PERIODIC SAFETY UPDATE REPORT (PSUR)

Product(s):	**Strattera (5mg, 10mg, 18mg, 25mg, 40mg, 60mg)**
Marketing Authorisation Holder:	**Eli Lilly and Company**
Active Constituent:	**atomoxetine hydrochloride**
Mutual Recognition Procedure:	
Reference Member State:	**United Kingdom**
Concerned Member States:	
Period of Assessment:	**27th May 2005 – 26th November 2005**

1. INTRODUCTION

Atomoxetine is a highly selective inhibitor of the pre-synaptic norepinephrine transporter. It is currently indicated in the EU for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents over the age of 6 years.

This is the 5th periodic safety update report for Strattera and covers the period 27th May 2005 to 26th November 2005.

2. WORLD-WIDE MARKETING AUTHORISATION STATUS

Atomoxetine was first authorised for the treatment of ADHD in the US on 26 November 2002. As of 26 November 2005, atomoxetine is approved for the treatment of ADHD in 42 countries world-wide (marketed in 30 of these countries). The EU Birthdate for Strattera is 26 May 2004 (United Kingdom).

Atomoxetine is approved for the treatment of ADHD in children over the age of 6 years, adolescents and adults in 25 of the 30 countries in which it is marketed. In the remaining 5 countries (Germany, Netherlands, Norway, Romania and UK) atomoxetine is approved for the treatment of ADHD in children and adolescents only.

3. REGULATORY ACTION OR MAH ACTIONS TAKEN FOR SAFETY REASONS

During the period covered by this PSUR major regulatory actions were taken for safety reasons.

On 27 September 2005, an urgent safety restriction procedure was implemented following a meta-analysis of clinical trial data which showed a statistically significant increased risk of suicidal behaviour (suicidal ideation/attempt) in children treated with atomoxetine compared to those who received placebo. A Dear Doctor Letter was sent at this time and revisions were made (or proposed) to the labels including the Company Core Data Sheet (CCDS), the EU Summary of Product Characteristics (SPC) and Patient Information Leaflet (PIL).

This updated cumulative review includes an additional 6-months data to the review which was considered as part of the risk:benefit assessment in January 2006.

A total of 263 reports of seizure-related events have been reported for the 3-year period 26 November 2002 – 26 November 2005.

One hundred and six of these 263 cases were categorised as possible tonic-clonic seizures. Confounding factors were identified in 46 of these reports. A further 34 reports were considered to be possibly confounded, however a causal association between atomoxetine and an aggravation of an underlying seizure disorder can not be completely excluded in some of these cases. There were nine cases in which there were no apparent confounding factors. The remaining 17 cases contained insufficient information for causality assessment.

Five of the 263 cases were cases of status epilepticus. Four of these cases were included in the previous review. In one of these cases the possibility that atomoxetine exacerbated the patients underlying seizure disorder can not be excluded.

There were 109 reports in which the seizure classification was indeterminate, 43 of which were considered to be clearly confounded and 23 were considered to be possibly confounded. A further 41 cases lacked sufficient information for causality assessment. Thre were two cases in which the role of atomoxetine can not be excluded.

The remaining 43 out of the 263 reports of seizure-related events were not considered to be tonic-clonic seizures. Three of these cases were considered to have no apparent confounding factors and had sufficient information for causality assessment.

Assessor's comments: *Seizures are listed in section 4.8 (Undesirable effects) of the EU SmPC for Strattera following the risk:benefit review in January 2006. The SmPC also contains a warning about the risk of seizures in section 4.4 (Special Warnings and Precautions for Use) and section 4.5 (Interactions). This updated review does not provide any further information regarding trends in time to onset, dose, or particular patient groups at risk which would warrant further any further amendment to the Strattera SPC concerning seizure-related events*
For the full review see Annex 3.

9.8.4 Cumulative Review of Spontaneous Adverse Event Reports of Movement Disorders

The MAH identified a total of 187 spontaneous case reports (28 serious) of movement disorders for review for the period 26 November 2002 – 30 October 2005. The estimated reporting rate is 0.005% (very rare). However, the MAH exluded 700 cases of psychomotor hyperactivity, 327 non-serious cases of tic, and 283 non-serious cases of tremor from this review.

The MAH provided a review of 70 cases of dyskinesia reported for atomoxetine. The majority of cases had confounding factors present such as concomitant medication or

medical history, or information was missing from reports preventing full causality assessment.

