, 11 listed). The serious, unlisted reactions were: neutropenia, myocardial infarction, viral myocarditis, electrogram QT corrected interval prolonged, dehydration, cerebrovascular accident (2 reactions), loss of consciousness, syncope, suicide attempt, nephritic syndrome, psoriasis and malignant hypertension.

These late breaking reports highlight some potential issues which have already been highlighted in this report for further assessment (QT interval prolongation (considered related to atomoxetine by the reporter in the late breaking case). Furthermore, these reports identify some other reactions which also require further cumulative review:

cerebrovascular accident (2 cases in late breaking information, and two reports in the line listing), neutropenia/other blood disorders (positive dechallenge with no concomitant medication in the late breaking case of neutropenia).

Drug Interactions

The MAH performed a review of the atomoxetine safety database for healthcare professional reports of drug interactions reported during the period 27 November 2004 – 26 May 2005.

A total of 12 case reports were identified. These were categorised as 'pharmacokinetic' interactions or 'pharmacodynamic' interactions by the MAH.

One of the reported cases had a fatal outcome. This was a case of acute ingestion of atomoxetine (960mg) which has previously been discussed in the overdose section (drug interaction, overdose, completed suicide). The reporter suggested that paroxetine may limit metabolism of atomoxetine by inhibition of CYP2D6.

The only drug interaction to be reported more than once was an interaction between atomoxetine, psuedoephedrine and brompheniramine which was reported in 4 cases (by the same reporter). This was categorised as a pharmacokinetic interaction by the MAH. In three of cases, patients who were already established on atomoxetine treatment reported that atomoxetine became less effective upon starting peudoephedrine/brompheniramine. The response to atomoxetine improved in all three patients when pseudoephedrine/brompheniramine were discontinued. In the fourth case, atomoxetine was titrated to obtain a response on ADHD (prescribed overdose). Atomoxetine had been added to established treatment with pseudoephedrine/brompheniramine.

The MAH suggests that it would seem plausible that pseudoephedrine may have caused an exacerbation of the ADHD due to stimulatory activity. However this would not explain the case in which the patient already established on pseudoephedrine/brompheniramine who could not achieve therapeutic response despite titration (prescribed overdose) of newly introduced atomoxetine therapy.

The remaining interaction cases are single cases and/or are adequately described in the SPC.

Use in Pregnancy and Lactation

The MAH conducted a search of their safety database for Healthcare professional reports where patients had used atomoxetine during pregnancy. The reports were categorised as prospective reports (reported before the outcome of the pregnancy is unknown) or retrospective reports (reported after delivery or abnormal diagnostic procedure).

During the period covered by this PSUR, 13 cases in which atomoxetine was used during pregnancy were identified. Three of these reports were from the previous reporting period with follow up information available.

Twelve of the 13 cases were prospective reports and one was retrospective. All but two of the reports were reported spontaneously with the two reports being identified in clinical trials (1 prospective, 1 retrospective).

Prospective Reports
Seven of the 12 prospective reports were pending delivery (estimated delivery date ranging from August 2005 – November 2005). Five of the 12 cases were successfully followed up.

There were 2 full-term delivery cases with no major congential abnormality reported. There was one premature birth (27 weeks gestation) with no congential abnormalities reported. However the infant later died due to severe sepsis and multiple organ failure. This was a clinical trial report and was considered unrelated to atomoxetine by the study investigator.

There were two elective termination cases with no congential abnormalities reported.

Retrospective Reports
The single retrospective pregnancy case was reported during a clinical trial. This case was a case of ectopic pregnancy in a 31-year old who was gravida 10 para 1 abortion 8. The ectopic pregnancy was considered not related to atomoxetine by the study investigator.

There were no cases involving a mother taking atomoxetine while breast feeding during the period 27 November 2004 – 26 May 2005.

Summary of Case Reports with Syncope or Loss of Consciousness
There have been a total of 14 cases (16 adverse reactions) of syncope (10 serious, 1 non-serious) or loss of consciousness (5 serious) reported during the period covered by PSUR4 (see Nervous System Disorder SOC).

Orthostatic hypotension was suggested as the possible cause of syncope by the reported in 4 cases. Orthostatic hypotension is a recognised adverse effect of atomoxetine and is listed in the SPC.

The possible causes of syncope/loss of consciousness in other reported cases are: tachycardia (listed), palpitation and unspecified arrhythmia in a patient who was also taking amphetamine/dexamphetamine; diarrhoea, vomiting and abdominal pain were reported in another case of syncope; low blood sugar was reported in the seventh case

(teenager did not have breakfast); and there were 3 cases in which no specified causes could be identified.

The MAH proposes to continue to monitor cases of syncope and loss of consciousness.

Drug Abuse and Drug Withdrawal Syndrome
Cases in which intentional, persistent, or sporadic, excessive use of atomoxetine inconsistent with the recommended use were coded as drug abuse. This section also looks at cases of addiction, dependence, and discontinuation/withdrawal symptoms associated with the use of atomoxetine.

During the six month period covered by PSUR 4, a total of 6 reports were received which coded to 'drug withdrawal syndrome' (4) and 'drug screen positive' (2). There were no reports of drug abuse.

No pattern in the symptoms of withdrawal can be detected from the small number of reports although the majority were psychiatric in nature. In two cases the patient recovered upon restarting atomoxetine. The outcome was unknown in one case and the reaction was continuing despite restarting atomoxetine in the remaining case. The MAH should continue to closely monitor reports of withdrawal reaction given that similar drugs are known to cause such events.

The two non-serious cases of 'drug screen positive' involved patients who had tested positive for amphetamines in a drug screen. No further information was available regarding these cases.

Efficacy Related Information
During the reporting period of PSUR 4 (27 November 2004 – 26 May 2005), there have been 64 spontaneous reports of lack of efficacy (including the terms 'drug ineffective', 'drug effect decreased' and 'therapeutic response decreased'). The MAH calculate a reporting frequency of 0.005%. All of the case reports were classified as non-serious. This is a decrease compared with the previous PSUR reporting period in which a reporting frequency of 0.015% was calculated for reports of lack of efficacy.

The dose of atomoxetine was provided in 46 of these reports and is summarised as follows: average daily dose (in 44 reports) was 57.5mg, the median dose was 40mg, with a range of 18mg to 180 mg daily. The remaining two reports reported the atomoxetine dose as 1.2mg/kg and 1.4mg/kg daily.

A total of 156 events were described in the 64 case reports of lack of efficacy. The most frequently reported event (except drug ineffective) was prescribed overdose (12). The MAH states that reports of prescribed overdose would typically be expected in lack of efficacy cases due to dose titration for a therapeutic effect.

Other frequently reported events in the 64 reports of lack of efficacy included abnormal behaviour (6), fatigue (5), abdominal pain upper (3), anxiety (3), disturbance in attention (3), headache (3), and irritability (3).

Twenty-five of the 64 case reports only contained the event 'drug ineffective' with no other reported events. Six reports contained 'drug ineffective' with 'prescribed overdose' with no other reported events. Thirty-three reports contained one or more non-serious adverse events.

The MAH concludes that the reports of lack of efficacy do not raise any safety concerns or identify any therapeutic or quality issues with atomoxetine.

Experience with Overdose, Deliberate or Accidental, and Its Treatment

The MAH conducted a search of their safety database for cases of overdose. An overdose of atomoxetine is considered to be a daily dose greater than 1.8mg/kg (for children and adolescents up to 70kg), or a daily dose greater than 120mg, which ever is less. This is in accordance with the CCDS dosing guidelines.

Assessor's comments:
The SPC states that for children under 70kg in weight "no additional benefit has been demonstrated for doses higher than 1.2mg.kg.day. The safety of single doses over 1.8mg/kg/day and total daily doses above 1.8mg/kg have not been systematically evaluated". For children/adolescents over 70kg in body weight the maximum recommended daily dose is 100mg. The MAH uses the CCDS definition of 'overdose' which are slightly higher doses than those recommended in the SPC.

During the reporting period, 116 cases of overdose were identified. Thirty-nine of these reports were received from a poison control centre and were published within a journal (see published literature section).

Of the 116 reports, 17 were categorised as serious. There were two cases with a fatal outcome. Two cases (including one of the fatal cases) were excluded from the analysis since upon review they were not considered to be atomoxetine overdoses. Thus the total number of cases analysed was 114 (1 fatal possible overdose of atomoxetine and other medications). Among the 114 cases, 67 cases of chronic overdose (including 62 cases of prescribed overdose) and 47 acute overdoses were identified.

Of the 67 cases of chronic overdose, 25 exceeded the CCDS recommended daily maximum dose and 42 did not exceed the CCDS recommended daily dose but were categorised as overdose since the reported doses exceeded
Prescribing Information maximum recommended daily dose. A total of 37 reports did not contain any adverse events and/or were coded to drug effect decreased/drug ineffective or were reported with disease exacerbations (irritability, psychomotor activity, abnormal behaviour, impulsive behaviour, disturbance in attention) and atomoxetine was being titrated upward. A significant number of the other case reports contained adverse

events which are considered listed (e.g. heart rate increased, tachycardia, weight decreased, dizziness, urticaria). Of note there were six cases that contained changes in liver function tests and three reports that involved seizure activity. These are included in the review of heaptobiliary disorders and seizure events at Annex 6 and Annex 7 of this report.

Of the cases of acute overdoses, 38 cases were provided in the publication 'Atomoxetine ingestions in children: A Report for Poison Centres' and are not discussed further by the MAH in this section (see published literature section). Of the remaining nine cases of acute overdose 5 were considered to be accidental and 4 were determined to be intentional overdoses. The patients were asymptomatic in 2 of the five cases of accidental overdose.

Seizures were reported in a 1–year old with a history of petit mal epilepsy and heart rate increased was noted in another patient. In the final case of accidental overdose no symptoms were provided but it is unclear from the MAH report whether the patient was actually asymptomatic.

Three of the four cases of intentional overdose involved mixed overdoses and one involved overdose of atomoxetine alone. Three of the four cases also reported suicide attempt/suicide complete. The four cases of intentional overdose have been discussed previously in the review of suicidal behaviour in Annex 4.

Assessor's comments:
The MAH have started to code cases of intentional overdose to the MedDRA preferred term 'Intentional misuse'. This seems completely inappropriate given that the MedDRA lower level term 'Intentional overdose' codes to the MedDRA preferred term 'non-accidental overdose'.

The MAH concluded that there is no new clinically significant information regarding atomoxetine in overdose during the reporting period. However the MAH has updated the company core data sheet (CCDS) regarding seizure in overdose during the period covered by the PSUR. Section 4.9 (Overdose) of the EU SPC should be updated to include seizure in line with the changes to the CCDS.

Experience in Special Patient Groups

Organ Impaired Patients

Hepatic Impairment

There were 10 reports in which the patient had a pre-existing hepatic disorder during the period covered by PSUR 4. Nine of these cases were spontaneously reported. The other remaining case was from a clinical trial. All of the spontaneously reported cases are included in the updated cumulative review of hepatic adverse events (30 month review), which will be reviewed in detail in due course.

The cases involved 2 male children, 1 male adolescent, 5 female adults, 1 male adult and 1 male of unknown age.

The pre-existing hepatic impairment was hepatitis (1 case), hepatitis C (3 cases), unspecified liver disease (1 case) and increased/abnormal liver function tests (5 cases).

Renal Impairment

There were no cases involving patients with underlying renal impairment during the reporting period.

Experience in Paediatric, Adolescent, Adult and Elderly Patients

Table 4 below provides an overview of the number of case of adverse events this period by age group.

Table 4

Age Groups	Age Range	PSUR 04 This reporting period		PSUR 03 Previous Reporting Period	
		Number of Cases	Percentage	Number of Cases	Percentage
Paediatric	1 to 12 years	395	38.7	424	40.8
Adolescent	13 to 17 years	198	19.4	172	16.6
Adult	18 to 64 years	200	19.6	211	20.3
Elderly	65 years and older	5	0.5	3	0.3
Unknown	Unknown	222	21.8	228	22.0
Total		1020	100	1038	100

The most frequently reported reactions and SOCs in these four age groups are provided in table 5 below.

Table 5

Age Groups	Top 5 System Organ Classes	Count (%)	Top 5 Reactions	Count (%)
Paediatric 1-12 years	Psychiatric disorders	226 (25.2)	Vomiting	41 (4.6)
	Gastrointestinal disorders	163 (18.2)	Nausea	34 (3.8)
	Nervous system disorders	114 (12.7)	Aggression	26 (2.9)
	Investigations	110 (12.3)	Somnolence	24 (2.7)
	General disorders and administration site conditions	64 (7.1)	Abdominal Pain	23 (2.6)
			Weight decreased	23 (2.6)

	Total Reactions	**895 (100)**		**895 (100)**
Adolescent 13-17 years	Investigations	102 (23.2)	Nausea	19 (4.3)
	Gastrointestinal disorders	64 (14.6)	Alanine aminotransferase increased	16 (3.6)
	Nervous system disorders	54 (12.3)	Aspartate aminotransferase increased	15 (3.4)
	Psychiatric disorders	53 (12.0)	Blood bilirubin increased	13 (3)
	General disorders and administration site conditions	38 (8.7)	Vomiting	13 (3)
			Weight decreased	13 (3)
	Total Reactions	**439 (100)**		**439 (100)**
Adults 16-64 years	Investigations	76 (17.0)	Alanine aminotransferase increased	18 (4.0)
	Psychiatric disorders	71 (15.9)	Aspartate aminotransferase increased	13 (2.9)
	Nervous system disorders	56 (12.6)	Nausea	13 (2.9)
	General disorders and administration site conditions	45 (10.0)	Ejaculation disorder	11 (2.5)
	Gastrointestinal disorders	42 (9.4)	Fatigue	11 (2.5)
	Total Reactions	**446 (100)**		**446 (100)**
Elderly 65 years and older	Psychiatric disorders	2 (25)	Insomnia	1 (12.5)
	Gastrointestinal disorders	2 (25)	Malignant hypertension	1 (12.5)
	Cardiac disorders	1 (12.5)	Myocardial infarction	1 (12.5)
	Immune system disorders	1 (12.5)	Nausea	1 (12.5)
	Vascular disorder	1 (12.5)	Nervousness	1 (12.5)
	Renal and urinary disorders	1 (12.5)	Season allergy	1 (12.5)
			Stomach discomfort	1 (12.5)
			Urinary retention	1 (12.5)
	Total Reactions	**8 (100)**		**8 (100)**

Atomoxetine is authorised in the EU for the treatment of ADHD in children 6 years and older and adolescents [but presumably this is worldwide data and in US there is an indication for adults?]. During the reporting period, the majority of the cases concerned patients age 6-12 years (380 reports). Fifteen reports concerned children aged 5 years and under and 5 reports concerned patients aged 65 years and over.

The same five SOCs are included in the 'Top five SOCs' for each age group, although they occur in a different order of frequency. In the paediatric group, vomiting, nausea, somnolence, abdominal pain, and weight decreased were the most frequently reported reactions. These are recognised adverse effects of atomoxetine and are listed in section 4.8 of the EU SPC accordingly. Aggression has recently been added to section 4.4 of the SPC.

The top five reported reactions in both the adolescent and adult groups are recognised reactions and are listed accordingly in section 4.8 of the EU SPC for atomoxetine.

There are too few cases in the elderly group to allow an adequate comparison with other age groups.

Studies

Newly Analysed Company Sponsored Safety Studies

During the period covered by this PSUR, one company-sponsored study has been reviewed and completed. This was the Medical Claims based study of seizures in an ADHD population. A summary of the results of this study is provided in Annex 7 (cumulative review of seizure events).

Targeted New Safety Studies Planned, Initiated or Continuing During the Reporting Period

There has been one completed epidemiologic study, five targeted ongoing safety studies and one ongoing epidemiological study during the reporting period. These are summarised in table 6 below.

Table 6

Protocol Title	Description
B4Z-FW-LYDP The Haemodynamic Effects of Inhaled Salbutamol in the Absence and Presence of Atomoxetine	Open-label, fixed sequence crossover study. Primary objective: to assess the heart rate response to a standard inhaled dose of salbutamol in the presence and absence of steady-state atomoxetine dosing. The study is ongoing.
B4Z-JE-LYDA Long-Term Extension, Open-Label Study of Atomoxetine Hydrochloride in Child Outpatients with ADHD	Open-label extension study: Primary Objective: to assess the long-term safety and tolerability of atomoxetine in Japanese patients who complete study B4Z-JE-LYBC. The study is ongoing.
B4Z-MC-LYAI Long-Term, Open-Label, Safety Study of Atomoxetine Hydrochloride in Patients 6 years and Older with ADHD	Primary objective: to assess long-term safety and tolerability of atomoxetine in patients who have participated in a previous atomoxetine study, who have been diagnosed with ADHD, and who are aged 6 years and older (but less than 18 years at the time of entry into their first atomoxetine study). The study is ongoing.
B4Z-MC-LYAR Long-Term, Open-Label Safety Study of Aomoxetine Hydrochloride in Adult Outpatients with DSM-IV ADHD	Primary objective: to assess long-term safety and tolerability in adult outpatients. The study is ongoing.
B4Z-MC-LYBU A Randomized, Double-blind Comparison of Atomoxetine Hydrochloride Augmented with	9 week, double blind, pilot study. Primary objective: to assess the safety of up to 1.4mg/kg/day of atomoxetine and placebo administered once daily, compared with

either Extended-Release Methylphenidate (Concerta™) or Placebo in Children with ADHD Who Have not Responded to Stimulant Mono Therapy.	1.4mg/kg/day of atomoxetine and 1.1mg.kg.day extended release methylphenidate administered once daily in children aged 6-12years with ADHD (stimulant non responders). The study is ongoing.
Atomoxetine and Cardiovascular and Cerebrovascular Outcomes in Adults	Retrospective cohort study using a proprietary insurance-claims database study (1 January 2003 – 31 December 2004). Aim: to study the incidence of selected cardiovascular and cerebrovascular outcomes among adult patients who initiate therapy with atomoxetine. The incidence for each outcome among atomoxetine initiators will be compared to the incidence in a cohort of similar patients who initiate stimulants and an age-and gender-matched general population cohort.

Published Safety Studies

There were 3 publications, all of which presented data from studies conducted by the MAH, during the period of PSUR 4. These were:

- interim analysis of ongoing, open-label study of adults with ADHD
- analysis of changes in symptoms and adverse events after discontinuation of atomoxetine. The MAH state that it was concluded that 'atomoxetine may be discontinued without risk for symptom rebound or discontinuation-emergent adverse effects. Tapering of dose is not necessary when atomoxetine is discontinued'.
- Presentation of clinical pharmacokinetics of atomoxetine. The study concluded that atomoxetine administration does not inhibit or induce the clearance of other drugs metabolised by CYP enzymes. The MAH states that in EMs, selective and potent CYP2D6 inhibitors reduce atomoxetine clearance; however, administration of CYP inhibitors to PMs has no effect on the steady-state plasma concentrations of atomoxetine.

Published Literature

Seven articles were published during the period covered by the PSUR. Four of these contained case reports of adverse reactions associated with the use of atomoxetine and these have been included in the MAHs safety database and presented either in this PSUR or in previous PSURs.

One publication (Henderson) indicated that atomoxetine induced extreme irritability, aggression, mania or hypomania in 33% of 153 children with ADHD. Section 4.4 of the EU SPC for atomoxetine was updated to include aggression, hostility and emotional lability. These events should be added to section 4.8 of the SPC also.

Conclusions of the Review of the PSUR Data (27 November 2004 – 26 May 2005)

- In this PSUR, the MAH have provided cumulative reviews of some key issues such as suicidal behaviour, hepatobiliary disorders, and seizures. The conclusions can be found in their respective assessment reports in Annex 4, Annex 6, and Annex 7 respectively.
- The MAH performed a review of Raynaud's phenomenon associated with atomoxetine. Raynaud's phenomenon should be added to section 4.8 of the SPC.
- Following preliminary assessment of the PSUR data the MAH was requested to submit a cumulative review of all cardiac disorders reported for atomoxetine. This review can be found in Annex 8.

Further review/assessment of the following adverse events is required.

