HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

19 January 2011

STRATTERA 10 mg, hard capsules
B/28 (CIP code: 347 086-4)

STRATTERA 18 mg, hard capsules
B/28 (CIP code: 347 090-1)

STRATTERA 25 mg, hard capsules
B/28 (CIP code: 347 094-7)

STRATTERA 40 mg, hard capsules
B/28 (CIP code: 347 098-2)

STRATTERA 60 mg, hard capsules
B/28 (CIP code: 347 101-3)

STRATTERA 80 mg, hard capsules
B/28 (CIP code: 347 107-1)

STRATTERA 100 mg, hard capsules
B/28 (CIP code: 347 110-2)

Applicant: LILLY

atomoxetine
ATC code: NO6BA09

List I

Initial biannual prescription in hospital reserved for specialists and/or departments specialized in neurology, psychiatry or paediatrics.

Date of Marketing Authorisation (mutual recognition): 28/06/2010

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Atomoxetine

1.2. Background

Atomoxetine is a selective noradrenaline reuptake inhibitor.
Atomoxetine is not a psychostimulant and is not an amphetamine derivative.

1.3. Indication

“STRATTERA is indicated for the treatment of Attention Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10.

Additional information for the safe use of this product
A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractability, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Pharmacological treatment is not indicated in all children with this syndrome and the decision to use the product must be based on a very thorough assessment of the severity of the child’s symptoms in relation to the child’s age and the persistence of symptoms".

1.4. Dosage

“For oral use. STRATTERA can be administered as a single daily dose in the morning, with or without food. Patients who do not achieve a satisfactory clinical response (tolerability or efficacy) when taking STRATTERA as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

Dosage in children/adolescents up to 70 kg 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 tolerance. The recommended maintenance dose is approximately 1.2 mg/kg/day (depending on the patient’s weight and available dosage strength of atomoxetine). No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day. The tolerance of single doses over 1.8 mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated. It some cases it might be appropriate to continue treatment into adulthood.

Dosage in children/adolescents over 70 kg body weight

STRATTERA should be initiated at a total daily dose of 40 mg. 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 80 mg.

No additional benefit has been demonstrated for doses higher than 80 mg (SPC). The maximum recommended total daily dose is 100 mg. The tolerance of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated. In some cases it might be appropriate to continue treatment into adulthood.

Additional information for the safe use of this product

Atomoxetine should be used in accordance with national clinical guidance on treatment of ADHD where available.

In the study programme, no distinct withdrawal symptoms have been described. In cases of significant adverse events, atomoxetine may be stopped abruptly; otherwise, the drug may be tapered off over a suitable time period.

Where patients are continuing treatment with atomoxetine beyond 1 year, re-assessment of the need for therapy by a specialist in the treatment of ADHD is recommended.

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with STRATTERA in adults is not appropriate.

Special populations “see SPC”

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

N	Nervous system
N06	Psychoanaleptics
NO6B	Psychostimulants, treatments used for ADHD and nootropics
NO6BA	Centrally acting sympathicomimetics
NO6BA09	Atomoxetine

2.2. Medicines in the same pharmaco-therapeutic category

Comparator medicines

Methylphenidate-based proprietary drugs with the same indication as STRATTERA:

- CONCERTA LP 18 mg, 36 mg and 54 mg, prolonged-release tablet
- QUASYM LP 10 mg, 20 mg and 30 mg, modified-release hard capsule
- RITALINE LP 20 mg, 30 mg and 40 mg, modified-release hard capsule
- RITALINE 10 mg, tablet

Reminder of IAB levels:

- RITALINE 10 mg tablet (Committee's Opinions dated 8 and 22 November 1995):

"The lack of validated therapeutic alternatives and the need for children to receive treatment so that their learning abilities are not compromised and in order to prevent them developing antisocial personality, lead us to propose a significant improvement in actual benefit (grade II) in terms of efficacy, despite some uncertainty as to long-term tolerance."

- RITALINE LP (Committee's Opinion dated 14 January 2004):

"The data submitted in the dossier is not sufficient to grant the proprietary drug RITALINE LP an improvement in actual benefit grade any higher than IV (minor IAB) in terms of ease of use compared to immediate-release methylphenidate.

The consequences of this ease of use in terms of management and clinical benefit are less certain than for CONCERTA LP, especially with regard to the effect more than 8 hours after administration."

- CONCERTA LP (Committee's Opinion dated 29 October 2003):

"The proprietary drug CONCERTA LP offers a minor improvement in actual benefit (IAB IV) in terms of ease of use compared to immediate-release methylphenidate."

- QUASYM LP (Committee's Opinion dated 10 March 2010):

"IAB V compared to other immediate-release or prolonged-release methylphenidate-based proprietary drugs."

2.3. Medicines with a similar therapeutic aim

None

3. ANALYSIS OF AVAILABLE DATA

Background:
Atomoxetine was granted marketing authorisation in 2002 in the United States, in 2004 in the United Kingdom, and subsequently under the mutual recognition procedure for other European countries between 2004 and 2005 (with the exception of France where marketing authorisation was granted on 28 June 2010 following the third wave of mutual recognition). This proprietary drug was supplied on a named-patient basis under the temporary authorisation of use system in France between 2004 and 2010.