The MAH concludes that a causal association between movement disorders and atomoxetine can not be made based on these data. This takes into account confounding by indication and concomitant medication. The MAH further concludes that the data do appear to support the clinical trial results which do not indicate a worsening of pre-existing tic disorders. However, as mentioned above details for only the 4 serious cases of tic were included in the review. No information was provided on the 327 non-serious cases of tic and thus it is difficult to perform any meaningful causality assessment for cases of tic when only a very small proportion (4/331) of the reported cases have been included for review.

Similarly, it is difficult to perform any meaningful causality assessment for cases of tremor. In two of the four serious cases included in the review, the role of atomoxetine could not be completely excluded despite the presence of confounding factors. Furthermore, tremor is mentioned in the EU SmPC for Strattera in the part of Section 4.8 (Undesirable Effects) which describes the ADRs reported more frequently in clinical trials in CYP2D6 poor metabolisers compared with CYP2D6 extensive metabolisers.

Assessor's comments: *There is insufficient evidence at present to establish a causal association between atomoxetine and cases of dyskinesia.*

It is difficult to perform any meaningful causality assessment for cases of tic when only a very small proportion (4/331) of the reported cases have been included for review. ***The MAH is requested to provide an overview of the non-serious cases of tic reported for atomoxetine.***

In addition, ***the MAH is requested to provide further clarification as to the criteria used for determining that the 700 reported cases of psychomotor hyperactivity were related to an exacerbation of the underlying ADHD which resulted in exclusion of these cases from this review.***

The MAH should justify not adding tremor to the main table of adverse events in section 4.8 of the SPC for Strattera.

9.8.5 Cumulative Review of Spontaneous Adverse Event Reports of Cerebrovascular Accident and Related Events

For the reporting period 26 November 2002 to 26 November 2005, there were a total of 16 reports (containing 17 reactions) of cerebrovascular adverse events reported in association with atomoxetine. All were considered to be serious. The reported suspected reactions were as follows: Cerebral haematoma (1); Cerebral ischaemia (1); Cerebrovascular accident (9); Cerebrovascular spasm (1); Embolic stroke (1); Haemorrhage intracranial (1); Thrombotic stroke (1); Transient ischaemic attack (2). These spontaneous adverse event reports of cerebrovascular adverse events for atomoxetine do not provide strong evidence of a causal association, except for one case involving an overdose of atomoxetine.

Four of the cases involved paediatric patients (aged 5 years (*cerebral ischaemia resulting from an acute overdose*), 8 years (*cerebrovascular accident*), 6 years (*cerebrovascular accident, cerebral spasm*), and a neonate who was exposed to maternal atomoxetine during the first trimester of pregnancy (*intraventricular haemorrhage*)). Three of these cases are unlikely to be related to atomoxetine or have other confounding factors such as concurrent medical conditions. A causal association is suspected between atomoxetine and the reported adverse events in the case of cerebral ischaemia in a 5-year old boy (USA0508106691), although the event of cerebral ischaemia is likely to be secondary to other reactions (seizures, respiratory depression, hypoxia). This case involves an acute accidental overdose (approx. 60 x 40mg) of atomoxetine which was prescribed for the boys mother and not the boy himself.

Eleven cases concerned adult patients (age range 20-69 years). The majority of these cases have clear confounding factors (medical history and concomitant medication). The final case concerned a patient of unknown age. Causality could not be established in this case due to lack of relevant information.

As a potent inhibitor of the presynaptic noradrenaline transporter, atomoxetine is recognised to cause Raynaud's phenomenon (peripheral vasoconstriction/vasospasm/ peripheral ischaemia) and thus it is not possible to completely exclude a similar effect in the brain. Whilst the spontaneous reports do not provide evidence of a strong causal association between atomoxetine and cerebrovascular adverse events, a recently completed epidemiological study (the 'Atomoxetine Cardiovascular and Cerebrovascular Safety Outcome Study in Adults') has identified a potential signal with regards to transient ischaemic attack in adult patients. However, at this stage it is uncertain as to whether the signal is 'real' or an artefact of the methodology. The MAH is following up the signal within the study.