- Serious skin reactions including erythema multiforme and Stevens Johnson syndrome
- blood dyscrasias including neutropenia
- haemorrhage urinary tract
- hypoaesthesia/paraesthesia; speech disorder/dysarthria; movement disorders (dyskinesia, dystonia, extrapyramidal disorder); and tremor.
- Myalgia/arthralgia

The following adverse events which are already listed in section 4.4 of the SPC should be added to section 4.8 of the SPC also:

- Allergic reactions. A review of the more serious reactions of anaphylaxis (1) and anaphylactic shock (2) should be conducted with a view of adding these reactions to the SPC as well as those already listed in 4.4.
- Aggression, hostility, emotional lability

It is also proposed that the SPC is restructured so that it reflects post marketing experience. Currently section 4.8 of the SPC is based on clinical trial data for children and adults, and the safety profile for each age is considerably different. Post-marketing data suggests that events from adult clinical trials have been reported in children (e.g. urinary retention) and vice versa.

ANNEX 4

Psychiatric Adverse Events including Cumulative review of spontaneous reports of suicidal and self-injurious behaviour

1.0 Overview of Reports of Psychiatric Adverse Events associated with Atomoxetine

Up to the 22 September 2005 the MAH has received a total of 6,751 reports involving 10,988 psychiatric reactions. Of these reports 2,383 were from healthcare professionals (hcps).

The reactions where more than 50 reports have been received are provided in the table below. As can be seen from this table the most commonly reported reactions (all reports or hcps reports only) include insomnia, abnormal behaviour, aggression mood swings, irritability and agitation.

Reaction PT	Total No of reports	No of HCP reports	Non HCP reports
Insomnia	1159	250	909
Abnormal behaviour	989	263	726
Aggression	763	314	449
Mood swings	763	188	575
Irritability	599	185	414
Crying	491	105	386
Anxiety	449	164	285
Depression	393	140	253
Agitation	363	177	186
Anger	354	106	248
Nervousness	275	49	226
Middle insomnia	201	18	183
Sleep disorder	169	32	137
Suicidal ideation	143	104	39
Impulsive behaviour	134	27	107
Depressed mod	121	33	88
Mania	115	96	19
Emotional distress	112	27	85
Emotional disorder	111	23	88
Thinking abnormal	108	23	85
Nightmare	106	51	55
Initial insomnia	103	8	95
Restlessness	99	22	77
Confusional state	86	44	42
Apathy	84	23	61
Hallucinations	80	56	24
Personality change	70	18	52
Psychotic disorder	70	55	15
Libido decreased	68	25	43
Fear	67	11	56
Social avoidant behaviour	67	17	50
Excitability	61	10	51
AttentionDeficit/Hyperactivity disorder	57	17	40
Disorientation	55	22	33
Mood altered	55	22	33

Affect lability	54	15	39
Logorrhea	54	9	45
Early morning awakening	50	10	40
Panic attack	50	30	20

The total number of other reactions of interest are 10 reports of completed suicide (all hcps reports), 33 reports of suicide attempt (24 HCP reports), 7 reports of depression suicidal (3 hcp reports), 5 feelings of despair (2 hcp reports), 19 reports of homicidal ideation (9 hcp reports), 21 reports of intentional self-injury (11 hcp reports), 11 reports of self-injurious ideation (5 hcp reports) and 5 reports of self-injurious behaviour (1 hcp report).

The MAH has provided a cumulative review of all reports of suicidal and self-harm and all reports of acute overdose. These are considered in more detail below.

2.0 Cumulative review of spontaneous reports of suicidal and self-injurious behaviour

The MAH has submitted a cumulative review of all spontaneous reports of suicidal and self-injurious behaviour that they have received during the period of 26 November 2002 to 22 September 2005. The MAH's safety database (Clintrace) was searched for all spontaneous (serious and non-serious) reports that had been coded to one of the following MedDRA (version 8) preferred terms:

Accident, Accidental exposure, Accidental overdose, Accidental poisoning, Alcohol poisoning, Completed suicide, Death, Depression suicidal, Drug level above therapeutic, Drug level increased, Drug toxicity, Excoriation, Gas poisoning, Head banging, Injury, Injury asphyxiation, Intentional misuse, Intentional self-injury, Laceration, Morbid thoughts, Multiple drug overdose, Multiple drug overdose accidental, Overdose, Poisoning, Poisoning deliberate, Self injurious behaviour, Self mutilation, Self-injurious ideation, Sudden death, Suicidal ideation., Suicide attempt and Therapeutic agent toxicity.

This search identified 475 reports all of which underwent medical review. A total of 174 reports were excluded for one of the following reasons:

i) patient not prescribed atomoxetine or not routinely taking atomoxetine prior to the event;
ii) suicidal/self-injurious events occurred > 1 month after atomoxetine was discontinued;
iii) relevant events were considered accidental, non-suicidal, or non-intentional overdoses.
iv) overdose was due to a prescribing error, pharmacy error, or administering error from a caregiver were likewise excluded.

The remaining 301 reports were assigned according to the approach described by the Columbia group and adopted by the FDA to one of the following categories.

Code 1 -Completed suicide
Code 2 -Suicide attempt
Code 3 -Preparatory acts toward imminent suicidal behaviour

Code 4 -Suicidal ideation
Code 5 -Self-injurious behaviour, intent unknown
Code 6 -Not enough information, fatal
Code 7 -Self-injurious behaviour, no suicidal intent
Code 8 -Other: accident; psychiatric; medical
Code 9 -Not enough information, nonfatal

An additional category – Code 10 self-injurious ideation- was created by the MAH which includes the cases where no self-injurious behaviour occurred, but the patients were having thoughts of harming themselves.

Information on the categories to which these reports were assigned and the seriousness of these reports is provided in table 1.

Table 1 Diagnostic Categorization and Seriousness of Case Reports

Code	Diagnostic Category	Fatal	Serious	Non-Serious	Total
1	Completed suicide	13	0	0	13
2	Suicide attempt	0	32	8	40
3	Preparatory acts toward imminent suicidal behaviour	0	3	2	5
4	Suicidal ideation	0	30	113	143
5	Self-injurious behaviour, intent unknown	0	13	21	34
6	Not enough information, fatal	4	0	0	4
7	Self-injurious behaviour, no suicidal intent	0	4	6	10
8	Other: accidental; psychiatric; medical	0	1	6	7
9	Not enough information, nonfatal	0	0	40	40
10	Self-injurious ideation	0	1	4	5
Total Case Reports		**17**	**84**	**200**	**301**

Patient age distribution in these cases ranged from 5 to 69 years. Of the 240 cases where age was known, the average patient age was 17.8 years, and the median age was 14 years. All the reports categorised as completed suicide occurred in adolescents aged 13-17 years (n=4) or adults (n=9). The same is true for the majority of reports (78%; 31 out of 40 reports) categorised as suicide attempts. The majority of reports of suicidal ideation (69%; 99 out of 143 reports) and self-injurious behaviour (79%; 27 out of 34 reports) occurred in children aged 12 years or below and adolescents. Information on the number of reports for each category broken down by age group can be found in Appendix A.

Of the 301 reports, a total of 191 were in males (63%), 93 in females (31%) and in 17 reports the gender was unspecified (6%). The ratio of male to female was higher in

paediatric and adolescent patients with a ratio of three to one, compared with adult patients at a ratio of almost one to one.

Where the information was provided, the atomoxetine daily therapeutic doses ranged from 10 mg to 180 mg daily, with an average dose of 51.3 mg daily, and the median dose of 40 mg daily. The time to onset of the events ranged from 1 day to more than 1 year. The time to onset in 45 cases was reported within 2 weeks after the start of atomoxetine treatment, 56 cases within 2 months, and in 50 cases from more than 2 months to more than 1 year. There were 8 cases where the events occurred after the first dose of atomoxetine.

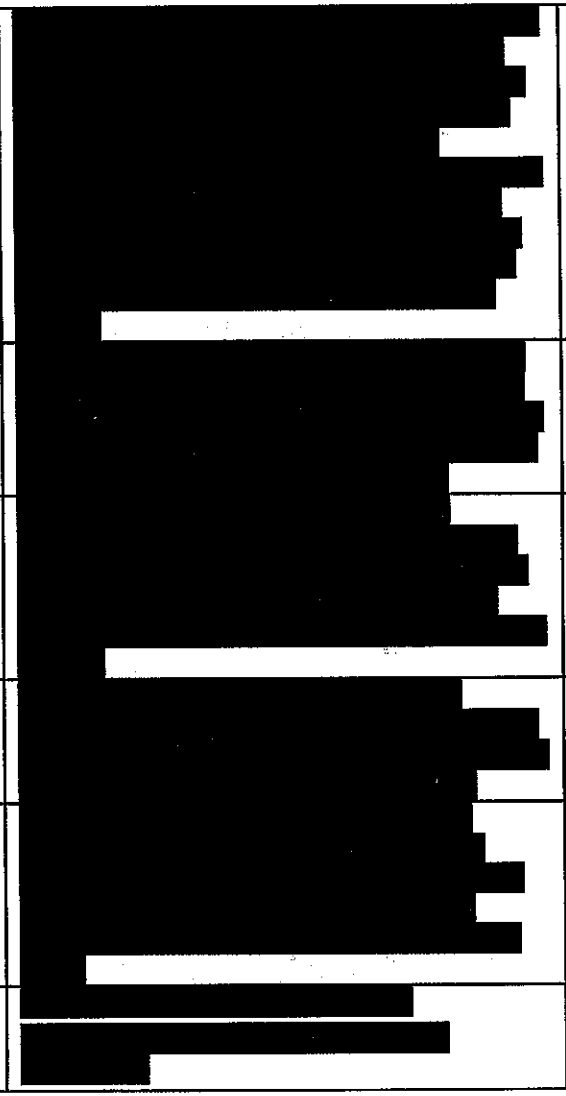
In 13 of the reports there was a fatal outcome – these reports will be considered in more detail in the discussion of the completed suicide category. In the remaining reports (n=237), in approximately one half of the cases the patients has recovered at the time of reporting.

Completed suicide (Code 1)
A total of 13 reports were placed in this category. All are hcp reports and a summary for the information for each case is provided in the table below. In three of these cases ([redacted]) it is questionable whether these were suicides.

As previously described all these cases occurred in either adolescents (n=4) or adults (n=9). In 10 of the 13 cases there was a pre-existing or history of a psychiatric disorder, such as depression (in 7 cases), prior suicidal ideation or attempts (6 cases) or other psychiatric disorders (5 cases). In two further reports information on medical history was not provided. This leaves one report which specified that the patient did not have a prior history of depression. The case narratives for these reports can be found at Appendix B.

Table 2 Code 1 – Completed Suicide (N=13)

Case ID	Age/ Sex	Daily dose	Time-to-onset	Brief descriptor of event	Risk or Confounding Factors	Cause of Death
[redacted]	[redacted]	40 mg	1 week	[redacted]	History of depression, suicide ideation, schizotypal personality disorders. Concomitant olanzapine, escitalopram and diazepam	[redacted]
[redacted]	[redacted]	80 mg	>4 months	[redacted]	History of suicide attempts, overdose of zoldipem 6 months prior to death. Had a disagreement with [redacted] parents prior to [redacted] death. Taking paroxetine, zoldipem, lamotrigine and quetiapine.	[redacted]
[redacted]	[redacted]	120 mg	~ 1 month	[redacted]	History of depression. Taking escitalopram.	[redacted]
[redacted]	[redacted]	60 mg	~ 1month	[redacted]	Unknown history. Four-year methylphenidate treatment stopped when atomoxetine started.	[redacted]
[redacted]	[redacted]	60 mg	Unknown	[redacted]	History of bipolar disorder, psychosis, previous suicide attempts, and possible schizophrenia. Multiple psychiatric concomitant medications.	[redacted]
[redacted]	[redacted]	60 mg	Unknown	[redacted]	Previous suicide attempts	[redacted]
[redacted]	[redacted]	20 or 40 mg	Unknown	[redacted]	History of depression. Taking escitalopram.	[redacted]

		10 mg for 5 days.	2-3 days after Atx stopped		History of depression. Taking paroxetine.	
		Unknown	1 week		History of suicide attempt 6 to 7 years ago and long standing depression.	
		60 mg	Unknown		Unknown medical history.	
		80 mg	1 month		No history of depression. Having —very bad" scoliosis. Taking amphetamine/ dextroamphetamine.	
		40 mg	7 months		History of schizoaffective and bipolar disorder. Taking olanzapine, celecoxib, fluoxetine and sertraline	
			Unknown		History of depression and anxiety. Taking escitalopram and methylphenidate.	

Suicide attempt (Code 2)

A total of 40 reports were placed in this category. These cases involved 9 children (8 male and 1 unknown gender), 15 adolescents (8 male, 6 female and 1 unknown gender), and 16 adults (7 male, 9 female).

An overview of the information relating to the 24 reports involving children and adolescents is provided in table 2 below. In these reports potential risk or confounding factors were reported in 14 cases, such as pre-existing depression (in 6 cases), prior suicidal ideation or attempts (2 cases), other psychiatric disorders (sensory intergration disorder and "acting out"), or concurrent psychosocial stressors (3 cases). In other 6 case reports, the patients' medical history was not provided. There were 4 cases ( ) where there was no pre-existing psychiatric disorders present. Case narratives for the 9 case reports concerning children under 12 years of age are provided at Appendix C.

Of the 16 case reports involving adult patients, potential risk or confounding factors were reported in 14 cases, including pre-existing depression (7 cases), suicide attempts (4 cases), concurrent psychosocial stressors (2 cases), and/or other psychiatric disorder or conditions. There were two cases medical history and information on concomitant medication was not provided.

Table 3. Suicide Attempts in Children and Adolescents

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
		18 mg twice, 38 days		
		60 mg, 5 œ 6 months	Unknown medical history. No concomitant medications.	
		60 mg, 5 months	ADHD. Unknown if taking any concomitant medications.	
		40 mg, Unknown	Unknown medical history. No concomitant medications.	
		Unknown	Got into a fight prior to overdose. Unknown if having a history of suicide or depression. No concomitant medications.	

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
[redacted]	[redacted]	80 mg, ~2 months	History of major depression with concomitant bupropion, risperidone and alprazolam.	[redacted]
[redacted]	[redacted]	18 mg, 1 day	History of attempt to start fire once, hearing voices. Conner's rating showed a markedly elevated ADHD index, global restlessness, impulsive, cognitive problems/inattentive and social problems. Concomitant clonidine.	[redacted]
[redacted]	[redacted]	60 mg, Unknown	History of depression, emotional and behavioral problems, being institutionalized in the past. Taking citalopram and clonidine.	[redacted]
[redacted]	[redacted]	60 mg, <2 months	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	40 mg, 6 days	History of depression and ADHD. No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	Unknown medical history. Concomitantly taking methylphenidate.	[redacted]
[redacted]	[redacted]	Unknown	Prior to [redacted] overdose, [redacted]. Concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	18 mg, 1 dose	Unknown medical history. No concomitant medications.	[redacted]
[redacted]	[redacted]	40 mg, >5 weeks	History of sensory integration disorder, being emotional sensitive to medications. Taking methylphenidate.	[redacted]
[redacted]	[redacted]	Unknown	Prior suicide attempt (not by overdose). No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	No prior history of suicidal ideation or attempts. No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown, ~1 month	History of depression, psychosis and ADHD with numerous medication treatments. Having been medication free for several months prior to atomoxetine initiation.	[redacted]

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Suicide Attempt
[redacted]	[redacted]	Unknown	History of depression. No prior history of suicide attempts. No ADHD. Atomoxetine was prescribed to [redacted] for an unknown indication. Taking hydrocodone/acetaminophen.	[redacted]
[redacted]	[redacted]	Unknown, 7 months	Negative for depression and prior suicide attempts. No concomitant medications.	[redacted]
[redacted]	[redacted]	18 mg, 5 months	History of —acting out" and being in counseling before. Unknown if taking concomitant medication	[redacted]
[redacted]	[redacted]	60 mg, Unknown	History of depression. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	25 mg, ~ 1month	No family history of mental illness, no social stressors. No concomitant medications.	[redacted]
[redacted]	[redacted]	60 mg, <1 month	Exposed to trauma relating [redacted] as [redacted]. Having an argument with [redacted] teacher, learning difficulties, and questioning of [redacted] graduation.	[redacted]

Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)
A total of 5 reports were placed in this category. These case reports involved 2 female children, 2 male adolescents and 1 male adult. Of these 5 patients, 4 had a medical history of psychiatric disorder and/or conditions (2 with depression) other than ADHD. In a further reports there was a family history of psychiatric disorder.

The acts towards suicide behaviour in these cases are as follows:

[redacted]

Suicidal Ideation (Code 4)
A total of 143 reports were placed in this category. The majority of reports of suicidal ideation (69%; 99 out of 143 reports) occurred in children aged 12 years or below and adolescents. Of these case reports with suicidal ideation, potential risk or confounding factors were reported in 29 cases (38%), including pre-existing depression suicide attempt/ideation concurrent psychosocial stressors and/or other psychiatric disorder or conditions.

Self-Injurious Behaviour, Intent Unknown (Code 5)
A total of 34 reports were included in this category. These cases involved 14 children (11 male and 3 female), 13 adolescents (6 male and 7 female), 4 adults (3 male and 1 female), and 3 unknown age patients (2 male and 1 female). A brief overview of these cases can be found in the table at Appendix D.

Of these 34 patients, 15 had a medical history of psychiatric disorder (including 5 depression and 3 suicide attempt) other than ADHD, 3 were concurrently taking psychiatric medications. In 12 cases the medical history was not provided. There were 4 reports in which there is no relevant history or it is clear that there is no history of previous events.

Not Enough Information, Fatal (Code 6)
There were 4 case reports with a fatal outcome placed in this category. Two cases involved [redacted] patients (1 aged [redacted], 1 age unknown) who died after receiving atomoxetine therapy (1 after one week of treatment) - cause of death not specified and medical history not provided in these cases.

A further case concerns a [redacted] with a history of anxiety, depression, seizure disorder, heroin and cocaine abuse and numerous drug overdoses. [redacted] received atomoxetine for about 2 months during which [redacted] complained of constant headaches, shortness of breath, and dizziness, and became swollen and heavy looking. [redacted] subsequently took an overdose of cocaine for which [redacted] was treated with naloxone and was in the intensive care unit for four days. About a month later, a day prior to [redacted] death, the patient reportedly contacted the prescribing psychiatrist to report feeling bad with constant headaches and dizziness. [redacted] died the next day it is thought that the death was a cardiac event related to an overdose of heroin.

The final case involves a [redacted] patient with a medical history including cardiovascular disease, hypertension, IDDM, kidney problems, mood problems, CHF, venous stasis, back pain, irritable bowel syndrome, sleep apnoea and drinking of alcohol. The patient began taking atomoxetine for ADHD at 40 mg daily and dose was increased due to not having the desired effect the patient wanted from the medication. About 4 months on atomoxetine, the patient died in [redacted] sleep. It was reported that the patient had begun drinking (alcohol) again prior to [redacted] death. Cause of death, as listed on the autopsy report, was complications of alcoholism, cardiomegaly, degeneration of mitral valve, morbid obesity, IDDM and venous stasis. The reporting psychiatrist stated that the atomoxetine did not contribute to the patient's death.

Self-Injurious Behaviour, No Suicidal Intent (Code 7)
A total of 10 reports were included in this category. These cases involved 3 children ([redacted]), 4 adolescents ([redacted], 2 adults ([redacted]) and 1 [redacted]atient of unknown age. Of these case reports, potential risk or confounding factors were reported in 8 cases, including pre-existing depression (2 cases), other psychiatric disorders or conditions. More details of these cases can be found in Appendix E.

Other: Accidental, Psychiatric, Medical (Code 8)
A total of 7 reports were placed in this category – 6 reports of accidental injury and a further report of self-inflicted injury due to [redacted] psychiatric conditions. In this later case a [redacted] who had taken atomoxetine for 2 years and concomitantly smoked hashish for 3 years, experienced persecutory delusion and aggression. [redacted] was hospitalized in a coma, with cerebral haematoma, and liver and kidney injury. Both atomoxetine and cannabis were discontinued. At the time of reporting, the patient was recovering, but remained hospitalized.