The dossier submitted by the pharmaceutical company contains 17 studies (two phase II, 14 phase III and one phase IV). The LYBO study evaluating the potential for misuse among adults will not be described here as it relates to a population which is not validated by the marketing authorisation.

3.1. Efficacy

3.1.1 Placebo-controlled studies

A. Short-term treatment

- **Children and adolescents who may or may not have previously received stimulant treatment:**

The efficacy and tolerance of atomoxetine in one or two daily doses have been evaluated in children and adolescents suffering from Attention Deficit/Hyperactivity Disorder (ADHD):

- subjects who may or may not have previously been treated with stimulants in six randomised, double-blind, placebo-controlled studies lasting six to nine weeks (LYAC, LYAT, LYAW, LYBG), two of which included a methylphenidate arm (HFBD, HFBK studies);
- subjects who had not previously been treated with stimulants in a randomised, double-blind, placebo-controlled study lasting 12 weeks (LYDM study).

Main inclusion criteria:
- ADHD diagnosed according to the DSM-IV criteria, documented by clinical assessment and a semi-structured psychiatric interview (K-SADS-E or K-SADS-PL);
- aged between six and 18 years depending on the study;
- severe symptoms, defined by the following scores:

- >1.5 standard deviation for age, gender and clinical sub-type on the ADHD-RS-IV-Parent:Inv scale[1] (studies HFBD, HFBK, LYAC, LYAT, LYBG and LYDM) and a CGI-ADHD-S score of ≥ 3 (only in the LYAC study).
- > 1 standard deviation on the ADHDRS-IV-Teacher:Inv scale[2] and a CPRS-R:S score of > 1.5 standard deviation for age and gender (LYAW study).

Main exclusion criteria:
- the following psychiatric history: risk of suicide or homicide, bipolar disorder or psychosis, antipsychotic treatment in the four weeks prior to inclusion (26 weeks for the LYAC study), MAOI treatment in the past 14 days or fluoxetine treatment in the past four or five weeks, concomitant psychotropic treatment;
- past or present abuse of psychogenic substances (alcohol, illegal drugs or medication);
- the following medical history: organic neurological disease, epilepsy, sympathicomimetic treatment, arterial hypertension, history of severe disease (HIV, leukaemia in remission, etc.), recently diagnosed and/or unstable thyroid disease (LYAT, LYAW studies), slow metabolisers (HFBD, HFBK studies);
- allergy to methylphenidate, history of glaucoma, tics or Tourette's syndrome for studies HFBD and HFBK which included methylphenidate treatment arms.

Treatments: see table 1

Primary efficacy endpoint: change in the total ADHDRS-IV-Parent:Inv score (or ADHDRS-IV-Teacher:Inv score in the case of the LYAW study) between inclusion and the end of the study.
For the HFBD and HFBK studies, the assessment was performed on all patients and on two sub-groups (patients who may or may not have been previously treated with stimulants).

Among the secondary endpoints:
- percentage of responsive patients among patients receiving treatment with atomoxetine and placebo for at least three weeks.
  Response was defined by a reduction in:
  - the total ADHDRS-IV-Parent:Inv score of ≥ 25% compared to the baseline value in the seven studies and the total ADHDRS-IV-Teacher:Inv score of ≥ 40% in study LYAW (definition 1);
  - the CGI-ADHD-I score (in studies HFBD, HFBK) or the CGI-ADHD-S score (in studies LYAC, LYAT, LYBG) to ≤ 2 at the end of the study (definition 2). For study LYDM, a reduction in the CGI-ADHD-S score of ≥ 2 points.
- for studies HFBD et HFBK: change in the total ADHDRS-IV-Parent:Inv score between inclusion and the end of the study in patients who had not previously been treated with a stimulant between the atomoxetine and placebo groups and the methylphenidate and placebo groups;

Results:
The characteristics of the 1,257 patients randomised in the seven studies were:
- average age between 9.5 and 11.2 years;
- proportion of boys between 71% and 81%;
- between 29% and 52% of patients had never previously received stimulant treatment (100% in the methylphenidate groups and in study LYDM);
- between 58% and 84% of patients had the mixed sub-type of ADHD (inattentive and impulsive) and between 16% and 41% had the inattentive sub-type;

[1] The ADHD-RS-IV-Parent:Inv scale allows doctors to evaluate ADHD symptoms present at home on the basis of the parents' reports. It contains 18 items (corresponding to the 18 ADHD symptoms listed in DSM-IV), scored from 0 (symptom never or rarely present) to 3 (symptom very often present). The total score (ranging from 0 to 54) is the sum of the scores for each item.
[2] This scale is identical to the ADHDRS-IV-Parent:Inv scale, except that the doctor evaluates the ADHD symptoms present at school on the basis of a telephone interview with the teacher.