***Assessor's comments**: This exact cumulative review was previously considered by PhVWP at the meeting in October 2006. PhVWP recommended that a possible interaction between atomoxetine, a previous medical history of migraine and a further increased risk of stroke should be investigated further. It was noted that in a number of the reported cases of cerebrovascular adverse events, the patients had a history of migraine. Whilst migraine itself is considered to be a risk factor for stroke, atomoxetine is known to have vasospastic effects in the peripheral vasculature and thus a similar effect in the brain cannot be excluded. See Annex 5 for the full assessment report.*

9.8.6 Cumulative Review of Spontaneous Adverse Event Reports of Serious Skin Reactions

A total of 19 spontaneous case reports of potentially serious skin reactions were identified for the period 26 November 2002 – 26 November 2005. Nine of these cases were considered to be serious. These cases are: Stevens Johnson syndrome (3, all considered serious); Erythema multiforme (5 in total, 4 considered serious); Dermatitis bullous (2 in total, 1 considered serious); Blood blister (2 cases, both considered to be non-serious); and Blister (7 cases, all considered to be non-serious).

Based on the available data there is not enough evidence at present to warrant an update of the SPC with regards to Stevens-Johnson syndrome, erythema multiforme, or other bullous skin reactions. Section 4.4 (warnings and precautions) of the current SPC for atomoxetine states that 'although uncommon, allergic reactions, including rash, angioneurotic oedema, and urticaria, have been reported in patients taking atomoxetine' and section 4.8 (undesirable effects) lists rash and pruritus. However, whilst the evidence is not strong at present, there are cases of erythema multiforme in which there is a possible association with atomoxetine and thus further similar cases may warrant an update to the SPC for Strattera in the future.

Assessor's comments: *This exact review of serious skin reactions reported for atomoxetine was presented to the PhVWP at the October 2006 meeting. The PhVWP concluded that there is insufficient evidence at present to establish a causal association between atomoxetine and serious skin reactions. For the full review see Annex 6.*

Stevens-Johnson syndrome and erythema multiforme are included as surveillance terms in the atomoxetine Risk Management Plan and the MAH should continue to closely monitor such events in the future. As proposed, the MAH should cumulatively review serious skin reactions as and when more data becomes available and in the next PSUR.

9.8.7 Cumulative Review of Spontaneous Adverse Event Reports of Blood Dyscrasia

A total of 107 unique case reports of blood dyscrasias were reported during the period 26 November 2002 – 26 November 2005. There were 80 reports of blood cell line decrements and 27 of blood cell line increments. Laboratory parameters were provided in only 33 of the 107 cases.

The most frequently reported cell-line decrements were white blood cell decrements: 'Neutropenia' (6); Leukopenia (5); White blood cell count decreased' (11); Neutrophil count decreased (2); and one report each of 'Neutrophil percentage decreased', 'Band neutrophil count decreased', 'White blood cell count abnormal', and 'Lymphocyte count decreased'.

There were also a significant number of cases relating to platelet disorders including 'Thrombocytopenia' (3); 'Platelet count decreased'; 'Idiopathic thrombocytopenic purpura' (2); 'Thrombocytopenic purpura' (2); 'Platelet function test abnormal' (3); and disorders indicative of possible platelet function abnormalities including 'Increased tendency to bruise' (9); 'Ecchymosis' (1). There were also 5 cases of 'prothrombin time prolonged'; 3 cases of 'bleeding time prolonged'; and 1 case of 'coagulation time prolonged'.

There were 8 cases relating to red blood cell disorders including 5 cases of anaemia.

Of the 27 cases of cell line increments reported for atomoxetine, 11 cases were cases of 'mononucleosis syndrome' and are considered to be unrelated to atomoxetine. A further 11 cases were of increases in white blood cells and 4 cases were of an increase in platelets.

Assessor's comments: *This exact review of blood dyscrasias reported for atomoxetine was presented to the PhVWP in the meeting of October 2006. The PhVWP concluded that there is insufficient evidence at present to establish a causal association between atomoxetine and blood dyscrasias (including both cell line decrements and cell line increments). For the full review, please see Annex 7.*

There is some concern regarding the methodology employed by the MAH in conducting this review. Further details can be found in Annex 7.

9.8.8 Summary of Adverse Drug Reactions Related to Cardiac Disorders During the PSUR Reporting Period.

A total of 20 serious (16 unlisted) and 41 non-serious (17 unlisted) ADRs coding to the Cardiac Disorders SOC were reported for atomoxetine during the 6-month reporting period (27 May 2005 – 26 November 2005). A further 9 serious (4 unlisted) and 53 non serious (20 unlisted) ADRs coding to the Cardiac and Vascular Investigations HLT of the Investigations SOC were reported.