Not Enough Information, nonfatal (Code 9)
There were 40 case reports placed in this category, of which 38 case reports were overdose cases from a literature publication (Spiller et al. 2005). This was case series concerning atomoxetine ingestion in children (aged ≤17 years) that had been conducted at 3 regional poison control centres in the US. In this publication, the authors specified that suicide attempt was the reason for exposure to atomoxetine in 4 of these cases, but did not provide background information on any individual case. The remaining 2 cases also involved overdose of atomoxetine, where the patients took 1 or 2 extra doses of atomoxetine, but their intent was unspecified.

3.0 Updated Review of Suicidal or Self-Injurious Behaviour associated with Atomoxetine (23 September 2005 – 25 October 2005)

This review covering the period 23 September 2005 – 25 October 2005 assesses the newly reported cases since the cut off date for the data discussed in the sections above (22 September 2005).

Using the same search methods as used in the review covering the period 26 November 2002 – 22 September 2005, a total of 135 case reports of 153 adverse events of possible suicide or self-injurious behaviour were identified in the atomoxetine safety database for the period 23 September 2005 – 25 October 2005. A total of 104 of the reports were reported by healthcare professionals, with 31 being reported by non-healthcare professionals.

Five case reports were excluded from the MAHs analysis. These were two reports of 'accidental overdose'; one report of 'overdose' in which a [redacted] took and extra 13 capsules of atomoxetine after [redacted] first dose when [redacted] was unsupervised; one report of 'overdose' in which an adult patient adjusted the dose (100mg-120mg) in order to reach the desired drug effect; and one report of 'suicide attempt' in an adult [redacted] who was not prescribed atomoxetine but attempted suicide by taking [redacted] child's atomoxetine with acetaminophen.

The remaining 130 reports were reviewed and diagnosed into one of the same 10 diagnostic categories used in the previous review. Table 4 below provides further details of the diagnostic cateogorisation of the reported cases.

Table 4. Diagnostic Categorization and Seriousness of Case Reports (23 September 2005 – 25 October 2005)

Code	Diagnostic Category	Fatal	Serious	Non-Serious	Total
1	Completed suicide	7	0	0	7
2	Suicide attempt	0	23	0	23
3	Preparatory acts toward imminent suicidal behaviour	0	2	0	2
4	Suicidal ideation	0	27	61	88
5	Self-injurious behaviour, intent unknown	0	1	0	1
6	Not enough information, fatal	0	0	0	0
7	Self-injurious behaviour, no suicidal intent	0	2	2	4
8	Other: accidental; psychiatric; medical	0	0	0	0
9	Not enough information, nonfatal	0	0	0	0
10	Self-injurious ideation	0	0	5	5
Total Case Reports		**7**	**55**	**68**	**130**

Patient age distribution in these cases ranged from 5 to 66 years. Of the 120 cases where age was known, the average patient age was 14.6 years, and the median age was 13 years. The seven reports categorised as completed suicide occurred in children aged ≤12 years (n=1), adolescents aged 13-17 years (n=3) or adults aged 18-64 years (n=2). There was one report of completed suicide in which the age of the patient is unkown. The reports categorised as suicide attempts (n=23) were predominantly reported in adolescents aged 13-17 years (n=16), however there were reports of suicide attempts in children ≤12 years (n=3) and in adults aged 18-64 years (n=4).

The majority of reports of suicidal ideation (84%; 74 out of 88 reports), self-injurious ideation (80%; 4 out of 5 reports); and self-injurious behaviour (no intent) (100%; 4 out of 4 reports) occurred in children aged 12 years or below and adolescents aged 13-17 years). Information on the number of reports for each category broken down by age group can be found in Appendix A.

Of the 130 reports, a total of 96 were in males (74%), 30 in females (23%) and in 4 reports the gender was unspecified (3%). The ratio of male to female was higher in paediatric and adolescent patients with a ratio of four to one, compared with adult patients at a ratio of two to one.

Where the information was provided (94 out of 130 cases), the atomoxetine daily therapeutic doses ranged from 10 mg to 100 mg daily, with an average dose of 46.3 mg daily, and a median dose of 40 mg daily. In another 3 cases the daily dose of atomoxetine was 0.5, 1.5 or 2.0 mg per kg body weight.

The time to onset of the events was provided in 79 out of the 130 case reports and ranged from 1 day to more than 2 years. The time to onset was reported as within 2

weeks in 12 cases (15%), between 2 weeks and 2 months in 28 cases (36%), and between 2 months and 2 years in 39 cases (49%).

In 7 of the reports there was a fatal outcome – these reports will be considered in more detail in the discussion of the completed suicide category. In the remaining reports (n=123), 42% of cases were recovering or had fully recovered. The events resolved in 42 out of 78 of the cases in which atomoxetine was discontinued. Atomoxetine was continued in 18 cases, 9 of which reported resolution of the event.

Completed suicide (Code 1)

A total of 7 reports were placed in this category and a summary for the information for each case is provided in the table below. Narratives for the seven cases are presented in Appendix B.

As previously described these cases occurred in children (n=1), adolescents (n=3) and adults (n=2). The age of the patient was unknown in the remaining case. In 5 of the 7 cases there was a pre-existing or history of a psychiatric disorder (in 2 cases), and/or concomitant psychiatric medications (4 cases). In two further reports information on medical history or current psychosocial environment was not provided.

Table 5. Code 1 – Completed Suicide (N=7)

Case ID	Age/ Sex	Daily dose	Time-to-onset	Brief descriptor of event	Risk or Confounding Factors	Cause of Death
[redacted]	[redacted]	Unk	Unk	[redacted]	Unknownmedical history. Possibly taking venlafaxine and ziprasidone concomitantly.	[redacted]
[redacted]	[redacted]	Unk	Unk		Unknown medical history. Possibly taking sertraline, amphetamine/dextroamphetamine.	[redacted]
[redacted]	[redacted]	40mg	30 weeks		History of musclar dystrophy (undetermined type), bipolar disorder, sleep apnoea, Pierre Robin sequence, Stickler syndrome, restless leg, attention disorder, and sleep disorder. Concomitant lithium, oxcarbazepine, ranitidine and alprazolam.	[redacted]
[redacted]	[redacted]	40mg	2 years		Unknown medical history. No concomitant medications.	[redacted]
[redacted]	[redacted]	60mg	<90 days		History of oppositional defiance disorder (ODD) and possible bipolar I disorder. Unknown if taking concomitant medication.	[redacted]
[redacted]	[redacted]	Unk	Unk		Unkown medical history. Taking sertraline, valproate and escitalopram.	[redacted]
[redacted]	[redacted]	Unk	8 weeks		Unknown medical history. Unknown if taking concomitant medications.	[redacted]

Suicide attempt (Code 2)

A total of 23 reports were placed in this category. These cases involved 3 male children, 16 adolescents (8 male, 8 female), and 4 adults (3 male, 1 female).

An overview of the information relating to the 23 reports is provided in table 6 below. In these reports potential risk or confounding factors were reported in 17 cases, such as pre-existing depression or anti-depressant treatment (in 6 cases), prior suicidal ideation or attempt (4 cases), and other psychiatric disorders or concurrent psychosocial stressors (7 cases). In the remaining 6 case reports, the patients'medical history was not provided.

Table 6. Suicide Attempts in Children and Adolescents

Case ID	Age/ Sex	ATX Daily dose/ Time to onset	Potential Confounding Factors	Actions of Suicide Attempt
[redacted]	[redacted]	Unknown	[redacted]	[redacted]
[redacted]	[redacted]	60 mg, 6 weeks	History of threatening suicide prior to atmoxetine. Family history of psychotherapy ([redacted]). No concomitant medications.	
[redacted]	[redacted]	40 mg, 4 months	History of social behaviour and emotional disorders, and learning disability.	
[redacted]	[redacted]	50mg, 12 days	Being treated for ADHD with methylphenidate with a non-satisfactory effect. Concomitantly taking methylphenidate. [redacted]	
[redacted]	[redacted]	40 mg, 2 months	History of previous impulsive overdoses and past substance misuse. The event occurred after an argument.	[redacted]
[redacted]	[redacted]	60 mg, 16 months	History of possible bipolar or pervasive developmental disorder and being in therapy twice a month for 3 years. Unknown if taking concomitant medications.	
[redacted]	[redacted]	60 mg, Unknown	Unknown medical history and concomitant medications	[redacted]
[redacted]	[redacted]	80 mg, 2 weeks	History of ADHD and bipolar disorder. No diagnosis of depression previously. No concomitant medications. Prior to the event, had an argument with [redacted].	
[redacted]	[redacted]	80 mg, 11 days	History of mild depression (prior treated with escitalopram), and self-injury ([redacted]) when taking Adderall. Concomitantly taking amphetamine/	[redacted]

			dextroamphetamine.	
[redacted]	[redacted]	Unknown	History of taking Adderral and unspecified tricyclic antidepressants (but unknown if taking at the time of the events).	[redacted]
[redacted]	[redacted]	80 mg, 28 months	Unknown medical history. No concomitant medications. Had a positive tuberculosis skin test result.	
[redacted]	[redacted]	25 mg, 2 days	History of spastic cerebral palsy and spastic dyslogia. Taking baclofen.	[redacted]
[redacted]	[redacted]	10 mg, 3 months	History of depression and suicidal ideation, being hospitalised for suicidal ideation 3 months prior to atomoxetine initiation. Concomitantly taking fluoxetine.	
[redacted]	[redacted]	60 mg, 1 month	History of depression, but no suicide attempt. Family history of mental illness. Concomitant methylphenidate was discontinued 5 days prior to the events.	[redacted]
[redacted]	[redacted]	60 mg, 50 days	History of depression or other (unspecified) mental disorder. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	40 mg, Unknown	Unknown medical history and concomitant medications.	
[redacted]	[redacted]	60 mg, 2 months	History of irritability and "focus issue".	
[redacted]	[redacted]	Unknown	Unknown medical history. Taking quetiapine. Taking atomoxetine due to the pharmacy dispense error.	
[redacted]	[redacted]	100 mg, 5 months	History of depression, social anxiety, bipolar disorder and lack of impulse control. Prior suicide attempts 3 times. Taking venlafaxine, valproate, esomeprazole, fexofenadine and amphetamine/dextroamphetamine.	[redacted]
[redacted]	[redacted]	43 mg, Unknown	Unknown medical history. No concomitant medications. Had a fight with [redacted] prior to the event.	[redacted]
[redacted]	[redacted]	50 mg, Since started 2 years ago	History of being postmenopausal, cancer, and a head injury. Taking estradiol, progesterone, montelukast and midodrine.	

[redacted]	[redacted]	100 mg, 1 year	[redacted]	[redacted]
[redacted]	[redacted]	40 or 60 mg, 1 year	Unknown medical history and concomitant medications.	

Preparatory Acts Toward Imminent Suicidal Behavior (Code 3)
A total of 2 reports were placed in this category (Table 7). These reports involved a [redacted] and a [redacted]. Both patients had pre-existing psychiatric disorders and concurrent social stresses.

Table 7. Code 3 – Preparatory Acts Toward Imminent Suicidal Behaviour (N=2)
Delete complete table

Suicidal Ideation (Code 4)
A total of 88 reports were placed in this category. The majority of reports of suicidal ideation (84%; 74 out of 88 reports) occurred in children aged 12 years or below and adolescents aged 13-17 years. Of these 88 reports of suicidal ideation, potential risk or confounding factors were reported in 34 cases (39%), including pre-existing depression (8 cases), suicide attempt/ideation (4 cases), concurrent psychosocial stressors (7 cases) and/or other psychiatric disorder or conditions. Details of the patient's medical history were not provided in 39 cases.

Self-Injurious Behaviour, Intent Unknown (Code 5)
There was 1 report included in this category. This case involved a male patient of unknown age who took atomoxetine 60 mg daily for an unknown length of time. The patient experienced self-mutiltation after starting atomoxetine (intent unspecified). His medical history was unknown and it was unknown if he was receiving concomitant medication.

Not Enough Information, Fatal (Code 6)
None.

Self-Injurious Behaviour, No Suicidal Intent (Code 7)
A total of 4 reports were included in this category. These cases involved 2 children (2 male), and 2 adolescents (1 male, 1 female). Of these case reports, potential risk or confounding factors were reported in 2 cases. Details regarding medical history were not provided in the remaining 2 cases. More details of these cases can be found in Appendix E. There are an additional 4 case reports in Code 4 in which the patients had non-suicidal self-injurious behaviour with suicidal ideation. Further details of these four additional reports are provided in Table 8 below.

Table 8. Suicidal Ideation with non-suicidal Self-Injurious Behaviour.
Delete complete table

Other: Accidental, Psychiatric, Medical (Code 8)
None

Not Enough Information, nonfatal (Code 9)
None.

Self-Injurious Ideation (Code 10)
A total of 5 case reports were placed in this cateogy. These five cases involved 4 children (3 males, 1 unknown gender) and one male patient of unknown age. One of the cases reported anxiety, tic and obsessive compulsive disorder as medical history. Medical history was unknown in the remaining 4 cases.

4.0 Overall Discussion
Up to 25 October 2005, a total of 431 reports of suicidal and behaviour have been received (301 cases during the period 26 November 2002 – 22 September 2005, 130 cases during the period 23 September 2005 – 25 October 2005).

These reports include 20 classified as completed suicide, 63 classified as suicide attempt, 231 classified as suicidal ideation, 35 classified as self-injurious behaviour and 10 classified as self-injurious ideation.

In the cases where patient age was provided (369/431; 86%), the patient age distribution ranged from 5 to 69 years and the majority of the suspected ADRs were in males (67%). In the cases where age is known, the majority of the completed suicides (95%) and the majority of suicide attempts (81%) occurred in adolescents or adults. There was one completed suicide in a [redacted] with a history of ADHD, oppositional defiance disorder (ODD) and possible bipolar I disorder. Further details regarding the case (including the manner of suicide) are not available. The majority of reports of suicidal ideation (81%) and self-injurious behaviour (87%) occurred in children aged 12 years or below and adolescents.

The time to onset of the events ranged from 1 day to more than 2 years. In the reports where information on the time to onset is provided, just under two thirds (61%) of the events occurred within 2 months of starting treatment. There was no apparent trend in the dose.

Where information is provided, there are confounding factors such as previous history, underlying illness or concomitant medication in the majority of reports of completed

suicide (15 out of 15 cases), suicide attempt (45 out of 49 cases) and suicidal ideation (63 out of 92 cases). Based on these data, however, one cannot exclude the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases.

If the cumulative number of reports (26 November 2002 – 25 October 2005) of suicidal and self-injurious behaviour are considered in the context of exposure to date (3.5 million patients) then such reports have been reported rarely (<0.1%). The overall reporting rate has changed from "very rare" (<0.01%) for the first set of data covering the period 26 November 2002 – 22 September 2005) to "rare" (≥0.01% - <0.1%) for the total period covered by the two reviews (26 November 2002 – 25 October 2005). The increase in reporting rate observed during the period 23 September 2005 – 25 October 2005 is not unexpected following the healthcare communications/public advisories and press coverage concerning this issue during that time. The reporting rates should be interpreted with caution given that they are based upon spontaneous reporting data and thus are subject to the same biases/limitations including under reporting and publicity surrounding the drug.

Overall the MAH consider that these data do not suggest an association between treatment with atomoxetine and suicide-related or self-injurious behaviours. The arguments to support this the confounding by underlying illness and concomitant medication and the parallels between these spontaneous reports and what is seen in the general population in relation to the pattern and prevalence of suicidal behaviour. However, as stated above, the possibility that atomoxetine may have exacerbated the individual's underlying condition in these cases can not be excluded.

With regards to reports of other psychiatric adverse events associated with atomoxetine, the table provided in Section 1.0 of this reports provides an overview. The MAH is cuurently performing a cumulative review of all psychiatric adverse events reported for atomoxetine and this is due in the first quarter of 2006.

Conclusion

A total of 431 spontaneous reports of suicidal and self-injurious behaviour associated with atomoxetine were reported during the period 26 November 2002 – 25 October 2005. There were 20 reports of completed suicide, the majority of which were in adolescents and adults although there was one report in a [redacted]. There was no apparent trend in dose and time to onset varied from 1 day to more than 2 years although almost two thirds of the events occurred within 2 months of starting atomoxetine.

Whilst a significant number of reports had confounding factors such as previous history, underlying illness or concomitant medication, the possibility that atomoxetine may have exacerbated the individuals underlying condition in these cases cannot be excluded.

The overall reporting rate has changed from "very rare" (<0.01%) to "rare" (≥0.01% - <0.1%). The increase in reporting rate observed during the period 23 September 2005 –

25 October 2005 is not unexpected following the healthcare communications/public advisories and press coverage concerning this issue during that time.

The MAH cumulative review of reports of psychiatric adverse events associated with atomoxetine is awaited in Q1 2006.

[redacted]

14 November 2005

Appendix A

Patient Demographics of reports with Suicidal or Self Injurious Behaviours (26 November 2002 - 22 September 2005)

Code	Diagnostic Categorization	Age Groups (years)					Total
		≤12	13-17	18-64	≥65	Unk	
1	Completed suicide	0	4	9	0	0	13
2	Suicide attempt	9	15	16	0	0	40
3	Preparatory acts toward imminent suicidal behavior	2	2	1	0	0	5
4	Suicidal ideation	64	35	32	1	11	143
5	Self-injurious behaviour, intent unknown	14	13	4	0	3	34
6	Not enough information, fatal	0	0	3	0	1	4
7	Self-injurious behaviour, no suicidal intent	3	4	2	0	1	10
8	Other: accidental; psychiatric; medical	3	2	2	0	0	7
9	Not enough information, nonfatal	1	2	1	0	36	40
10	Self-injurious ideation	3	1	0	0	1	5
Total of Case Reports		**99**	**78**	**70**	**1**	**53**	**301**
Age Grouping Percentage of Reports		**32.9%**	**25.9%**	**23.3%**	**0.3%**	**17.6%**	**100%**
Atomoxetine Patient Exposure (cumulative)		**44.3%**	**22.3%**	**32.7%**	**0.6%**	**0.1%**	**100%**

Patient Demographics of reports with Suicidal or Self Injurious Behaviours (23 September 2004 - 25 October 2005)

Code	Diagnostic Categorization	Age Groups (years)					Total
		≤12	13-17	18-64	≥65	Unk	
1	Completed suicide	1	3	2	0	1	7
2	Suicide attempt	3	16	4	0	0	23
3	Preparatory acts toward imminent suicidal behavior	0	1	1	0	0	2
4	Suicidal ideation	49	25	7	1	6	88
5	Self-injurious behaviour, intent unknown	0	0	0	0	1	1
6	Not enough information, fatal	0	0	0	0	0	0
7	Self-injurious behaviour, no suicidal intent	2	2	0	0	0	4
8	Other: accidental; psychiatric; medical	0	0	0	0	0	0
9	Not enough information, nonfatal	0	0	0	0	0	0
10	Self-injurious ideation	4	0	0	0	1	5
Total of Case Reports		**59**	**47**	**14**	**1**	**9**	**130**
Age Grouping Percentage of Reports		**45%**	**36%**	**11%**	**1%**	**7%**	**100%**