Arrhythmias

There were 13 serious case reports relating to arrhythmias. These 13 cases contained 14 unlisted ADRs, 7 of which were considered to be serious. The seven serious unlisted reactions were *atrial fibrillation* (2); unspecified *arrhythmia* (3); *ventricular extrasystoles* (1); *supraventricular tachycardia* (1). Three of these cases reportedly involved paediatric patients (aged 4, 15 and 16 years). The remaining 6 cases reported non-serious arrhythmias including *extrasystoles* or *heart rate irregular* (3 young female patients); *heart rate decreased* or *heart rate abnormal* (2 adult patients); and *pulse abnormal* (patient age unknown).

Assessor's comments: *Arrhythmias were cumulatively reviewed as part of the risk benefit assessment in January 2006). This previous cumulative review covered more than half of this PSUR reporting period with a data lock date of 30 September 2005. The MAH continues to closely monitor arrhythmias reported in association with atomoxetine. Many of the reported cases have clear or possible confounding factors present.*

The case of supraventricular tachycardia (16-year old female) resulted in a syncopal episode. However, in the other cases of syncope reported during this PSUR period a cardiac cause is not suggested. The MAH proposes to perform a comprehensive review in order to evaluate the potential causal relationship of syncope events reported in the atomoxetine spontaneous database.

Tachycardia and Heart Rate Increased

A total of 53 cases reported ADRs coding to tachycardia, sinus tachycardia or heart rate increased.

Assessor's comments: *Atomoxetine has noradrenergic effects on heart rate. Tachycardia is a recognised side effect of atomoxetine and the EU SmPC lists*

tachycardia in section 4.8 (Undesirable Effects).

Cardiac Conduction Disorders

Two serious cases of unlisted ADRs relating to cardiac conduction disorders were reported during the reporting period. One case reported a worsening of Wolff-Parkinson White syndrome in a 12-year old male patient and the other case reported atrioventricular block in a 9-year old male with a normal ECG prior to starting atomoxetine. He was continuing on treatment at the time of reporting.

Assessor's comments: *Wolff-Parkinson White syndrome is a congenital condition and thus is unlikely to be related to atomoxetine treatment.*

A total of 5 serious cases of AV block have been reported for Strattera since first launch – 'Atrioventricular block' (1); 'Atrioventricular block first degree' (2); and 'Atrioventricular block second degree' (2). Four of these cases were included in the cumulative review of cardiac disorders that was performed as part of the risk:benefit assessment in January 2006. It was concluded that there was insufficient evidence of a causal association at that time.

Myocardial Disorders

There were two serious cardiac ADRs relating to myocardial disorders (Congestive cardiomyopathy and myocardial infarction). The case of congestive cardiomyopathy had a fatal outcome. Both are included in the section relating to the Cardiac Disorders SOC (Section 6.1.2).

Assessor's comments: *The fatal case concerns a 6-year old male who died due to cardiac arrest and congestive cardiomyopathy. This case is confounded by the patients medical history (Polands syndrome). This case was also included in the risk:benefit assessment in January 2006 and also in the PhVWP review of cases of Sudden death reported for atomoxetine. The review of sudden death was presented to the PhVWP in the meeting of October 2006.*

The case of myocardial infarction in a 45-year old male is confounded by the patients medical history of obesity and high cholesterol.

Abnormal ECG Findings

There were 5 cases containing unlisted ADRs relating to abnormal ECG findings (4 serious). Four of the serious cases reported QT (or QTc) interval prolongation in 8-year old, 11-year old, 15-year old (overdose case), and 18-year old patients. One of these patients had a history of left ventricular hypertropia. The fifth case reported an unspecified '*electrocardiogram abnormal*' in a 7-year old patient who was concomitantly receiving mirtazepine, aripiprazole and clonidine.

Assessor's comments: *Following the risk:benefit assessment of Strattera in January 2006 QT interval prolongation is now listed in section 4.8 (Undesirable Effects) of the EU SmPC for Strattera.*

The MAH has conducted a retrospective epidemiological study of cardiovascular and cerebrovascular safety outcomes in adults. The final study report was considered by PhVWP at the meeting in October 2006. The study results appeared reassuring with respect to cardiac arrhythmias however the MAH is conducting further analyses of codes relating to cardiac arrhythmias as part of a List of Questions which resulted from the PhVWP assessment and discussion.