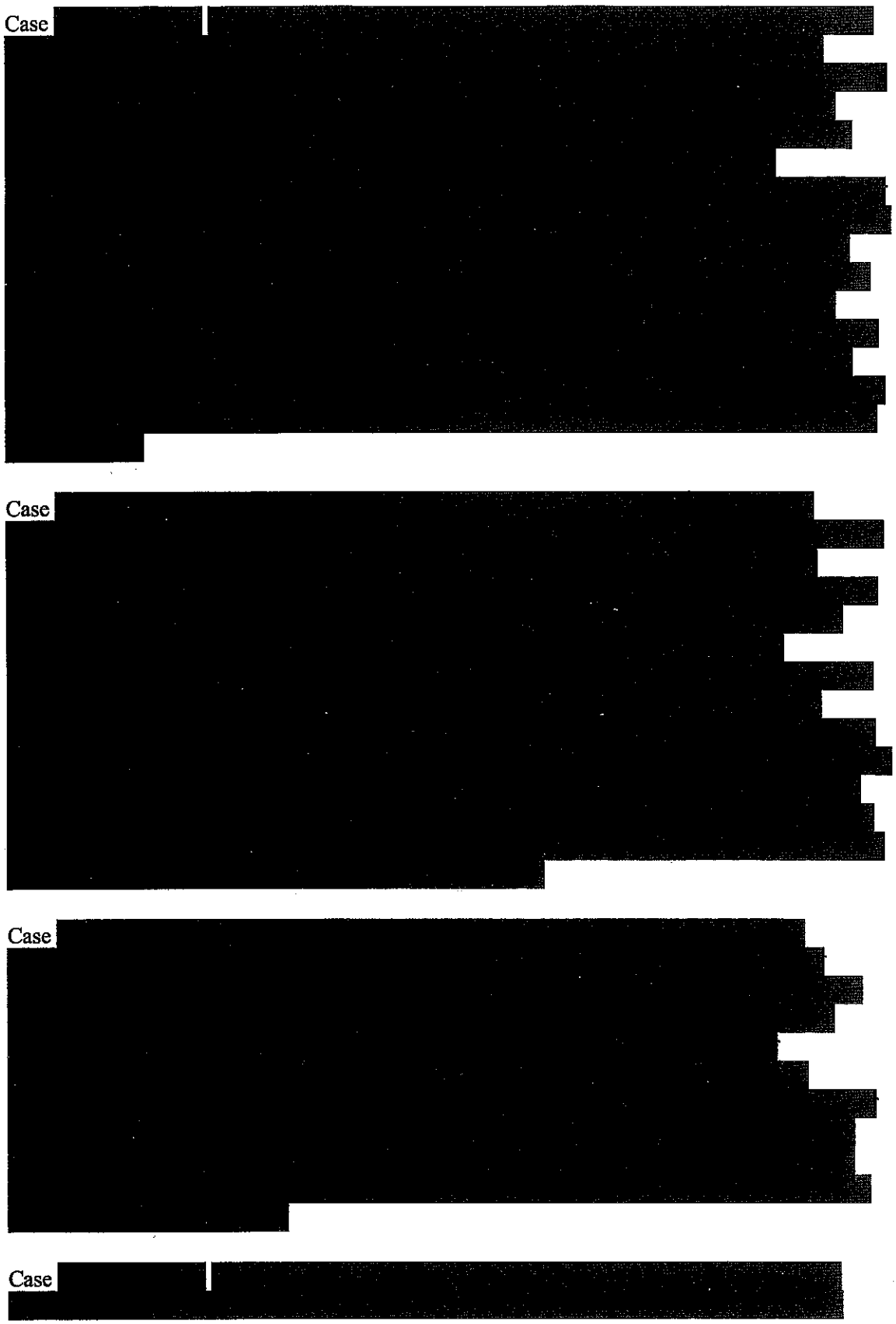
Appendix B

Case narratives for all reports categorised as completed suicide (26 November 2002 – 22 September 2005)

Case [redacted]

Case [redacted]

Case [redacted]


Case
Case
Case
Case

[redacted]

Case [redacted]

Case [redacted]

Case [redacted]

[redacted]

Case [redacted]

Case [redacted]

Case [redacted]

Case narratives for all reports categorised as completed suicide (23 September 2005 – 25 October 2005)

Case [redacted]

[redacted]

Case [redacted]

Case [redacted]

Case [redacted]

Case [redacted]

Case [redacted]

[redacted]

Case [redacted]

Appendix C

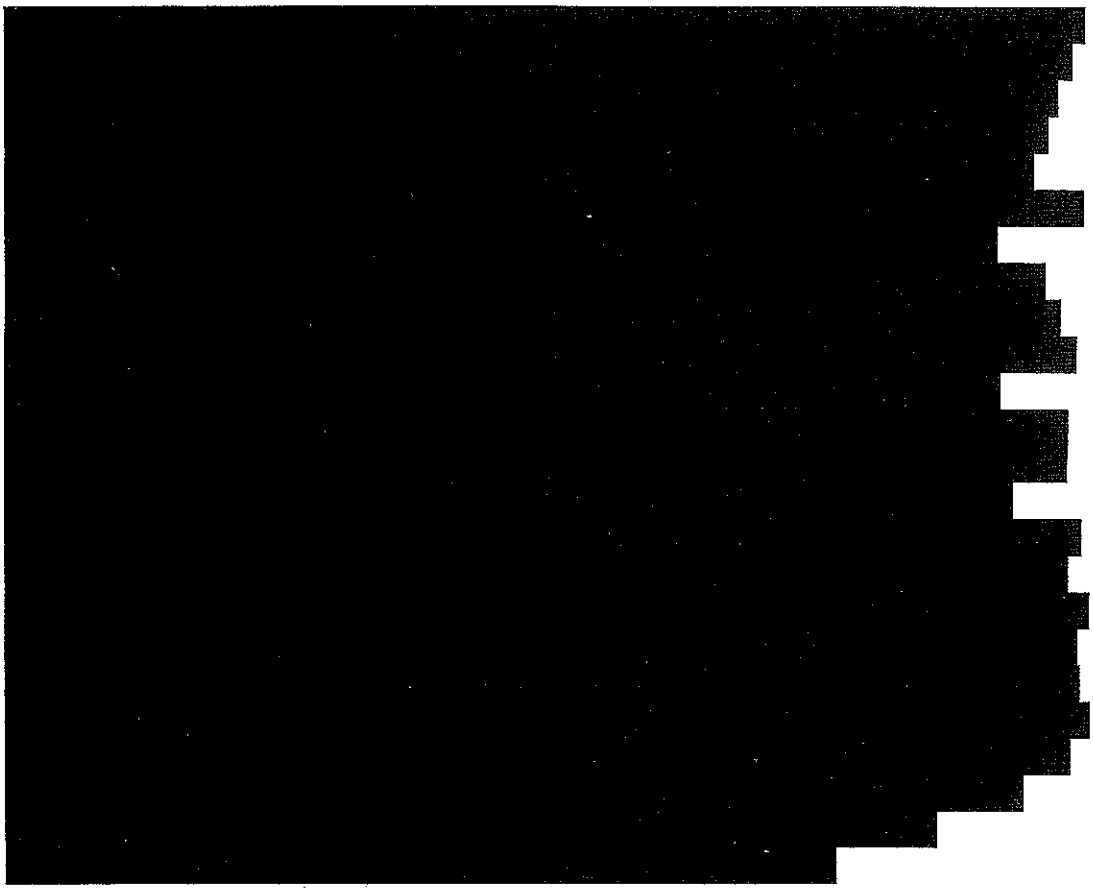
Case narratives for all reports in children (≤12 years) categorised as suicide attempt (26 November 2002 – 22 September 2004)

Case [redacted]

Case [redacted]

Case [redacted]

Case [redacted]



Case

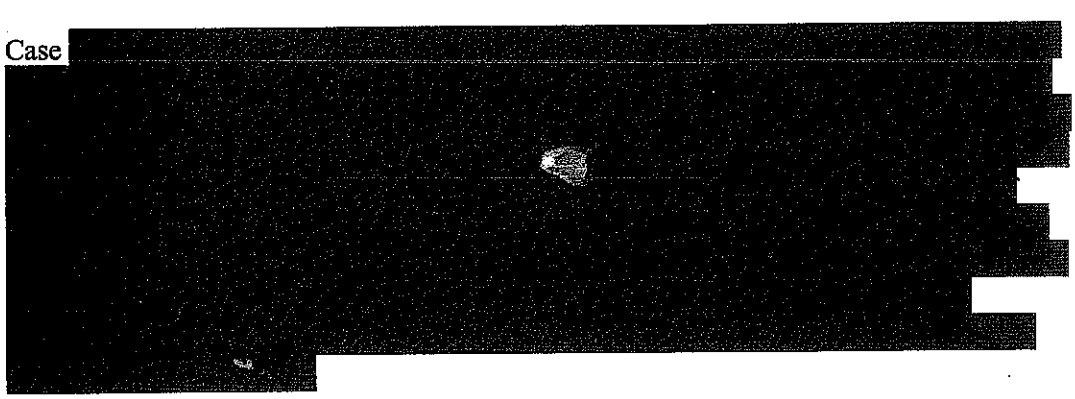
Case

[redacted]

Case [redacted]

Case [redacted]

Case [redacted]



Appendix D

Reports of Self-Injurious Behaviour, Intent Unknown (Code 5) – 26 November 2002 – 22 September 2005

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
[redacted]	[redacted]	25 mg, 3 weeks	Mildly cognitive deficit. No other medical history was provided. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	120 mg, 2 months	Medical history was not provided. No concomitant medications.	[redacted]
[redacted]	[redacted]	40 mg x2, 6 months	History of depression. Taking citalopram and paracetamol.	[redacted]
[redacted]	[redacted]	Unknown	Medical history was not provided. Taking an unidentified stimulant.	[redacted]
[redacted]	[redacted]	40 mg, 7 months	History of depression, intermittent mood lability, oppositional defiant behaviours, victim of abuse, and hurting [redacted]. Having problems with primary support and social environment (peers). No concomitant medications.	[redacted]
[redacted]	[redacted]	80 mg, 2 months	History of ADHD. Taking methylphenidate.	[redacted]

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
[redacted]	[redacted]	Unknown	Medical history was not provided. No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	40 mg, 8 days	History of autism and ADHD. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	History of depression. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	40 mg x 2, Unknown	Medical history was not provided. No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	History daily use marijuana and excessive drinking over weekend.	[redacted]
[redacted]	[redacted]	40 mg x 2, <2 months	History of tics while on methylphenidate. No concomitant medications.	[redacted]
[redacted]	[redacted]	25 mg, 10 days	Was adopted. History of generalized anxiety disorder and panic attacks. Taking risperidone and bupropion.	[redacted]
[redacted]	[redacted]	40 mg, 1 month	History of bipolar disorder, oppositional defiant disorder, depression, Asperger's syndrome, ADHD and mood disorder.	[redacted]
[redacted]	[redacted]	25 mg, 10 days	History of ADHD.	[redacted]

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
[redacted]	[redacted]	Unknown, 3 to 4 weeks	History of ADHD and an emotional component. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	40 to 60 mg, Unknown	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	40 mg, Unknown	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	25 mg, 12 days	No prior history of similar events. Taking sertraline.	[redacted]
[redacted]	[redacted]	40 mg, 11 days	History of suicide attempts and ADHD. [redacted] Taking methylphenidate and lithium. [redacted]	[redacted]
[redacted]	[redacted]	18 mg, 1 dose	History of autism, hyper, prone to agitation and non-verbal. Taking risperidone and guanfacine.	[redacted]
[redacted]	[redacted]	60 mg, Unknown	History of autism and seizure. No concomitant medications.	[redacted]
[redacted]	[redacted]	40 mg, 1 dose	History of abnormal EEG without seizure or treatment. No concomitant medications.	[redacted]
[redacted]	[redacted]	Unknown	Medical history was not provided. Taking aripiprazole and fluoxetine.	[redacted]

Case ID	Age/ Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-injury
[redacted]	[redacted]	Unknown if she was prescribed ATX	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	40 mg, 23 days	History of oppositional defiant disorder, ADHD, explosive temper and a sleep disorder. Experienced traumatic events during the last year. No concomitant medications.	[redacted]
[redacted]	[redacted]	80 mg, Since started	History of anxiety, which was resolved with sertraline. Methylphenidate was discontinued when atomoxetine started.	[redacted]
[redacted]	[redacted]	25 mg, Unknown	Concomitant use of dexmethylphenidate.	[redacted]
[redacted]	[redacted]	Unknown, 1 to 2 months	No history of suicidal ideation or attempts, no chronic illness. No concomitant medications.	[redacted]
[redacted]	[redacted]	60 mg, 2 to 3 weeks	Unknown medical history. Taking methylphenidate and risperidone.	[redacted]
[redacted]	[redacted]	50 mg, Unknown	History of mild mental retardation, ADHD, bipolar, anxiety, depression, suicide attempt and hallucination. Taking sertraline, paroxetine, haloperidol, lorazepam, and lithium, olanzapine, several other meds.	[redacted]
[redacted]	[redacted]	Unknown	Medical history and concomitant medications were not provided.	[redacted]
[redacted]	[redacted]	40 mg x 2, 8 days	History of schizophrenia, chronic mental illness, and suicide attempts, setting fires, and inpatient psychiatric treatment. Taking clonazepam, quetiapine, escitalopram, oxcarbazepine and ziprasidone.	[redacted]

Appendix E

Reports of Self-Injurious Behaviour, No Suicidal Intent (Code 7) – 26 November 2002 – 22 September 2005

Case ID	Age / Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-Injury
[redacted]	[redacted]	40 mg x 2, Unknown	Drug abuser. Taking olanzapine for treatment of psychosis.	[redacted]
[redacted]	[redacted]	60 mg, 45 days	History of autism (high functioning), Tourette's syndrome and ADHD.	[redacted]
[redacted]	[redacted]	60 mg, <1 month	History of depression, ADHD, sleeping problem and self-mutilation. Taking bupropion and trazodone.	[redacted]
[redacted]	[redacted]	Unknown	History of depression and illegal drug use. Taking citalopram and risperidone.	[redacted]
[redacted]	[redacted]	25 mg, Unknown	No prior history of aggression. Taking clonidine.	[redacted]
[redacted]	[redacted]	40 mg, <1 month	History of impulsive behavior and [redacted]. Taking methylphenidate and citalopram.	[redacted]
[redacted]	[redacted]	25 mg, 3 days	Unknown medical history. No concomitant medications.	[redacted]
[redacted]	[redacted]	25 mg, 2 to 3 weeks	History of obsessive-compulsive disorder, tics and ADHD. Taking sertraline, clonazepam and clonidine.	[redacted]
[redacted]	[redacted]	25 mg, 5 days	History of ADHD, learning disorder and acne. Taking amphetamine /dextroamphetamine.	[redacted]
[redacted]	[redacted]	60 mg, ~2 weeks	Suspected [redacted]. No history of alcohol or drug abuse. Taking zoldipem.	[redacted]

Reports of Self-Injurious Behaviour, No Suicidal Intent (Code 7) – 23 September 2005 – 25 October 2005)

Case ID	Age / Sex	ATX Daily dose/ Time-to-onset	Potential Confounding Factors	Actions of Self-Injury
[redacted]	[redacted]	40 mg, Unknown	History of Tourette's and ADHD. Unknown if taking concomitant medications.	[redacted]
[redacted]	[redacted]	10 mg, Unknown	Unknown medical history and concomitant medications.	
[redacted]	[redacted]	40 mg, 2 weeks	History of anxiety, low self-esteem, a little bit aggressive and learning, speech and language difficulties. [redacted] Taking dexamfetamine (stopped a couple of days prior to the events).	[redacted]
[redacted]	[redacted]	18 mg, ~2 months	Unknown medical history. No concomitant medications.	

ANNEX 5

MHRA assessment of Hepatoxicity associated with the use of atomoxetine

(Paper presented to the UK Committee on Safety of Medicines 27 January 2005)

NOT FOR PUBLICATION

COMMITTEE ON SAFETY OF MEDICINES

Title of paper: Strattera (atomoxetine) and severe liver injury **Type of paper:** For Advice

Products: Strattera (atomoxetine) PL 00006/0374-0379	**Assessor:** [redacted]
MAHs: Eli Lilly	**Previous Assessment:**
Legal status: POM	

1. ISSUE

On 17th December 2004, a Dear Doctor Letter was circulated in the US which informed healthcare professionals of two reported cases of severe liver injury in which the role of Strattera (atomoxetine) was deemed probable. A rechallenge was performed in one of the cases and this resulted in a severe acute hepatitis with focal hepatocellular necrosis.

The EU product information was updated according to an expedited timetable and this was finalised on 13 January 2005.

On 21 January 2005, we were informed by the Marketing Authorisation Holder (Eli Lilly) that a case of fatal liver failure associated with the use of atomoxetine and/or methylphenidate had been reported in [redacted]. Details regarding this case are vague at present although the report is being followed up by the MAH.

These cases of liver toxicity are of concern. Whilst there was no evidence of liver toxicity in pre-clinical studies or in clinical trials, the cases of liver damage suspected to be associated with the use of atomoxetine post-marketing are severe. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after the drug is stopped. Furthermore, due to its idiosyncratic, unpredictable nature and rarity, routine monitoring of liver function tests is unlikely to be of benefit. These factors combined raise serious concerns about the risk benefit of Strattera.

2. BACKGROUND

Strattera is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter (its presumed mechanism of action) without directly affecting the serotonin or dopamine transporters. Strattera is predominantly metabolised by CYP2D6 and therefore its clearance is affected by CYP2D6 polymorphism.

Strattera (atomoxetine) was first authorised in the United States in November 2002 for the treatment of attention deficit/hyperactivity disorder (ADHD) in children, adolescents and adults. Strattera was later authorised in the UK in July 2004 for the treatment of ADHD in children, adolescents and adults. It has been marketed in the UK since July 2004.

Strattera has since been subject to a Mutual Recognition procedure in the EU with the UK acting as Reference Member State (RMS) and The Netherlands, Germany and Norway are concerned Member states. The UK is the only EU Member State in which Strattera is currently marketed although it is used under compassionate use in a number of others. During the European procedure, the adult indication was removed from the Marketing Authorisation.

It is estimated that more than 2 million patients world wide have received Strattera since it was first authorised in the US in November 2002. The UK usage since first marketing in July 2004 is estimated to be a maximum of 14,663 patients.

Upon receipt of a case report of an apparent positive rechallenge to atomoxetine in a 14-year old patient who experienced liver injury (severe acute hepatitis with focal hepatocellular necrosis) the Marketing Authorisation Holder (MAH) performed a review of hepatobiliary events in all preclinical, clinical trial and post marketing data. A Type II safety variation was submitted by the MAH in order to update the product information. After submission of the variation, a second case of severe acute hepatitis in a [redacted] triggered a Dear Doctor Letter in the US. The EU variation was assessed according to an expedited timetable and was finalised on 13 January 2005.

The following changes were made to the EU SPC and PIL

Summary of Product Characteristics (SPC)

4.4 Special Warning and Special Precautions for Use
Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported.

Section 4.8 Undesirable Effects
Post-marketing experience
The following events have been very rarely reported: Abnormal liver function tests, jaundice and hepatitis.

Patient Information Leaflet (PIL)

4. Possible Side Effects
Very rarely, there have been reports of liver injury. You should stop taking Strattera and call your doctor immediately if you have dark urine, yellow skin/eyes, upper right side abdominal tenderness, or unexplained nausea, tiredness, itching or flu-like symptoms.

Since completion of the variation the MAH have informed us of a fatal case of liver failure associated with the use of atomoxetine and/or methylphenidate in a [redacted] in [redacted]. Details regarding this case are vague at present although the report is being followed up by the MAH.

The two previously reported cases of severe liver injury (including a positive rechallenge), this new fatal case and the idiosyncratic, unpredictable nature of these events, raise serious questions about the risk-benefit balance of Strattera.

The assessment report for the type II safety variation forms the basis of this assessment report. Additional details regarding the new fatal case of liver injury and further discussion have been added.

3. EVALUATION OF THE DATA

Metabolism and Disposition

Based on preclinical studies of the metabolic and dispositional profile of atomoxetine, the MAH conclude that it is unlikely that treatment with atomoxetine would be associated with hepatic injury. The pharmacokinetics of atomoxetine were shown to be generally predictable with no metabolic or dispositional characteristics of concern.

Toxicology

There was no major target-organ toxicity in studies of atomoxetine in adult mice (3 months duration), adult rats (3 & 12 month duration), adult dogs (3 & 12 month duration) or juvenile rats and dogs. Hepatic toxicity was not observed in rats given daily IV doses of up to 20mg/kg or in dogs given IV daily doses of up to 12mg/kg. Repeat-dose oral toxicity studies of atomoxetine in 10-day old rats given doses of up to 50mg/kg/day through adulthood (approx. 2.5 months duration) and in 8-week old dogs given atomoxetine up to 16mg/kg/day for one month showed no hepatotoxic effects.