In addition to this epidemiological study in adults, the MAH has proposed a study protocol for a thorough QT study in CYP2D6 metabolisers to further assess the risk for QT interval prolongation associated with atomoxetine treatment. An assessment of the protocol proposals will be circulated to CMSs and discussed at a meeting of the PhVWP in Spring 2007.

In summary, this overview of cardiac ADRs reported to be associated with atomoxetine for the 6-month period covered by this PSUR does not highlight any significant new safety signals. The MAH should perform a comprehensive review of syncope as proposed and continue to closely monitor all cardiac adverse events reported for atomoxetine.

CONCLUSIONS

This is the 5th Periodic Safety Update Report for Strattera and covers the 6-month period from 27 May 2005 to 26 November 2005.

Atomoxetine was first authorised in the United States on 26 November 2002. During the 36-month period from first authorisation to the end of this PSUR period (26 November 2005) it is estimated that the worldwide patient exposure for atomoxetine was 3,710,000 patients. For the 6-month period covered by this PSUR the worldwide patient exposure for atomoxetine is estimated to be 1,302,000 patients.

A total of 1601 medically confirmed case reports have been reported during the 6-month reporting period from 27 May 2005 to 26 November 2005. Based on the 1324 reports that provided details regarding the patients age, the average patient age was found to be 15.9 years and the median age was 12 years. A total of 2963 ADRs are presented by the MAH in the summary tabulations. Of these 2963 reactions, 365 were classified as serious.

Adverse Drug Reactions coding to the Psychiatric Disorders SOC were the most frequently reported ADRs for this PSUR period (1001 reactions or 38% of total reactions). The most commonly reported psychiatric disorders were: aggression (121); suicidal ideation (112); abnormal behaviour (46); depression (46); irritability (45) and insomnia (40). The majority of these are labelled reactions. In addition, following review of the reported psychiatric ADRs in section 6.1.19, the MAH is requested to justify not adding 'depressed mood' and 'anxiety' to the main table of adverse events in section 4.8 (Undesirable Effects) of the SPC for Strattera, as well as to perform cumulative reviews of all reported cases of hallucinations, mania, agitation, and psychotic reactions with a view to adding these to section 4.8 of the SPC should there be evidence of a causal association between these events and atomoxetine treatment. Section 4.4 of the SPC already states that 'As with all other

psychotropic medication, the possibility of rare, serious psychiatric adverse effects cannot be excluded'.

The second, third, fourth and fifth most frequently reported System Organ Classes were the 'Nervous System Disorders' (342 reactions, 11.5%), 'Gastrointestinal Disorders' (318 reactions, 10.7%), 'Investigations' (292 reactions, 9.9%), and 'General Disorders and Administration Site Conditions' (243 reactions, 8.2%) SOCs respectively. The most frequently reported reactions in the Gastrointestinal Disorders and Investigations SOCs are listed in the EU SmPC for Strattera as recognised adverse effects of the drug. Headache (62 cases) and psychomotor hyperactivity (14 cases) are two of the most frequently reported nervous system disorders and are unlisted reactions. Headache is not listed in section 4.8 of the SPC for children (although it is for adults) and the MAH is requested to add headache to the SPC for children should there be cases reported in children. Psychomotor hyperactivity was considered in the cumulative review of movement disorders. Drug ineffective (60), feeling abnormal (27), and chest pain (14) are unlisted reactions coding to the General Disorders and Administration Site Conditions SOC. A review of efficacy related information in section 8 of this report did not raise any new concerns. 'Feeling abnormal' is a vague term and it is questionable as to whether further review of these cases would provide better characterisation of these events. The MAH should continue to monitor these cases. With respect to chest pain, the MAH is requested to provide a cumulative review of all reported cases with a view to adding this term to the SPC should evidence of a causal association be found.

A comparison with data from the previous 6-month PSUR review period indicates that the top five reported System Organ Classes are the same. However, there is a large increase in the number of psychiatric adverse events for the current review period compared with the last PSUR. This is likely due to stimulated reporting following the Dear Doctor Letters and media activity around the issue of suicidal behaviours.

Analysis of data presented in Section 6 and the relevant line listings also raised potential signals regarding rhabdomyolysis, paraesthesia and dysaesthesias, and migraine. The MAH is requestsed to cumulatively review all serious and non-serious reports of these events with a view to adding them to Section 4.8 of the SPC should there be evidence of a causal association.