Studies in adult male rats given dietary concentrations of ≥14mg/kg/day (equivalent) for 3 or 12 months showed changes in the liver including mottling and pallor of the liver, increased relative liver weights, hepatocellular vacuolation (vacuoles containing lipids) and increased serum transaminases. Similar findings were observed in male and female mice given dietary concentrations of 600mg/kg/day (equivalent) but not in mice given dietary concentrations of150mg/kg/day (equivalent), although these changes were not observed in juvenile animals or in dogs treted for 3 or 12 months. Furthermore, these changes were not due to the metabolic generation of reactive species. It was suggested that this vacuolation was due to exaggerated pharmacology (near toxic doses) since lipolysis is under adrenergic control, however no abnormal adipocyte pathology was observed.

In mice, rats and dogs, atomoxetine was found to be a weak inducer of hepatic microsomal enzymes. However, no inflammation or hepatic cellular necrosis was observed in rodents. Lack of enzyme induction in humans was confirmed (Sauer et al. 2004).

Clinical pharmacology

In 2001 the MAH performed an integrated assessment of liver injury biomarkers across all clinical pharmacology studies. This assessment has been included in previous reports to regulatory agencies. Table 1. below summarises the number of patients who developed an abnormal test result or a worsening of a pre-existing abnormal result:

Table 1.

Laboratory parameter	Subjects 1.5x above UL Normal Range (n)	Subjects>2 x Above UL Normal Range (n)
Alanine aminotransferase (ALT/SGPT)	4	2
Aspartate aminotransferase (AST/SGOT)	7	1
Alkaline phosphatase	0	0
Total bilirubin (TBILI)	1	0
Total subjects with HIGH	12	3
Total subjects with A Dose	275	.

(abnormal threshold: 2 x ULN for AST and ALKPH and ALT, and 1.5 x ULN for TBILI)

Two healthy male subjects developed 2-fold elevations in ALT above ULN. Both were asymptomatic and recovered during further observation. One healthy male developed 2-fold elevation in AST above ULN. Again this patient was asymptomatic and he recovered. A further male patient developed a TBILI 1.5x (or greater) ULN (asymptomatic) although this patient's TBILI had increased prior to administration of atmoxetine (during administration of fluoxetine). His ALT, AST and ALKPH were normal throughout the study.

Cirrhotic patients given a single 20mg dose of atomoxetine (study of pharmacokinetic changes as a result of liver damage) did not show a worsening of their liver biomarkers. However this study involved a small number of patients and the patients received a single small dose.

During clinical pharmacology studies, 10 patients were discontinued due to adverse events that were considered to be potentially related to atomoxetine. Three subjects were genotypically poor metabolisers (PM) and a further three subjects were phenotypically PMs due to coadministration of fluoxetine. None of the reported adverse events were hepatic events.

Assessor's comments: The metabolic and dispositional profile of atomoxetine suggests that it is unlikely to be associated with hepatic injury. The toxicology studies indicate mild effects on the liver, particularly at high doses. In clinical pharmacology studies no clinically significant events were reported and no patient experienced symptoms consistent with liver injury.

Clinical Trials

The data is derived from 27 clinical trials that were locked on or prior to 1 July 2004. These trials comprise approximately 6000 patients who were treated with atomoxetine. Twenty of these trials were in paediatric patients with ADHD, 4 were in adult patients with ADHD, 1 in paediatric patients with enuresis and 2 were conducted in adults with a history of drug use. Nine historical studies of atomoxetine treatment in adults with major depressive disorder (MDD) were also included in the MAHs adverse event assessment. Also, all serious adverse events from Lilly sponsored clinical trials were queried for potential hepatic adverse events.

The MAH employed a comprehensive search strategy in order to identify cases of interest. This included text strings for relevant preferred terms and laboratory test searches.

The atomoxetine safety database includes data for 4016 children and adolescents with ADHD (4025 patient years), 657 adults with ADHD (429 patient years). Data for 1275 patients with MDD and 106 patients from non-ADHD trials are also included.

Hepatic Adverse event data

A search of the database identified a total of 135 possible cases of liver injury during clinical trials. Upon further review, the MAH considers that only 20 of these reports were possibly related to atomoxetine and therefore has only provided details for these 20 cases.

In 16 of the cases the patients were male, which the MAH state is similar to the sex distribution of patients in the ADHD population. The median time to onset in these cases was 362 days (range 16 -1058 days). In one half of these cases (10 out of 20) the increases were in the range of 1.5 to 3 x ULN. In a further six cases the elevations was of the order of ≤ 5 x ULN. Another patient experienced an increase in ALT that 13 x ULN but this was associated with gastrointestinal illness and paracetamol use. In two further cases, the increases in AST (33 x ULN in one case and 5.5 x ULn in another) and ALT (4 X ULN) can be explained by the patient's concurrent muscle injury. In the remaining case the elevation of ALKPH was present prior to starting atomoxetine treatment.

Treatment emergent changes in hepatic enzymes levels

The MAH has also provided data on elevations in hepatic enzymes levels that occurred during treatment from the studies in adult and paediatric populations. For these analyses a treatment emergent high value was defined as a change from a value of less than or equal to the ULN at baseline to a value greater than the ULN at any post baseline assessment. The significance of the overall differences was assessed using the Cochran-Mantel-Haenszel general association test stratified by study group.

Change from baseline to endpoint and baseline to maximum were also calculated for all hepatic enzymes (ALT, AST, ALKPH, TBILI and GGT) using a last observation carried forward (LOCF) approach. The mean change from baseline between treatments was assessed using analysis of variance (ANOVA).

Paediatric clinical trials

In the paediatric clinical trial population the percentage of patients who developed elevations of >3-5 x ULN in ALT (atomoxetine 1.0% (1/908) vs placebo 2.0% (1/540)) and >1.5 x ULN in TBILI (atomoxetine 0.3% (2/724) vs placebo 0 (0/436)) was similar to that in placebo-treated patients. Very few atomoxetine treated patients in these paediatric trials had an ALT >3 x ULN (0.3%, 11/3736), TBILI > 1.5 x ULN (0.8%, 25/3143) or ALKPH > 2 x ULN (0.1%, 2/3738).

Placebo treated patients compared with atomoxetine treated patients had statistically greater increases in mean change from baseline to maximum in ALT (atomoxetine -1.25 vs placebo 1.32, p=<0.001), AST (atomoxetine -0.63 vs placebo 0.69,

p=<0.001), GGT (atomoxetine 0.04 vs placebo 0.40, p=0.009) and ALKPH (atomoxetine 0.09 vs placebo 11.84, p=<0.001).

Adult clinical trials

In the adult clinical trial population the percentage of patients who developed elevations of >1-3 x ULN in ALT (atomoxetine 0.4% (1/243) vs placebo 1.2% (3/241)) and TBILI (atomoxetine 0.5% (1/218) vs placebo 0 (0/225)) was similar to that in placebo-treated patients. Furthermore, no adult patients had an ALT >3 x ULN, TBILI > 1.5 x ULN or ALKPH > 2 x ULN.

Atomoxetine treated patients had significantly greater increases than placebo-treated patients in mean change from baseline to maximum for ALKPH (atomoxetine 4.75 vs placebo 0.90, p=<0.001). Whilst placebo treated patients had statistically greater increases than atomoxetine treated patients in mean change from baseline to maximum in TBILI (atomoxetine 0.37 vs placebo 1.12, p=0.021).

Assessor's comments: Whilst the available clinical trial data do not raise concerns about the risk of hepatic disorders in association with atomoxetine it is recognised that the patient population studied in clinical trials does not necessarily reflect the population which receive a product in routine clinical practice. Therefore these do not provide reassurance that atomoxetine does not cause serious hepatic disorders in some individuals.

Further details regarding the pre-clinical and clinical trial data relating to effects on the liver are provided in the pre-clinical and clinical modules of the licensing assessment report for atomoxetine which were previously considered by CSM in July 2004. These are attached at Annex 1 and Annex 2 respectively.

Spontaneous Adverse Event Reports

Between 26 November 2002 and 31 July 2004, a total of 14,472 spontaneous reports with 35,334 adverse events had been entered onto the MAH world-wide safety database. Potential reports of liver injury were identified via a comprehensive search strategy involving adverse event preferred terms, high level group terms and text string searches.

A total of 121 spontaneous reports of interest were identified. These reports were assessed and categorised by the MAH both diagnostically and etiologically. The etiological classification is outlined below (also Table 2). Diagnostic categorisation was based upon an algorithm.

Class 0. Excluded: (1) the event was not liver related; or (2) none of the liver biomarker test results, ALT, AST, ALKPH or TBILI met diagnostic criteria; or (3) atomoxetine was administered after the event.

Class 1. Unlikely: (1) clear confounding/contributory factors present, such as chronic alcoholism, viral hepatitis, genetic disorders (Gilbert's syndrome), or other medical conditions; or (2) negative rechallenge of atomoxetine (e.g. liver biomarker test results remained normal even if atomoxetine was readministered).

Class 2. Possible: (1) confounding or contributory factors present, such as concomitant medications known to cause liver injury; or (2) positive dechallenge of atomoxetine, but no rechallenge information available.

Class 3. Probable: (1) No other confounding or contributory factors present; or (2) positive rechallenge of atomoxetine.

Class 4. Indeterminate: Insufficient information available for evaluation (e.g. no information on medical history of concomitant medication available).

Table 2. Diagnostic Categorisation and Etiologic Classification of Spontaneous reports

Etiologic classification	Diagnostic categorization of Liver Injury						Total
	Gilbert's Syndrome	Hepatocellular	Cholestatic	Mixed type	Unknown type	Not liver injury	
Class 1 (Unlikely)	2	8		2	5		**17**
Class 2 (Possible)		3	4		7		**14**
Class 3 (Probable)				1			**1**
Class 4 (Indeterminate)		1			8		**9**
Class 0 (Excluded)						80	**80**
Total	**2**	**12**	**4**	**3**	**20**	**80**	**121**

Eighty of these reports were excluded (Class 0) since the reported adverse events were not liver injury events. A further 17 cases were considered to be not related to atomoxetine since there were clear confounding/contributing factors present that were more likely to have been responsible for the reported events (although an association cannot be entirely ruled out) (Class 1). In the remaining 24 reports, the possibility of atomoxetine induced liver injury could not be ruled out (Class 2, 3 or 4).

Class 1 (Unlikely)

There were a total of 17 Class 1 reports. These reports were considered to have clear contributing or confounding factors. These include concomitant medication and concomitant illness (Hepatitis C, alcoholism, infectious mononucleosis).

Three of these reports had a fatal outcome [redacted]. The cause of death was given as acute viral myocarditis ([redacted]); cardiomegaly, complications of alcoholism (hepatic cirrhosis), mitral valve degeneration and morbid obesity [redacted]; and liver congestion consistent with dilated cardiomyopathy ([redacted].

Tabel 2 above shows eight of the seventeen reports of liver injury in Class 1 were diagnosed as hepatocellular liver injury. Two were diagnosed mixed-type and a further two were diagnosed Gilbert's syndrome (by the MAH). The remaining five reports were diagnosed as unknown type due to insufficient information.

Assessor's comments: It is unlikely that atomoxetine alone is responsible for these cases of liver injury. Alternative explanations are possible in all cases (concomitant medication, concomitant disease including hepatitis C, infectious mononucleosis, and alcoholism).

Class 2 (Possible)
There were 14 adverse event reports of liver injury where possible confounding/contributing factors were present but an association with the use of atomoxetine could not be excluded. None of these reports had a fatal outcome.

The age of the patients ranged from 7 to 37 years. The dose of atomoxetine ranged from 25mg to 100mg daily and the duration of treatment ranged from 1 day to 14 months.

Three cases were categorised as hepatocellular and 4 were categorised as cholestatic. In the remaining 7 reports, the type of liver injury was unknown.

The majority of these cases reported elevated liver enzymes and some appeared to be coincidental findings on investigation of other adverse events ([redacted]). Two reports ([redacted]) described more serious hepatic events of Cholangitis sclerosing and hepatic cirrhosis and Hepatic steatosis and hepatomegaly respectively. These reports are described in more detail below.

Case [redacted] is that of a [redacted] patient who received treatment with atomoxetine up to 90mg daily for ADHD. The patient was also receiving escitalopram. After three months of treatment the patient developed hand tremor and night sweats and was feeling generally unwell. Laboratory tests revealed ALT 250IU/L, AST 150 IU/L, ALKPH 260IU/L, GGT 600 IU/L, bilirubin normal, C-reactive protein 0.1mg/L and sedimentation rate 6. Early liver cirrhosis was reported. Atomoxetine and escitalopram were discontinued but the liver enzyme levels decreased only slightly after 2.5 months. Abdominal ultrasound and MRI were normal. Hepatitis screen was negative. A liver biopsy performed 3 months after discontinuation of atomoxetine indicated findings "consistent with either drug reaction or primary sclerosing cholangitis; results were inconclusive." Endoscopic retrograde cholangiopancreatography (ERCP) failed to confirm sclerosing cholangitis but showed normal or variant small bile duct narrowing.

Ten months after discontinuation of atomoxetine the patients liver enzyme levels remain elevated with slight improvement. The patient had no history of alcohol or drug use and was otherwise healthy. [redacted] had normal LFTs 2 years prior to this event.

Case [redacted] is that of a [redacted] patient who began atomoxetine 40mg/day for ADHD. The dose was then increased to 80mg and reduced again to 40mg (dates unknown). The patient was also taking amphetamine/dextroamphetamine, trazodone and lactulose. After 14 months on atomoxetine the patient experienced elevated AST and ALT. Blood count was normal. All medications were discontinued. Fifty days after discontinuation of medication LFTs were normal except for mildly elevated ALT and AST. Hepatitis A, B and C negative. Abdominal ultrasound showed hepatomegaly with diffuse fatty

infiltration and mild splenomegaly. CT scan showed fatty infiltration of the liver and mildly prominent spleen (noted to be possibly within normal limits for this patient). The patient has not recovered and atomoxetine was not restarted.

Assessor's comments: In these two cases, the role of atomoxetine in the liver injury is difficult to assess, especially in the case of the [redacted]. The patient has not fully recovered despite atomoxetine having been withdrawn ten months previously and the liver biopsy is inconclusive. The patient does not appear to have any obvious risk factors in terms of past medical history. In the second case the role of atomoxetine in the events is less likely. The patient has a family history of liver disease ([redacted] died of cirrhosis and hepatic failure with no history of alcohol use, [redacted] also diagnosed with fatty liver), the child is obese and is receiving concomitant amphetamine/dextroamphetamine.

The remaining 12 reports contain limited information with regard to the liver injury. As mentioned above, most report elevated liver enzymes and some appear to be coincidental findings. A number of reports mention concomitant medication, the role of which can also not be ruled out ([redacted] (fluphenazine), [redacted] (olanzapine, bupropion, valproate), [redacted] (valproate), [redacted] (sertraline, amphetamine/dextroamphetamine), [redacted] (sertraline, risperidone, quetiapine) and U[redacted] (minocycline). Report [redacted] states that the patient had slightly elevated bilirubin before starting treatment with atomoxetine although this increased within the first month of treatment.

In 4 cases the role of atomoxetine cannot be entirely excluded [redacted]). However, some of these cases provide too few details for assessment and some have concurrent illness which also complicates the cases (e.g. diagnosis of diabetes mellitus).

Class 3 (Probable)

There was one report in which atomoxetine was believed to have probably played a role in the liver injury – a positive rechallenge was observed.

Case [redacted]

[redacted]

[redacted]

Assessor's comments: The positive rechallenge in this case is striking. [redacted] The MAH comments that questions still remain about the etiology of this case and the interpretation of the histology. A second opinion is being sought from an outside hepatologist.

Class 4 (Indeterminate)

There were nine reports of liver injury in which the MAH considered there to be inadequate information for causality assessment. These reports were of abnormal liver function tests and increased bilirubin. One included a case of jaundice.

Assessor's comments: Information regarding the outcome of the events, concomitant medication and previous medical history is absent from the majority of these reports which makes assessment of causality difficult. However, for this reason, these reports also cannot be completely discounted.

Class 0 (Excluded)
A total of 80 reports were excluded since they were not considered to be liver related injury.

Assessor's comments: Of the 80 reports that were excluded, 70 were retrieved through text string search. These reports were those in which the patient did not experience a hepatic event (except one case of Hepatitis C in a patient with a history of hepatitis C). These reports were retrieved in the search due to recording of laboratory tests of normal liver function tests or a history of liver events e.g. hepatitis C, jaundice at birth. However, the 10 case reports that were retrieved through the MedRA preferred term search did report hepatic events as suspect reactions to atomoxetine although the liver enzyme tests did not meet the diagnostic criteria.

Comparison Analysis of Selected Hepatic Adverse Events: FDA Adverse Event Reporting System Database (AERS)

In addition, the MAH have provided a copy of a comparative analysis of the hepatic potential of atomoxetine, other selected ADHD therapies, other drugs and drugs with known hepatotoxic effects. The data were derived from the US FDA's Adverse Event Reporting System Database (AERS) (cut-off date 30 June 2003).

The analysis uses two of the most commonly used and studied methods for analysing potential signals: proportional reporting ratio (PRR) and empirical Bayesian geometric mean (EBGM).

The PRR is a measure of the disproportionality of reports for a particular event for a drug on interest versus all other drugs in the database. The EBGM is an alternate measure of disproportionality in adverse event reports for a particular drug. It represents a measure of observed versus expected counts of a particular drug-event combination, adjusted for frequency of reports.

The interpretation of the PRR and EBGM is essentially the same. A value less than 1.0 indicates that the proportion or number or events is less than expected based on all other reports in the database. A value greater of 1.0 indicates a greater than expected proportion or number of events.

During the study period there were 6 reports of hepatic events associated with Strattera. The EB05 was 0.04 and the PRR was 0.11. These values do not highlight a

signal with regards to Strattera and hepatic adverse events. Table 3 below compares these results for Strattera with the other drugs studied.

Table 3. Frequency, EBGM, and PRR for Hepatic Events
Strattera and Selected Comparators
Cumulative AERS Data
Data Cut off date 30 June 2003

Drug	N	EBGM	90% CI*	PRR	X^2	p-value**
Labelled Hepatotoxic Potential						
Cylert (pemoline)[a]	445	4.96	4.59-5.36	6.15	2004.1	<0.001
Depakote (divalproex sodium)	903	2.04	1.93-2.15	1.89	397.2	<0.001
Rezulin (troglitizone)	2362	9.41	9.09-9.73	10.04	20114.2	<0.001
ADHD Therapies						
Adderall (amphetamine, dextro)	23	0.63	0.44-0.87	0.86	0.6	0.45
Dexedrine (dextroamphetamine)	13	0.51	0.32-0.79	0.54	5.32	0.02
Focalin	1	1.01	0.20-3.44	2.36	0.82	0.37
Ritalin (methylphenidate)	121	0.76	0.65-0.88	0.85	3.57	0.06
Strattera (atomoxetine)	6	0.08	0.04-0.15	0.11	46.6	<0.001
Control						
Albuterol	28	0.13	0.09-0.17	0.11	205.7	<0.001

Assessor's comments: This analysis does not highlight any potential safety signal for hepatic events associated with Strattera. However, in June 2003 (the cut off date) Strattera had only been authorised for 6 months. This analysis is based on spontaneous reporting and therefore is subject to the same limitations as the original data – including under reporting.

Information received after submission and/or finalisation of the variation

A second report of liver injury associated with the use of atomoxetine in which the causality was considered to be probable by the MAH was received at the beginning of December, after submission of the variation. The receipt of this second case triggered the Dear Doctor Letter in the US. Details of this case are as follows:

Case [redacted] is that of a [redacted] patient who started treatment with atomoxetine 18mg daily for attention deficit symptoms. The patient was also receiving bupropion 300mg.

Over the next two months [redacted] dose of atomoxetine was increased to 25mg then 40mg and the dose of bupropion was decreased and stopped. Three months after starting treatment the patient presented with nausea and jaundice. Laboratory tests showed a severe acute hepatitis with cholestasis. Atomoxetine was discontinued. Hepatitis A IgM antibody was negative but total Hepatitis A antibodies were positive which suggested a previous Hepatitis A infection but no current or recent infection.

Hepatitis B was negative. Based on a liver needle biopsy the differential diagnosis of adverse drug reaction, systemic viral infections and less likely, autoimmune hepatitis was made.

The final diagnosis was acute hepatitis with cholestasis and no fibrosis. Approximately one month after discontinuing atomoxetine, prednisone was started due to concerns of autoimmune hepatitis. Six days after starting prednisone [redacted] lab results had improved. Approximately four months after onset of the event all lab results were within normal limits. Atomoxetine remained discontinued. It is stated that the reporting physician believed that "while this case was not classic for drug-induced liver disease, it supported this diagnosis over any other including autoimmune hepatitis. [redacted] believed that the prednisolone played no role in the resolution of the hepatitis".

On 21st January 2005, after completion of the safety variation, the MAH informed us of a fatal case of liver failure associated with the use of atomoxetine and/or methylphenidate in [redacted]. Details of this case are outlined below:

This case is of a [redacted] patient who had taken numerous medications prior to starting atomoxetine for the treatment of ADHD that were discontinued due to lack of effect. All drug screens for the previous six months were negative.

The patient took atomoxetine 80mg daily for several months. It was stated that [redacted] would take atomoxetine when [redacted] ran out of methylphenidate. [redacted]

The week of [redacted], the patient was fine for approximately three days, but abruptly became ill on the fourth day with vomiting. [redacted] was taken to the ER and was found to have an increased prothrombin time and an INR of 5.0. The patient died due to hepatic and renal failure. It was 'heard' that the patient died of liver failure due to acetaminophen toxicity. However this was questioned since no bottles of acetaminophen were found in the patient's residence and no traces were found in [redacted] blood. No traces of alcohol or antifreeze were found in the patient's blood either.

The case is on active follow up by the MAH.

Assessor's comments: This case is difficult to assess due to the absence of specific details regarding when atomoxetine/methylphenidate were used in relation to onset of the events. Details of the patient's medical history are also lacking. A possible alternative explanation - the original diagnosis of paracetamol toxicity, also confuses things however no traces of paracetamol were found in the patient's blood and no bottles of paracetamol were found at the patient's residence. The report is being actively followed up by the MAH although this is currently proving difficult due to privacy laws. Abnormal liver function ranging from transaminase elevation to hepatic coma has been reported in association with the use of methylphenidate and the product information reflects this.

[redacted] ADROIT reports of Hepatobiliary Events

A total of three case reports of hepatobiliary events have been reported in [redacted] via the Yellow Card Scheme since Strattera was first marketed in July 2004.

Case 1: An [redacted] patient experienced passing out, yellow/jaundice and vomiting one week after starting Strattera 18mg for ADHD. [redacted] was hospitalised for 2 days and atomoxetine was discontinued 3 days later. Patient recovered 5 days after stopping atomoxetine.

Risperidone and methylphenidate were reported as concomitant medication although both had been recently discontinued. The patient had asthma, for which [redacted] had recently been given an unspecified inhaler. No other medical history was reported.

The MAH stated that on follow up, a child psychiatrist stated that the patient was not clinically jaundice when he saw [redacted].

Case 2: A [redacted] patient with severe obesity started atomoxetine 40mg for the treatment of ADHD and violent and aggressive outbursts. The dose was increased to 60mg daily one week later, with improvement in the patient's symptoms. Routine obesity testing of LFTs showed some impairment. A paediatrician diagnosed hepatitis, probably viral, although not confirmed. Patient was recovering.

Atomoxetine was started approximately 8 months after the initial evidence of liver dysfunction, and has since been discontinued The patient was on a high dose of atomoxetine due to obesity. Reported concomitant medications were paracetamol and ibuprofen for unspecified aches and pains. [redacted] was reported to have a medical history of severe obesity (90kg) and self-harm (overdose 8 tablets ibuprofen mid 2004). The reporter was unaware of any family history of liver disease or of any concomitant viral infection.

Case 3: A [redacted] patient was treated with sodium valproate for 6 years for epilepsy. [redacted] started atomoxetine 50mg for the treatment of ADHD. Within three months of starting atomoxetine the patient experienced reduced fit control, weight loss, raised bilirubin, leucopenia, lymphocytopenia, neutropenia and thrombocytopenia. The reporter suspected a drug interaction between atomoxetine and sodium valproate in terms of the reduced fit control. The reporter considered the event to be medically significant: 'weight loss and low platelets possible liver involvement'.

The patient was receiving no other medications. No medical history was reported.

At the time of the report, treatment with atomoxetine was ongoing with plans to reduce the dose, and sodium valproate was ongoing with plans to change to lamotrigine. The adverse events were ongoing. The report is on follow up.

Assessor's comments: Whilst these UK reported cases are not as severe as those described above, the role of atomoxetine can not be completely excluded. Case 1 does not appear to have any obvious confounding factors and there is a good temporal

relationship between starting atomoxetine and the onset of the events. The patient was also hospitalised possibly indicating severe events and a positive dechallenge was noted. Case 2 is less likely related to atomoxetine since the patient is severely obese and there was some evidence of liver dysfunction 8 months prior to starting treatment with atomoxetine. [redacted] received a high dose of atomoxetine due to obesity. Case 3 reports increased bilirubin and involves sodium valproate which is a known hepatotoxic medicine. However, the patient had been on sodium valproate for six years without incident before starting atomoxetine. This patient also developed blood dyscrasias and the reporter queried if these were indicative of liver dysfunction. Treatment with atomoxetine and sodium valproate was ongoing at the time of the report, as were the adverse events. The patient was on no other medication.

4. DISCUSSION

At the time of licensing in the UK, pre-clinical and clinical trial data for atomoxetine did not indicate any significant hepatotoxic effects. Further details regarding the pre-clinical and clinical trial data relating to effects on the liver are provided in the pre-clinical and clinical modules of the licensing assessment report for atomoxetine which were previously considered by CSM in July 2004. These are attached at Annex 1 and Annex 2 respectively.

The risk-benefit in children and adolescents was clearly positive for both short term and long term treatment, including poor metabolisers. Data from a three way acute treatment study with active comparator as well as placebo indicate that the efficacy of atomoxetine might be a little less than that of methylphenidate although this was not deemed to be significant in the overall evidence of efficacy for atomoxetine. Atomoxetine and methylphenidate were both well tolerated, with no serious safety concerns to either drug and there was not a clinically significant difference between active treatments in effects on cardiovascular tone.

Atomoxetine clearly has important advantages over the stimulants used to treat ADHD in terms of abuse potential.

During assessment of the safety variation regarding liver injury, a total of 41 reports were identified using laboratory data or other information. The calculated spontaneous reporting rate of liver related adverse events associated with atomoxetine was 41 in 1,961,000 patients (less than 0.01%, very rare). However, this should be interpreted with caution since it is based on spontaneous reporting and the extent of under reporting is not known.

Among the 41 reports of possible liver injury, 17 were considered unlikely to be related to the use of atomoxetine. The role of atomoxetine could not be excluded in 24 reports. A further report of liver injury received after submission of the variation was also considered to be probably related to atomoxetine by the MAH. This will be included in the following trend analyses below.

In the 25 reports in which the role of atomoxetine can not be ruled out (2 probable, 14 possible, 9 indeterminate causality) the type of liver injury reported included all three

types – hepatocellular, cholestatic and mixed type, although a large number were unknown.

There does not appear to be any obvious trends in dose, with reports of hepatic events occurring with doses ranging from 0.67mg/kg to 1.57mg/kg in children, and 25mg to 100mg in adults

The time to onset in those cases considered to be possibly related (14 cases), ranges from 1 day to 14 months although the majority were reported to be within the first 3-4 months of treatment (2 months, 50 days, 5-6weeks, 1 day, <1 month, 2 weeks, 2 months, 3 months, 1 month, 14 months, 1 month and <4 months). The two cases which were considered probably related both had an onset time of 3 months. The onset times were not provided in the majority of the 'indeterminate causality' cases. However, those provided were 11 days, 1 year, 1 month and <2 months.

Where the information was available, there did not appear to be link between dose and time of onset i.e. higher dose, earlier onset.

It is not known if any of the cases had CYP2D6 polymorphism or if this is likely to be a possible risk factor for the development of hepatotoxicity with atomoxetine. The effects of CYP2D6 polymorphism on the tolerability and safety profile of atomoxetine before licensing is discussed in detail in the clinical module of the licensing assessment report which can be found in Annex 2.

There has been a report of a fatal case of liver failure associated with the use of atomoxetine and/or methylphenidate in [redacted] in [redacted]. This case is confused by an original diagnosis of paracetamol toxicity although no traces of paracetamol were found in the patient's blood. The case is on follow up. Time to onset in this case was 'several months' and the dose was reported as 80mg.

Medicines with a clear therapeutic role and positive risk:benefit balance may be able to remain on the UK market, despite a known risk of hepatotoxicity if the adverse reactions are predictable, the mechanism of hepatotoxicity is known and measures can be taken to minimise the risk of this adverse effect. Examples of such medicines include the treatments for cancer and AIDs.

Whilst there was no evidence of liver toxicity in pre-clinical studies or in clinical trials of atomxoetine, the cases of liver damage suspected to be associated with its use post-marketing are severe. Such reactions have occurred up to several months after therapy is started, but laboratory abnormalities have worsened for several weeks after the drug is stopped. Furthermore, due to its idiosyncratic, unpredictable nature and rarity, routine monitoring of liver function tests is unlikely to be of benefit in minimising the risk. These factors combined raise serious concerns about the risk benefit of Strattera.

5. ADVICE SOUGHT

The regulatory options available to address this risk are as follows:

1. No Action (other than the product information update already agreed)
If the Committee considers that the action taken to date to update the product information is sufficient to address the risk, this could be communicated widely to healthcare professionals.

2. Update of the product information to strengthen warnings and/or recommend monitoring of patients. Communication of risks to healthcare professionals via a 'Dear Healthcare Professional' letter.
It is unclear how the warnings could be strengthened to minimise risk. There is no clear 'at risk' population which could be excluded from treatment. Monitoring of liver function is unlikely to be of benefit given the nature of the ADRs.

3. Suspension of the Marketing Authorisation pending further investigation/evaluation of the risks.
Suspension of the Marketing Authorisation is appropriate in the event of an urgent risk to public health where no lesser measures could be considered to provide adequate safeguards.

4. Revocation of the Marketing Authorisation
Revocation of the Marketing Authorisation if the product proves harmful in the normal conditions of use.

Based on the data presented in this report on the risk of serious hepatic adverse events associated with Strattera (atomoxetine), the Committee's advice is sought as to which of these regulatory options is most appropriate.

[redacted]
24 January 2005

ANNEX 6

MHRA assessment of the updated (30 month) cumulative review of hepatic disorders associated with atomoxetine

(26 November 2002 – 26 May 2005)

UPDATED CUMULATIVE REVIEW OF HEPATIC ADVERSE EVENTS ASSOCIATED WITH THE USE OF ATOMOXETINE (26 NOVEMBER 2002 – 26 MAY 2005)

1. Introduction

The previous cumulative review of reports of hepatic adverse events associated with atomoxetine which was assessed by the RMS covered the period 26 November 2002 – 31 July 2004 (named by the MAH "the October Review"). The "October Review" was initiated following the receipt of a spontaneous case report of hepatitis in which there was a positive rechallenge. The review also considered pre-clinical and clinical trial data and led to a revision of the Company Core Data Sheet (CCDS) and EU Summary of Product Characteristics (SPC) and Patient Information Leaflet to include hepatic adverse effects.

Between 26 November 2002 and 31 July 2004, a total of 14,472 spontaneous reports with 35,334 adverse events had been entered onto the MAH world-wide safety database. A total of 41 reports were identified using laboratory data or other information. The calculated spontaneous reporting rate of liver related adverse events associated with atomoxetine was 41 in 1,961,000 patients (less than 0.01%, very rare). A review of this data can be found in Annex 5 of the main risk benefit assessment report.

As a result of this review, the Summary of Product Characteristics for atomoxetine was updated to include abnormal liver function tests, jaundice and hepatitis as very rare side effects of the drug. Further more the Special Warnings and Special Precautions for Use section of the SPC was updated to warn prescribers of the risk of severe liver injury associated with atomoxetine and that atomoxetine should be discontinued and not restarted in patients who have laboratory evidence of liver injury.

There has been an increase in the number of reports of hepatic adverse events reported for atomoxetine following the update of the SPC and PIL and distribution of the Dear Healthcare Professional letter. The MAH have conducted a further updated cumulative review of spontaneous reports of hepatic adverse events reported for atomoxetine which covers a 30 month period from 26 November 2002 to 26 May 2005.

2. Updated Cumulative Review of Spontaneous Reports of Atomoxetine and Hepatic Events (26 November 2002 – 26 May 2005)

A total of 19,345 atomoxetine spontaneous reports with 47,931 adverse events were received by the MAH and had been entered into the MAH safety database between 26 November 2002 and 26 May 2005. Approximately 5.2% of the reports contained serious adverse events. Healthcare professionals reported 44% of reports (initial and follow up information). The remainder of the cases were reported by consumers.

The MAH atomoxetine safety database was searched for reports of hepatic adverse events using 4 MedDRA high level group terms (HLGT) *"hepatic and hepatobiliary disorders"*, *"hepatobiliary investigations"*, *"bile duct disorders"*, and *"gall bladder disorders"*.

A further 20 MedDRA Preferred Terms (PT) which are not included in the 4 HLGTs above were also used to search the MAH atomoxetine safety database. These 20 PTs are *"alagille syndrome"*, *"bilirubinaemia"*, *"blood alkaline phosphatase"*, *"blood alkaline phosphatase abnormal"*, *"blood alkaline phosphatase increased"*, *"Cholangitis suppurative"*, *"chromaturia"*, *"Coma hepatic"*, *"Gilbert's syndrome"*, *"hepatic cyst"*, *"hepatic cyst ruptured"*, *"hepatic encephalopathy"*, *"hepatic trauma"*, *"hyperammonaemia"*, *"jaundice acholuric"*, *"jaundice neonatal"*, *"liver operation"*, *"liver transplant"*, *"ocular icterus"*, and *"polycystic liver disease"*.

Finally the MAH safety database was also searched using text strings in the case medical history field, case narratives, CIOMS comments field, MedDRA preferred terms field, and the actual terms and laboratory test results fields. The text strings used were Liver, Hepato, Hepati, Alkaline phos, ALT, SGPT, AST, SGOT, Bilir, Transaminase, Cholesta, Dark urine, Icterus, Jaundice, Encephalopathy, Alanine, Ammonia, Gamma-glut, and Urobili.

The identified reports were reviewed by the MAH to determine the type of liver injury (diagnostic categorisation) and etiologic classification.

Diagnostic categorisation of reports of liver injury
The following definitions were used by the MAH for diagnostic categorisation of hepatic adverse events.

FDA guidance (FDA 2000)

'Liver injury' - any increase to more than 2- to 3- fold of upper limits of normal (ULN) in alanine amniotransferase (ALT) or conjugated bilirubin (CBILI).

'Hepatitis' - histological description of liver pathology (biopsy or autopsy), described as infiltration of mononuclear cells that may or may not be associated with hepatocellular changes.

'Severe liver injury' - combined elevations in total bilirubin (1.5 X ULN) and transaminase(s) (3 X ULN).

Table 1 below provides details of the definitions for categorisation of reports which were used by the MAH. The definitions are based on the Council for International Organisations of Medical Sciences (CIOMS) Guidance and the FDA Clinical White Paper.

Table 1. Definitions and Types of Liver Injuries

Category of Liver Injury	ALT	ALKPH	ALT/ALKPH Ratio	Comments
Hepatocellular	≥2 X ULN	Not elevated	≥ 5	Parameter for ALT must be met, along with one of the other two parameters.

Cholestatic	Not elevated	≥2 X ULN	≤ 2	Parameter for ALKPH must be met, along with one of the other two parameters.
Mixed Injury (Hepatocellular & cholestatic)	≥2 X ULN	≥2 X ULN	> 2 and <5	All 3 parameters should be met.

'Possible liver injury' - An increase in ALT, AST or ALKPH values ≥2 times ULN or an increase of total bilirubin (TBILI) or CBILI to ≥1.5 times ULN.

The value of bilirubin is not listed in table 1 but the MAH considered the case to be liver injury if the TBILI or CBILI were elevated. When only unconjugated bilirubin (UBILI) is increased, TBILI is less than 5mg/dL, and AST, ALT and ALKPH are within normal range, the MAH assigned Gilbert's syndrome as the most likely cause of the rise in UBILI.

Etiological Classification of reports of liver injury
The etiological classification is outlined below.

Class 0. Excluded: (1) the event was not liver related; or (2) none of the liver biomarker test results, ALT, AST, ALKPH or TBILI met diagnostic criteria; or (3) atomoxetine was administered after the event or the event was considered "non-treatment emergent".

Class 1. Unlikely: (1) clear confounding/contributory factors present, such as chronic alcoholism, viral hepatitis, genetic disorders (Gilbert's syndrome), or other medical conditions; or (2) negative rechallenge of atomoxetine (e.g. liver biomarker test results remained normal even if atomoxetine was re-administered at the same dose for the same duration).

Class 2. Possible: (1) confounding or contributory factors present, such as concomitant medications known to cause liver injury; or (2) positive dechallenge of atomoxetine, but no rechallenge information available.

Class 3. Probable: (1) No other confounding or contributory factors present; or (2) positive rechallenge of atomoxetine.

Class 4. Indeterminate: Insufficient information available for evaluation (e.g. no information on medical history of concomitant medication available).

Spontaneous Reports of Liver Injury Retrieved from the MAH Database

A total of 419 spontaneous reports of possible liver injury were retrieved from the MAH atomoxetine safety database for the period 26 November 2002 – 26 May 2005 (41 cases were included the previous cumulative review 26/11/02-31/07/04). Of these 419 cases, 253 cases were retrieved using the 4 MedDRA HLGT terms and 20 PTs outlined above. The remaining 166 case reports were identified following a text-string search of the database.

A summary of the MAHs diagnostic categorisation and etiological classification of these 419 cases is provided in Table 2.

Table 2 MAH Diagnostic Categorisation and Etiologic Classification of Spontaneous reports of Liver Injury associated with Atomoxetine

Diagnostic Categorisation of Liver Injury	**Etiologic Classification**					**Total**	
	Class 1 (Unlikely)	Class 2 (Possible)	Class 3 (Probable)	Class 4 (Indeterminate)	Class 0 (Excluded)		
Gilbert's Syndrome	11	N/A	N/A	N/A	N/A	11	**Total of Liver-Injury cases: N=175**
Hepatocellular	17	33	0	7	1	58	
Cholestatic	0	5	0	3	0	7	
Mixed Type	2	2	1	0	0	5	
Unknown Type	12	15	0	65	2	94	
Not Liver Injury	N/A	N/A	N/A	N/A	244	**Not Liver Injury N=244**	
Total	**42**	**55**	**1**	**74**	**Excluded: N=247**	**Total Cases Retrieved from database N=419**	
	Total of Liver-Injury Cases in temporal association with atomoxetine: N=172						

Two hundred and forty-seven of the 419 reports were excluded since the reported adverse events were not liver injury events or were not considered to be treatment emergent events (Class 0). A further 42 cases were considered to be not related to atomoxetine since there were clear confounding/contributing factors present that were more likely to have been responsible for the reported events (although an association cannot be entirely ruled out) (Class 1). In the remaining 130 reports, the possibility of atomoxetine induced liver injury could not be ruled out (Class 2, 3 or 4).