The reviews of efficacy related information, drug interactions, experience with overdose, drug abuse and drug withdrawal syndrome, use in pregnancy and lactation, and the effects of long-term treatment do not highlight any new safety issues.

Analysis of reports relating to use in special patient groups (paediatric, adolescent, adult, elderly, and organ impaired patients) did not highlight any new safety issues.

In the 'Special Topics' section of this PSUR the MAH provided cumulative reviews of spontaneous ADRs relating to suicidal and self-injurious behaviours, hepatic effects, seizure-related events, movement disorders, cerebrovascular accident and related events, serious skin reactions, and blood dyscrasias. An overall summary of the ADRs relating to Cardiac Disorders which were reporting during this 6-month

PSUR reporting period was also provided in this section. The following conclusions were drawn from these reviews:

- With respect to suicidal and self-injurious behaviours, hepatic events, and seizure-related events, these ADRs are listed in the EU SmPC for Strattera and the data presented in these updated reviews do not provide any new information which would warrant any further updates to the SPC at present.
- Based on the data reviewed there is insufficient eveidence of a causal association between atomoxetine and cases of serious skin reactions, and blood dyscrasias.
- There is insufficient evidence at present to establish a causal association between atomoxetine and cases of dyskinesia. However, the MAH is requested to (i) provide further clarification as to the criteria used for determining that the 700 reported cases of psychomotor hyperactivity were related to an exacerbation of the underlying ADHD which resulted in exclusion of these cases from this review; (ii) provide an overview of the 327 non-serious cases of tic reported for atomoxetine which are excluded from the review; and (iii) should justify not adding tremor to the main table of adverse events in section 4.8 of the SPC for Strattera.
- The overview of cardiac disorders reported during this PSUR period does not provide any evidence of a causal association between atomoxetine and the reported events. The MAH should perform a review of syncopal events as proposed and continue to closely monitor cardiac disorders in future PSURs.
- The PhVWP previously reviewed the review of Cerebrovascular adverse events at the meeting in October 2006. PhVWP recommended that a possible interaction between atomoxetine, a previous medical history of migraine and a further increased risk of stroke should be investigated further. It was noted that in a number of the reported cases of cerebrovascular adverse events, the patients had a history of migraine. Whilst migraine itself is considered to be a risk factor for stroke, atomoxetine is known to have vasospastic effects in the peripheral vasculature and thus a similar effect in the brain cannot be excluded.

The overall balance of risks and benefits of Strattera in its licensed indication remains favourable. However, it is recommended that the Marketing Authorisation Holder (MAH) should be requested to address the points outlined in the Recommendations section below to ensure the future safe use of the product.

RECOMMENDATIONS

(1) The MAH is requested to submit a type II variation to update section 4.8 (Undesirable effects) of the SPC for Strattera as follows;

- To include allergic/hypersensitivity reactions in-line with the information already included in section 4.4 of the SPC.
- To include 'depressed mood', 'anxiety', and 'tremor' in the table of adverse events.
- To include 'headache', 'urinary retention', 'urinary hesitation', and 'hyperhidrosis' in the adverse events table for children and adolescents in line with the information included in the SPC for adults (if it is confirmed that these ADRs have been reported in children and adolescents)

(2) The MAH is requested to perform a review of all spontaneous reports (serious and non-serious) of the following adverse events with a view to inclusion in Section 4.8 (Undesirable Effects) of the SPC should there be evidence of a causal association with atomoxetine:

- Hallucinations
- Mania
- Agitation
- Psychotic reactions
- Rhabdomyolysis
- Paraesthesia & dysaesthesias
- Chest pain
- Migraine & migraine aggravated
- Syncope (as proposed by the MAH)

(3) The MAH is requested to submit further information regarding the review on movement disorders as follows:

- Provide further clarification as to the criteria used for determining that the 700 reported cases of psychomotor hyperactivity were related to an exacerbation of the underlying ADHD which resulted in exclusion of these cases from this review;
- Provide an overview of the 327 non-serious cases of tic reported for atomoxetine which are excluded from the review.

(4) The MAH should continue to closely monitor the following:

- Cardiac disorders
- Psychiatric adverse events including suicidal behaviours and self-injurious behaviours
- Hepatobiliary disorders
- Glaucoma
- Anorexia, weight loss, and growth retardation