The MAH has provided patient demographics for the 172 cases which were designated 'liver-injury cases in temporal association with atomoxetine'. The age range of patients in the 172 reports ranged from 2 years to 61 years (28.5% were aged 0-12 years, 34.3% were aged 13-17 years, 27.3% were aged 18-64 and the age was unknown in 9.9% of cases).When the age distribution of the case reports are compared with the age distribution of the total number of atomoxetine spontaneous reports, there was a significantly higher percentage of adolescent patients (34.4% liver injury reports, 15% total spontaneous adverse event reports). Of the 172 case reports, 118 (69%) involved male patients and 48 (28%) involved female patients

Four case reports (3 Class 1 'Unlikely' and 1 Class 4 'Indeterminate') had a fatal outcome. These cases are discussed in further detail in the relevant class sections below.

2.1 Class 1 (Unlikely)

There were a total of 42 Class 1 reports, 39 of which were reported by healthcare professionals and 3 were reported by consumers. There were a total of 17 Class 1 reports in the previous review of this issue (Annex X).

The Class 1 reports involved 11 children, 18 adolescents, 10 adults, and 2 unknown-age patients.

Table 2 above shows that 17 of the 42 reports of liver injury in Class 1 were diagnosed as hepatocellular liver injury, two were diagnosed mixed-type and a further 11 were diagnosed Gilbert's syndrome (3 by the reporter and 8 diagnosed by the MAH based on the LFTs provided in the report). The remaining 12 reports were diagnosed as unknown type due to insufficient information.

Information regarding dose is provided in 35 of the 42 cases and ranged from 20mg to 120mg (mean 59.1mg, median 60mg). The time to onset of these events (where specified) ranged from a few days to 14 months.

Three of the Class 1 reports had a fatal outcome [redacted] and [redacted]. The cause of death was given as acute viral myocarditis in a [redacted] who had raised ALT, AST and TBILI; cardiomegaly, complications of alcoholism (hepatic cirrhosis), mitral valve degeneration and morbid obesity in a [redacted]; and liver congestion consistent with dilated cardiomyopathy in [redacted]

The 42 Class 1 reports were considered to have one or more clear contributing or confounding factors (31 reports) or the event had resolved before atomoxetine was discontinued (11 reports) or whilst treatment with atomoxetine continued or there was a negative rechallenge of atomoxetine.

Of the 39 non-fatal cases, there was a negative dechallenge of atomoxetine and a positive rechallenge of somatropine in a [redacted] who had hepatic fibrosis. In a case of fatty filtration of the liver in a [redacted], the patient had a family history of liver disorders including [redacted] who was not receiving atomoxetine and who was also diagnosed with a fatty liver. The patients ALT remained elevated at 5X ULN approximately 3 months after stopping atomoxetine. Another case of fatty filtration of the liver was reported in a [redacted] who had a history of possible hepatitis A. [redacted] mild ALT elevation (2X ULN) returned to normal prior to stopping atomoxetine. A "hardening of the liver" suggestive of cirrhosis was revealed on an abdominal ultrasound in a 7-year old with cystic fibrosis and ALT of 2X ULN who was being treated with atomoxetine. The ultrasound also revealed concurrent intussusception of ileocecal valve.

A further 11 cases were diagnosed with Gilbert's syndrome (either by the reporter or by the MAH based upon the reported LFT/bilirubin results). Five of these patients developed mild jaundice, 2 further patients had concurrent gastroenteritis and another patient was later diagnosed with mononucleosis. Atomoxetine was discontinued in 10 of these 11 cases and the TBILI or jaundice returned to normal in 7 cases. The outcome of the event was not provided in 4 cases.

There was one case in which the [redacted] patient developed a slight elevation of TBILI whilst hospitalised with gastroenteritis. [redacted] recovered whilst hospitalised after atomoxetine was discontinued.

Nine patients were diagnosed with infectious mononucleosis or Epstein-Barr viral infection and one patient had a concurrent gasteroenteritis. Two of these patients continued on treatment with atomoxetine. Seven patients had discontinued atomoxetine although in three patients who restarted atomoxetine there was no recurrence of the adverse events.

A further three patients had a history of or were diagnosed with hepatitis C.

There were no clear confounding factors in the remaining 11 reports. These 11 reports have been placed in Class 1 (Unlikely) since in three cases LFTs returned to normal and jaundice abated prior to stopping treatment with atomoxetine; in a further three cases the events resolved whilst treatment with atomoxetine was continued and in the final five cases, there was a negative rechallenge of atomoxetine.

Assessor's comments: It is unlikely that atomoxetine alone is responsible for these cases of liver injury. One or more alternative explanations are possible in these cases including concomitant medication, concomitant disease (hepatitis C, infectious mononucleosis and EBV infection, alcoholism, Gilbert's syndrome). In other cases, the role of atomoxetine in the reported hepatic adverse events is unlikely since the events resolved whilst continuing on treatment or there was a negative rechallenge.

2.2 Class 2 (Possible)

There were a total of 55 case reports of liver injury where possible confounding/contributing factors were present but an association with the use of atomoxetine could not be excluded. The majority of these cases were reported by healthcare professionals. Only 2 cases were reported by consumers.

There were 14 adverse event reports in Class 2 in the previous review of this issue which covered the period 26 November 2002 – 31 July 2004 (see Annex X).

Of the 55 reports, 16 involved children, 21 involved adolescents and 18 involved adults. The age ranged from 2 years to 57 years (mean 19.1 years, median 15 years).

The dose of atomoxetine (provided in 45 of the 55 cases) ranged from 10mg to 120mg daily (mean 58.8mg, median 60mg) and the time to onset of events ranged from 3 days to 1.5 years with an onset time of one month or less in 11 cases, 2 months in 6 cases, 3-4 months in 8 cases, 5-11 months in 6 cases, and 1 year or more in 10 cases.

Thirty-three cases were categorised as hepatocellular, 5 were categorised as cholestatic, and 2 as mixed type liver injury. The type of liver injury was unknown in the remaining 15 cases.

Twenty-three of the 55 cases were considered serious. There were no fatal cases. Treatment with atomoxetine was discontinued in 50 cases. Of the 50 cases in which atomoxetine was discontinued, the event resolved in 26 cases, continued in 12 cases and the outcome was unknown in 12 cases. Treatment with atomoxetine was continued in 4 cases (dose decreased in 1 case) and the events resolved in 1 case (dose reduction case), the events continued in 2 cases and the outcome was unknown in 1 case. The action taken with atomoxetine was unknown in the final case, as was the outcome of the event.

Seven cases reported that a liver biopsy was performed although the results of the liver biopsy were provided in only 5 of the 7 reports. The results of the biopsies indicated hepatocellular inflammations with no significant fibrosis or cirrhosis in 4 cases and sclerosing cholangitis in the fifth case. Possible autoimmune hepatitis was considered in four of the five cases.

The first case [redacted] was previously identified as a Class 3 case as the reported case of hepatitis was considered probably related to atomoxetine following a positive dechallenge. This case and case [redacted] were considered probably related to atomoxetine during the previous review and type II variation assessment. These cases were the 2 cases highlighted in subsequent communication with healthcare professionals (Dear Healthcare professional letter). In this cumulative review, this case has been reclassified to Class 2 (Possible) since follow up information now contradicts the positive dechallenge outcome previously assigned to the case. The [redacted] patient experienced jaundice and elevated liver enzymes two and a half months after starting atomoxetine. Laboratory tests indicated a severe acute hepatitis with cholestasis. Atomoxetine was discontinued. One and a half months after stopping atomoxetine the patient started prednisolone due to concerns over a possible autoimmune hepatitis since the liver enzymes were still markedly elevated. Prednisolone was discontinued after 50 days use. About 4 months after atomoxetine dechallenge (and one month after stopping prednisolone) the patients liver biomarkers were all within normal limits. The patient experienced a second episode of hepatitis with ALT 23X ULN several months after recovery from the first episode without rechallenge of atomoxetine. The patient was given prednisolone and azathioprine and within 7 days ALT was reduced to half peak value. Although autoimmune antibody markers (ANA, anti-KLM antibodies) were negative, the diagnosis of autoimmune hepatitis was considered for this case.

There were three further cases of possible autoimmune hepatitis, 2 of which were reported by the same hepatologist. None of these patients were receiving any concomitant medication and none had any previous history of hepatic disorders. Antinuclear antibody tests were positive in all three cases although a false positive was suspected in one case. Atomoxetine was discontinued in all three cases. In the first case the events resolved without further intervention and the reporting physician considered atomoxetine to be the probable cause of the patient's hepatitis. In the second case the patient recovered after steroid treatment and the reporting physician considered that the liver injury was not causally related to atomoxetine. In the third case a false positive antinuclear antibody test was suspected. The patient had not yet recovered at the time of reporting. The reporting physician considered this case of hepatitis was due to atomoxetine which was a diagnosis of exclusion.

The fifth case (in which the results of liver biopsies were available) involved a [redacted] who developed sclerosing cholangitis and early liver cirrhosis after 3 months of treatment with atomoxetine and escitalopram (unknown duration of treatment). After discontinuation of atomoxetine and escitalopram the patients liver enzymes had decreased only slightly over a 2.5 month period. Antinuclear antibody tests were negative. A liver biopsy performed 3 months after discontinuation of atomoxetine showed findings consistent with either drug reaction or primary sclerosing cholangitis. After 13 months the liver function tests had returned to normal. About a year prior to starting atomoxetine the patient had experienced an allergic reaction to naproxen (possible alternative cause of [redacted] primary sclerosing cholangitis) and it was also reported that [redacted] had a rash and a virus (unspecified).

In two further cases it was stated that liver biopsies had been performed although the results were not provided. Neither case met "Hy's Law" (ALT/AST ≥3X ULN and TBILI ≥1.5 ULN which represent signs of severe liver injury). In the first case ([redacted]) the liver biopsy confirmed "medication induced liver damage" without further details of the biopsy. The patient recovered after atomoxetine was discontinued. In the second case a [redacted] developed ALT 3X ULN and AST 2.8X ULN after 3 months treatment with atomoxetine. Tests were negative for Wilson's disease. [redacted] liver function tests remained abnormal 4 weeks after discontinuing treatment with atomoxetine.

There were two cases in which a positive rechallenge of atomoxetine was observed. Both of these cases were considered to be possibly related to atomoxetine. However, the MAH is inconsistent in their categorisation. A positive rechallenge should carry greater weight than possible confounders and therefore these 2 cases should be categorised as probably related to atomoxetine (Class 3).

The first case of a positive rechallenge ([redacted]) involved a [redacted] patient with no relevant medical history who was not receiving any concomitant medication. The patient had elevated bilirubin levels prior to starting atomoxetine (TBILI 31umol/L ULN 17). Four months after starting atomoxetine 40mg daily, the patient developed jaundice and raised bilirubin. Atomoxetine was discontinued. Three weeks after discontinuation, atomoxetine 25mg was restarted as the jaundice was improving. Approximately 1 week after restarting atomoxetine the patient developed flu-like illness and jaundice again. The patient was unwell and could not get out of bed. The rechallenge was reportedly similar to the initial illness although it was greater in severity (in line with positive rechallenge seen in Class 3). The patient had fatigue, dark urine, itching, slight abdominal rash, nausea and anorexia and increased prothrombin time. Three weeks after discontinuing atomoxetine the events were improving but the patient was still unwell and jaundiced. The patient was started on methylphenidate.

The second positive rechallenge case ([redacted]) involved a [redacted] patient who was born with biliary atresia with liver problems and had bile duct surgery at 6 months of age and a "bout of liver problems" at 6 years of age. The patient had previously been on the liver transplant list. [redacted] was concomitantly receiving allopurinol. The patient experienced jaundice and raised bilirubin which was suspected as a viral infection after receiving atomoxetine 80mg daily for about 6-7 months. All medicines were discontinued. [redacted] blood tests were normal within 2-3 months except WBC which was low due to splenectomy. [redacted] liver function tests were also normal. Atomoxetine was restarted 80mg daily about 1-2 months after the first dechallenge. The patient experienced another bout of liver problems with extreme jaundice and itching 2 months after atomoxetine was rechallenged. Atomoxetine was discontinued and within 48 hours the itching and jaundice had started to resolve. Two weeks after the second discontinuation the jaundice and itching had almost completely recovered.

There were a further 5 cases in which the ALT and/or AST were >10XULN and two of these cases appeared to meet Hy's Law. In the first case ([redacted]) viral hepatitis profile indicated hepatitis B surface antibody positive, hepatitis B core antibody negative, and hepatitis C virus antibody negative. The second case involved a [redacted] who had a positive hepatitis B test (unspecified). Atomoxetine was discontinued but patient was still very jaundiced and was in a serious condition. Both patients were receiving concomitant medication. The other 3 cases did not meet Hy's Law (only ALT and/or AST raised without other abnormal test results). In one of these cases the patient was receiving concomitant minocycline and the events of muscle cramps and elevated AST and ALT recovered after minocycline and atomoxetine were discontinued. In one case the patient was receiving concomitant lithium and underwent a cholecystectomy and experienced elevated ALT/AST. Atomoxetine was discontinued. The outcome of the event is unknown. In the final case the patient was had asymptomatic elevation of AST after 19 months of taking a prescribed overdose of atomoxetine. The patient fully recovered after atomoxetine was discontinued.

In four further cases the patients were hospitalised due to hepatic adverse events. These four cases were cases of AST and ALT increased; hepatic enzyme increased, abdominal pain, jaundice, vomiting, pyrexia and dehydration; jaundice, mental disorder, hepatic enzymes increased, white blood cell count decreased; and the final case was of hepatic enzyme increased. Atomoxetine was discontinued in all four cases. Three of the patients recovered following discontinuation of atomoxetine, the outcome was unknown in the fourth case.

There were two cases in which the patient developed hepatomegaly, one of which was considered to be a possible autoimmune hepatitis and is discussed above. The second case of hepatomegaly involved a [redacted] who had a history of jaundice. [redacted] was treated with atomoxetine for three months and developed nausea, vomiting and dark urine. The patient was receiving concomitant risperidone and thioridazine. Atomoxetine was discontinued and the patient was treated with ranitidine, omeprazole, domperidone and cisapride. An ultrasound showed "continued liver with increased size". The outcome was unknown.

None of the remaining 36 of the 55 Class 2 reports had an elevation of liver enzymes >10X ULN or met Hy's Law. Twenty cases presented mild symptoms and signs such as abdominal pain, nausea, vomiting, headache or feeling unwell. Sixteen cases did not report symptoms and signs other than elevated liver enzymes.

Assessor's comments: A total of 55 cases of hepatic injury were identified by the MAH as Class 2 (possibly related to atomoxetine). Of note are the two cases of a possible rechallenge of atomoxetine. In both cases the patients had underlying hepatic disorders, however the temporal association with starting atomoxetine and the positive rechallege suggest that atomoxetine could be responsible for the aggravation of pre existing liver disorders in these cases. The patients were recovering or had recovered after discontinuing atomoxetine. Whilst atomoxetine is not causally related to the underlying hepatic disorder the positive rechallenge in these cases provide good evidence of an exacerbation of the underlying hepatic disorder by atomoxetine. The MAH is inconsistent in their categorisation. A positive rechallenge should carry greater weight than possible confounders and therefore these 2 cases should be categorised as probably related to atomoxetine (Class 3).

Twenty three of the reports were considered to be serious and liver biopsy confirmed liver damage in 7 cases. Possible autoimmune hepatitis was considered in 4 cases. Nine cases had elevations of liver biomarkers which were more than 10X ULN and 5 cases met Hy's Law indicating a possible severe liver injury.

A positive dechallenge of atomoxetine was observed in 26 cases (of 50 cases) in which atomoxetine was discontinued. The outcome was unknown in 12 of these cases.

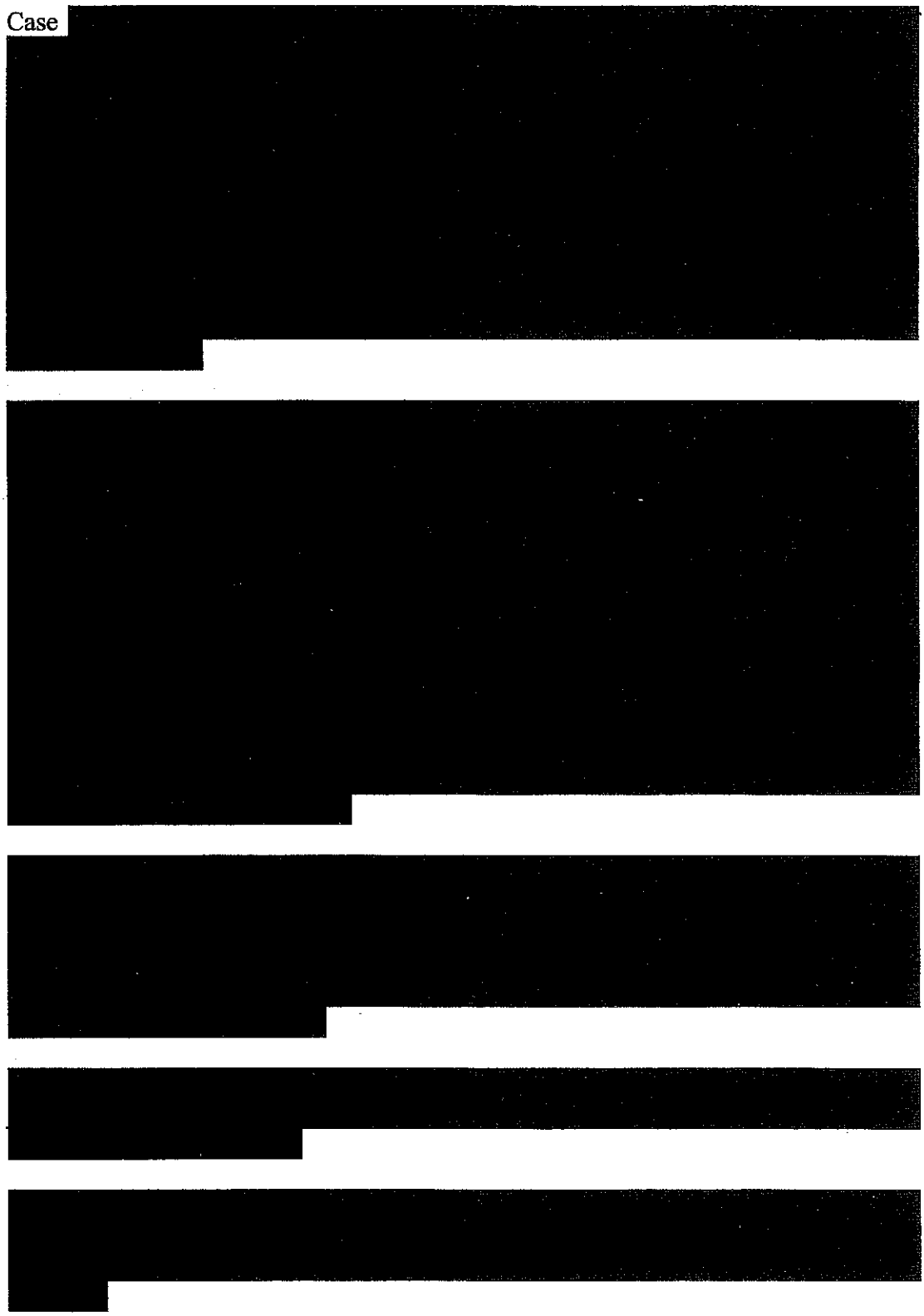
No trend in time to onset was observed in these cases with time to onset ranging from 3 days to 1.5 years. There was also no obvious trend in the dose although this relationship is not easy to assess based on the data provided since the doses according to weight were not always provided and this is significant give some of the cases occurred in adults and some occurred in children. The type of liver injury reported was predominantly hepatocellular (33 cases) although cases of cholestatic and mixed-type liver injury were also reported.

In these 55 case reports, the role/contribution of atomoxetine can not be excluded. These cases therefore confirm the previous signal that atomoxetine is associated with liver injury. These cases further confirm the idiosyncratic nature of the liver injury (no trend in time to onset or dose) and the potentially severe nature of the events. The current product information for atomoxetine lists abnormal liver function tests, jaundice and hepatitis as very rare recognised adverse effects of the drug. Furthermore, the Special Warnings and Special precautions for Use section of the Summary of Product Characteristics for atomoxetine warns prescribers that atomoxetine is associated with severe liver injury and that treatment should be stopped and not restarted in patients who have laboratory evidence of liver injury. The new Class 2 cases considered in this updated cumulative review do not provide any further information which would allow further characterisation of these reports over and above what is already known (i.e potentially severe and idiosyncratic reaction), therefore no further updates to the product information are necessary.

2.2 Class 3 (Probable)

There was one report in which atomoxetine was believed to have probably played a role in the liver injury – a positive rechallenge was observed. This report was included in the previous review (see Annex X). Details of the case are provided below.

Case



[redacted]

Assessor's comments: The positive rechallenge in this case is striking. The liver injury was also severe, particularly in the rechallenge, as indicated by the bone marrow depression and the fact that the patient was evaluated for a possible liver transplant. This patient underwent extensive testing to find other causes and with extensive follow up by the MAH, there were no other potential causative factors identified during the course of this patient's hepatitis. Atomoxetine was identified as the probable causative factor. Both the initial exposure and rechallenge showed a mixed-type liver injury.

Since the reporting of this case and the subsequent cumulative review and type II variation assessment (covering the period 22/11/02-31/07/04) the EU product information has been updated to include abnormal liver function tests, jaundice and hepatitis as very rare recognised adverse effects of atomoxetine. Warnings were also added to the product information which instructed physicians to stop and not restart atomoxetine in patients with laboratory evidence of liver injury. The newly identified risk of very rare but potentially severe idiosyncratic liver injury associated with atomoxetine was communicated to healthcare professionals in February 2005.

2.3 Class 4 (Indeterminate)

There were 74 reports of liver injury in which the MAH considered there to be inadequate information for causality assessment (compared with nine Class 4 case reports in the previous review). A total of 68 of these cases were reported by healthcare professionals.

A total of 22 of these reports involved children, 19 involved adolescents, 19 involved adults and 14 cases involved patients whose ages were unknown. The ages ranged from 6 years to 61 years (mean 20 years, median 15 years).

Of the 74 cases, the dose was provided in 44 cases. The dose ranged from 18mg to 120mg (mean 58mg, median 60mg). The time to onset was provided in 45 cases and ranged from 2 weeks to 2 years. An onset of 2 months or less was reported in 16 cases, 3-4 months in 8 cases, 5-11 months in 15 cases, and 1-2 years in 6 cases.

Insufficient information regarding the results of liver function tests was provided for diagnositic categorisation of 65 case reports. In some cases, liver function tests were not performed and the diagnosis of liver injury was based upon the patient's symptoms, in particular jaundice. As outlined in Table 2 above, only 7 cases were categorised as hepatocellular liver injury and 2 case reports were categorised as cholestatic liver injury.

One of the Class 4 reports ( ) resulted in a fatal outcome. The case involved a patient who took acetaminophen occasionally for aches and pains and had previously taken dexamphetamine salts for ADHD. was described as a "social drinker" and had a history of "soft drug" use for which had been drug tested every 6 months as part of a restraining order. Drug tests during this time were negative. The patient was possibly taking methylphenidate at the time of the event but this was unconfirmed. The patient started atomoxetine 40mg approximately 2 years ago but was not always compliant with treatment. After 2 years of treatment the dose of atomoxetine was increased to 80mg daily which took uninterrupted for "several months, maybe a year" up until the time of the event. . The patient abruptly became sick and vomited. had been well in the 3 days leading up to the event (no jaundice observed). was found to have an increased prothrombin time and an INR of 5.0. The patient died the same day due to hepatic and renal failure. No liver biopsy was performed. No autopsy was performed. The death was initially reported as "liver failure due to acetaminophen toxicity" however no traces of acetaminophen, antifreeze or alcohol were found in the patient's blood. acetaminophen levels were reportedly "lower than usually seen". This fatal case was reported to the MAH following the circulation of a 'Dear Healthcare Professional Letter' in the US which informed healthcare professionals of the risk of liver injury associated with atomoxetine. The reporter has declined to provide further information regarding the case.

Of the non-fatal cases, the outcome of the event was not provided in the majority of cases (69 cases). The MAH reports that in four cases the reaction resolved after discontinuation of atomoxetine. In fact there are 6 cases in which the events recovered after atomoxetine was discontinued ( ). The first case involved an who was hospitalised due to vomiting and dizziness, lost consciousness and was jaundice following 1 week of treatment with atomoxetine 18mg (0.6mg/kg). The jaundice was reported by but the psychiatrist stated that it was not clinically jaundice. The patient was also receiving an unspecified inhaler for asthma. No lab tests provided. Atomoxetine was discontinued and the patient recovered.

The second case involves a who, after 13 days of treatment with 80mg atomoxetine, was jaundice). The reported adverse events were hepatotoxicity, jaundice, chromaturia, somnolence, malaise and nausea. The patient refused all blood tests. The psychiatrist suspected hepatotoxicity without seeing the patient. The patient had a history of substance abuse including cannabis. Atomoxetine was discontinued and the patient recovered.

The third case involves a [redacted] who developed an increased AST, increased LDH and increased blood iron 5 months after starting atomoxetine 40mg. All tests were normal 20 days after stopping atomoxetine. The patient's medical history and concomitant medication were unknown.

The fourth case is that of a [redacted] who developed increased LFTs, ketonuria, blood glucose increased, nausea, vomiting, upper abdominal pain, and change of bowel habit 2 months after starting atomoxetine 25mg. The patients had concurrent bronchitis. No baseline tests were performed. Atomoxetine was discontinued and all the events resolved.

The fifth case involves a [redacted] who developed abnormal liver function tests 2 weeks after starting an unknown dose of atomoxetine. [redacted] 'LTs elevated to 2X to 4X ULN'. [redacted] had no symptoms of liver problems. After 8-10 days of stopping atomoxetine the patient recovered. [redacted] medical history and concomitant medication are unknown.

The sixth and final case is that of a [redacted] who also developed abnormal liver function tests less than two months after starting atomoxetine 60mg. Atomoxetine was discontinued and the patient recovered. The patient's medical history and concomitant medication are unkown.

Assessor's comments: Information regarding the outcome of the events, concomitant medication and previous medical history is absent from the majority of these reports which makes assessment of causality difficult. However, for the same reason, the role of atomoxetine in these reports of liver injury cannot be excluded. The current product information for atomoxetine lists abnormal liver function tests and hepatitis as very rare recognised adverse effects of the drug and warns that treatment with atomoxetine should be stopped and not restarted in patients with laboratory evidence of liver injury.

The fatal case ([redacted]) was not included in the initial review (the type II variation) of this issue as it was reported after the variation assessment was completed. The EU product information was updated on 15 January 2005. The UK (RMS) was notified of this case by the MAH on 21 January 2005 and the issue was discussed by the UK Committee on Safety of Medicines on 27 January 2005. At that time, limited details regarding the case were available, in particular in was unclear whether the patient was taking atomoxetine at all at the time of onset of the events. The updated information provided in this updated cumulative review states that the patient had been taking atomoxetine uninterrupted at 80mg daily for "several months, maybe a year" at the time of onset of the events. Despite the cause of death being initially reported as liver failure due to acetaminophen toxicity, this is unlikely given that the results of blood tests showed that blood levels of acetaminophen were lower than usually seen. Drug tests had also been clear for six months. It was unknown if the patient was also taking methylphenidate. No autopsy was performed. The reporter has declined to provide further information regarding the case. The role of atomoxetine in this death can not be completely excluded.

2.4 Class 0 (Excluded)

A total of 247 reports were classed by the MAH as Class 0. In the previous review, a total of 80 reports were excluded as Class 0 reports.

Three of the 247 Class 0 cases did contain events relating to liver injury, however the events were considered to be non-treatment emergent by the MAH. Two of these cases were excluded by the MAH because the liver injury events occurred prior to starting treatment with atomoxetine and the third case was a case of hepatic trauma which was caused by the patient's intentional self injury. The first case was of viral hepatitis in a severely obese [redacted] who had raised ALT 8 months prior to starting atomoxetine, raised ALT, ALK PHOS and GGT 6 months prior to starting atomoxetine and in the month while starting atomoxetine [redacted] had raised ALT, and ALK PHOS. The second case was of vomiting and malaise in a [redacted] who had TBILI of 71, ALKPH = 57 and ALT = 33 prior to starting atomoxetine. The patient was not clinically jaundice. Atomoxetine was continued and the events resolved. The third case was that of a [redacted] who suffered hepatic and renal injury caused by intentional self-injury ([redacted]).

The remaining cases were considered by the MAH as "not liver injury". These reports include cases in which, although the reporter stated that the liver enzyme results were abnormal, the values of the test results did not reach 2X of ULN which is the minimum elevation required for the diagnosis of liver injury outlined in the MAH methods in the Diagnositic Categorisation section above.

There were four case reports that were primarily muscle injury with significant elevations of CPK, one case of liver injury in a patient with Duchenne muscular dystrophy and three cases in which a diagnosis of rhabdomyolysis was made. The mild to moderate elevations of ALT in these cases are considered by the MAH to be more likely due to the coincident muscle injury events.

Assessor's comments: Three of the 247 Class 0 cases did contain events relating to liver injury, however the events were considered to be non-treatment emergent (occurred before starting atomoxetine or resulted from trauma). In a further 8 cases the observed elevated ALT was more likely to be muscular in origin. The remaining cases were not cases of liver injury either because the liver function tests were less than 2X ULN or the cases did not involve hepatic adverse events. The majority of the reports which did not involve hepatic adverse events were retrieved via the text-string search and include references to abnormal liver function tests and/or hepatic disorders in the history field, or involved adverse events which could be (although were not) liver related such as 'encephalopathy' or 'chromaturia'.

3. Discussion

A total of 419 reports of possible hepatic adverse events were retrieved from the MAH atomoxetine safety database and upon review 247 reports were considered to be 'not cases of liver injury'. Of the 172 reports which were considered to be cases of liver injury, 42 cases were considered to be unlikely related to atomoxetine due to

other possible contributing/confounding factors. In the remaining cases an association with atomoxetine could not be completely ruled out and these included one case in which the events were considered to be probably related to atomoxetine and 55 cases in which the events were considered to be possibly related to atomoxetine. The calculated spontaneous reporting rate of liver related adverse events associated with atomoxetine following the 30 month review was 172 in 2,902,000 patients worldwide (less than 0.01%, very rare).

The reporting rate of hepatic adverse events associated with atomoxetine has increased since the previous review of the issue (type II variation January 2005) and subsequent communication with healthcare professionals. Hepatic injury associated with atomoxetine is still considered to be very rare. However, the reporting rates should be interpreted with caution since they are based on spontaneous reporting which is influenced by many factors including publicity and under reporting. In the previous review of this issue (type II variation) a total of 42 reports were identified (including the late reported case of severe hepatitis and positive dechallenge in a [redacted]). Among the 42 reports of possible liver injury, 17 were considered unlikely to be related to the use of atomoxetine. The role of atomoxetine could not be excluded in 25 reports (2 probable, 14 possible, 9 cases of indeterminate causality). The calculated spontaneous reporting rate of liver related adverse events associated with atomoxetine was 41 in 1,961,000 patients (less than 0.01%, very rare).

In this updated 30 month cumulative review, there were four fatal cases, 3 of which were considered unlikely due to atomoxetine and were included in the previous type II variation assessment of this issue and one case in which the relationship was considered 'indeterminate'. The latter case was reported after the type II variation assessment of liver injury associated with atomoxetine, however it was this fatal case which triggered the UK Committee on Safety of Medicines consideration of this issue in January 2005 and thus it has been already been considered prior to this 30 month cumulative review. At the time of the CSM review there were limited details available concerning this case and it was unclear as to whether the patient was actually taking atomoxetine at the time of onset of the events. Follow up information on this case was included in this 30 month cumulative review and whilst the relationship between atomoxetine and the events was classified as 'indeterminate' by the MAH (Class 4), the role of atomoxetine can not be excluded.

There were three cases in which a positive rechallenge of atomoxetine was observed one of which was considered probably related and 2 were considered possibly related. The case which was considered probably related to atomoxetine was the case which triggered the first review 'October review' of this issue in October 2004 and led to the subsequent type II variation. The two 'possibly' related cases are new cases and involve a positive rechallenge of atomoxetine in patients with underlying liver disorders (exacerbation of underlying liver disorder).

One case of severe hepatitis associated with atomoxetine was previouslyconsidered in the type II variation assessment of this issue and at that time was considered to be probably related to atomoxetine due to a positive dechallenge. However, based upon follow up information which now contradicts the positive dechallege (patient subsequently experienced a second episode of hepatitis after discontinuation of

atomoxetine) a possible autoimmune hepatitis was considered for this case despite antinuclear antibody tests being negative.

No obvious trend in time to onset was observed in the reported cases. There was also no obvious trend in the dose although this relationship is not easy to assess based on the data provided since the doses according to weight were not always provided and this is significant give some of the cases occurred in adults and some occurred in children. The type of liver injury was predominantly hepatocellular (58 cases) where the information was available however the type of liver injury was unknown in 94 cases.

4. Conclusion

This 30 month updated cumulative review confirms the previous signal that atomoxetine is associated with liver injury and further confirm the very rare, idiosyncratic nature of the liver injury (no obvious trend in time to onset or dose) and the potentially severe nature of the events. The data suggest that the type of liver injury is predominantly hepatocellular in those reports where this information was available, however this information was unknown in 94/175 cases. The current product information for atomoxetine lists abnormal liver function tests, jaundice and hepatitis as very rare recognised adverse effects of the drug. Furthermore, the Special Warnings and Special precautions for Use section of the Summary of Product Characteristics for atomoxetine warns prescribers that atomoxetine is associated with severe liver injury and that treatment should be stopped and not restarted in patients who have laboratory evidence of liver injury. This updated cumulative review does not provide any further information which would allow further characterisation of these reports over and above what is already known (i.e potentially severe and idiosyncratic reaction), therefore no further updates to the product information are necessary.

[redacted]

14 November 2005

ANNEX 7

MHRA assessment of Seizure Events associated with atomoxetine

(Review of data submitted by MAH in PSUR 4 including MAH review of Clinical Trial database, Medical Claims database and Post-Marketing Spontaneous reports).

There have been a number of spontaneous post-marketing reports of seizure events associated with atomoxetine world-wide. Spontaneous reports of seizure events among patients taking atomoxetine following US approval in 2002 have been the most common serious adverse event reported by healthcare professionals and consumers. Seizures are not currently a recognised side effect of atomoxetine and thus are not listed as such in the product information for the drug. Seizures were however, identified as a potential risk in the Pharmacovigilance Risk Management Plan for the drug.

The MAH have conducted a review of the available data for atomoxetine with respect to seizures. The review was conducted in order to investigate a possible relationship between atomoxetine and seizures following a number of post-marketing reports.

The MAHs's review forms the basis of this assessment of the issue and includes data from the following sources:

- Atomoxetine clinical trial database
- Spontaneous post-marketing adverse event reports
- Medical Claims Database study

1.0 Preclinical data

Little information on preclinical data for atomoxetine is provided in the MAH review. A very brief overview is presented in the introduction to the review and includes the following statements:

- Preclinical studies suggest that atomoxetine is not proconvulsive.
- No changes in pentylenetetrazol precipitated convulsions were observed in mice (General Pharmacology Report 15, submitted with the initial NDA).
- In a second model of seizure liability, higher currents were needed to elicit electroschock-induced convulsions compared to vehicle treated control mice, suggesting that atomoxetine might have anticonvulsant properties.
- Seizures were observed in a number of toxicological studies but this observation was not considered relevant to doses used in the clinical setting.

Further details of preclinical data for atomoxetine are provided in the repeat use MRP assessment report **(Annex 2)**.

2.0 Clinical Trial Data

Trials included in the analyses

The cut off date for adverse event text string searches in the clinical studies was 26 November 2004. All patients in all studies, including ongoing and completed Phase 2, 3, and 4 studies are included in the analyses.

The analyses included: 21 completed and 8 ongoing clinical studies in children and adolescents with ADHD; 3 completed and 2 ongoing clinical studies in adults with ADHD; 19 completed clinical pharmacology studies involving more than 300 healthy adults; 2 completed abuse-potential studies involving 66 adults (drug users); 1 completed paediatric study involving 44 children with enuresis; 9 historical

depression trials in more than 1200 adults with major depressive disorder; 1 in adult depression and 1 study in adult Alzheimer's.

A core set of exclusion criteria is used in all studies in the ADHD clinical trial databases. Patients with a history of seizure disorder (excluding febrile seizures) were excluded from the trials along with patients with uncontrolled hypertension, patients at serious risk for suicide and patients with ongoing alcohol or drug abuse.

Methodology

The MAH performed a comprehensive search of the clinical trial database The following 29 text strings were used to search for 63 possible seizure-related terms: *Aura, Coma, Cons, Conv, Cyan, EEG, ELECTROENCEPHALO, Epil, Roll, Faint, Fall, Hyperto, Ictal, Incoh, Incont, Muscle, Myoclon, Nystag, Oculog, Rigid, Seiz, Slur, Stiff, Strab, Syncop, Tongue, Trem, Tris, Twitch.*

Reports unrelated to seizures were removed from the search results and the remaining cases were reviewed for diagnostic categorisation and etiological classification according to the following guidelines:

Diagnostic Categorisation

Category 1.	Report of probable/possible generalised tonic-clonic seizure
Category 2.	Report of status epilepticus
Category 3.	Event reported as a seizure, but the seizure classification was indeterminate due to insufficient information in the report
Category 4.	Event reported as a seizure, but not considered a generalised tonic-clonic seizure based on the information provided in the report
Category 5.	Event was determined to **not** be a seizure based on the information provided in the report

Etiologic Classification

Class A.	Clear confounding or contributing factors (e.g. personal history of seizures, diagnosis of benign seizure disorder)
Class B.	Possible confounding or contributing factors (e.g. concomitant medication use, neurological conditions, family history of seizures)
Class C.	Indeterminate etiology with insufficient information available for evaluation
Class D.	No apparent confounding or contributing factors, with sufficient information available to evaluate.

Summary of All Identified Possible Seizure Cases Reported

A total of 19 possible seizure events (15 patients) were identified.

Two of the reports of seizures occurred in patients who were **not** exposed to atomoxetine (exposed to other treatments) and these cases are not considered further by the MAH in the review. Both events ('seizure activity' and 'seizure') occurred in

adult patients ([redacted]). Both patients were on other medication with known risk of seizures – sertraline and desimipramine.

The remaining 17 events (13 patients) were categorised as follows.

Category 1 (Reports of Probable/Possible Generalised Tonic-clonic Seizure)

One report was considered by the MAH to fall into Category 1. This report was classified Class A – clear confounding or contributing factors (complicated perinatal period, twin gestation). The report is of a [redacted] who suffered grand mal convulsion 2 days after discontinuing atomoxetine.

Category 2 (Status Epilepticus)

None

Category 3 (Event reported as a seizure, but the seizure classification was indeterminate due to insufficient information in the report)

Nine AE reports in 7 patients were assessed as Category 3. Five of these were classified Class A, one classified as Class B and one classified as Class C.

The first report is of 'seizure activity' in a [redacted]. The patient had an abnormal EEG after atomoxetine was discontinued and was subsequently diagnosed with Juvenile Myoclonic Epilepsy.

The second report is of a seizure in a [redacted] who had sustained head injuries after falling from the roof of [redacted] house.

The third report describes 'myoclonus' and 'hypoglycaemic seizure' in a [redacted] with a history of Type I Diabetes (onset 3 years prior to entering study).

The fourth case was that of a [redacted] who experienced 'epilepsy'. [redacted] had a history of developmental delay, staring spells, abnormal EEG prior to atomoxetine use. No further events occurred on continued therapy at higher doses of atomoxetine.

'Convulsive syncope' and 'Groggy due to convulsive syncope' were reported in a [redacted]. The events followed a vasovagal episode after phlebotomy. No further events in continued treatment for 13 months at higher doses of atomoxetine.

A [redacted] experienced 'possible seizure' (Class B). The MAH stated that long duration of treatment before and after the event without any other related event to be the confounding factor.

The final report in Category 3 is classified as Class C (Indeterminate etiology, insufficient information). It is that of a [redacted] who experienced 'seizure'.