- between 19% and 54% of patients had oppositional defiant disorder.

In each of the 7 studies, the decline in the score measured on the ADHDRS scale (primary efficacy endpoint) was significantly higher with atomoxetine taken once or twice daily (between -12.8 and -16.8 points) than with placebo (-5 to -7.2 points) after 6 to 12 weeks of treatment (see table 1).

Table 2 : Change in the total ADHDRS score from inclusion to the end of the study (primary efficacy endpoint)

Studies	Treatment	Length of treatment	N	Average baseline score	Average change at end of study	p *vs.* placebo	% responders at end of study			
							Definition 1	p *vs.* placebo	Definition 2	p *vs.* placebo
HFBD N=147 Phase II	Atomoxetine 5 to 90 mg/d in 2 doses	9 weeks	64	41.2	-15.6	<0.001	64.1%	<0.001	46.9%	0.019
	Placebo		61	41.4	-5.5	-	24.6%	-	14.8%	-
HFBK N=144 Phase II	Atomoxetine 5 to 90 mg/d in 2 doses	9 weeks	63	37.8	-14.4	<0.001	58.7%	0.048	44.4%	0.024
	Placebo		60	37.6	-5.9	-	40%		24.6%	-
LYAC N=296 Phase III	Atomoxetine 0.5 mg/kg/d in 2 doses	8 weeks	43	40.2	-9.9	NS	46.5%	NS	16.3%	NS
	Atomoxetine 1.2 mg/kg/d in 2 doses		84	39.2	-13.6	<0.001	56%	<0.001	22.6%	NS
	Atomoxetine 1.8 mg/kg/d in 2 doses		82	39.7	-13.5	<0.001	56.1%	<0.001	20.7%	NS
	Placebo		83	38.3	-5.8	-	30.1%	-	12%	
LYAT N=171 Phase IV	Atomoxetine 1.5 mg/kg/d or 100 mg/d in 1 dose	6 weeks	84	37.6	-12.8	<0.001	59.5%	<0.001	28.6%	0.003
	Placebo		83	36.7	-5.0	-	31.3%	-	9.6%	-
LYBG N=197 Phase III	Atomoxetine 1.8 mg/kg/d or 120 mg/d in 1 dose	8 weeks	126	42.1	-16.8	<0.001	62.7%	<0.001	27%	<0.001
	Placebo		60	42.3	-7.0	-	33.3%	-	5%	-
LYAW N=153 Phase III	Atomoxetine 1.8 mg/kg/d or 120 mg/d in 1 dose	7 weeks	100	38.9	-14.5	<0.001	48%	NS	-	-
	Placebo		51	36.7	-7.2	-	31.4%		-	-
LYDM N=149 Phase III	Atomoxetine 1.2 mg/kg/day in 1 dose	12 weeks	99	39.7	-13.1	<0.001	62.6%	<0.001	39.4%	<0.001
	Placebo		50	39.6	-5.1	-	22%	-	14%	-

Secondary endpoints:

- The percentage of responsive patients was higher in the atomoxetine groups (16.3 to 64.1%) than in the placebo groups (5 to 40%) depending on the study and the definition of responders (see table 1).

- In the two phase II studies (HFBD and HFBK) which included a methylphenidate arm, the following findings were established for patients who had not previously received stimulant treatment (naïve patients):
    - the reduction in the ADHDRS score was significantly higher with atomoxetine (-15.1 points) than with placebo (-4.2 points) in the HFBD study, while no difference between the two groups (-18 vs. -9.1 points) was found in the HFBK study.
    - the decline in the ADHDRS score was significantly greater with methylphenidate than with placebo in both studies (-17.3 vs. -4.2 points in the HFBD study and -23.2 vs. -9.1 points in the HFBK study) (see table 2).

Table 4: Change in the ADHDRS-IV-Parent:Inv score in the two strata (studies HFBD and HFBK)

Studies	Strata	Treatment	N	Average baseline score	Average change at end of study	p vs. placebo
HFBD Phase II	Naïve patients	Atomoxetine 5 to 90 mg/d in 2 doses	30	39.4	-15.1	0.0015
		Placebo	27	39.6	-4.2	-
		Methylphenidate 5 to 60 mg/d in 2 doses/d	30	38.6	-17.3	0.0003
	Non naïve patients	Atomoxetine 5 to 90 mg/d in 2 doses	34	42.8	-16.0	0.0091
		Placebo	34	42.9	-6.6	-
HFBK Phase II	Naïve patients	Atomoxetine 5 to 90 mg/d in 2 doses	25	36.6	-18.0	NS
		Placebo	24	35.9	-9.1	-
		Methylphenidate 5 to 60 mg/d in 2 doses	17	37.9	-23.2	0.0071
	Non naïve patients	Atomoxetine 5 to 90 mg/d in 2 doses	38	38.6	-12.1	0.0059
		Placebo	36	38.7	-3.7	-

- **Children with oppositional defiant disorder (ODD): LYBX**

Randomised, double-blind, phase III study evaluating the effects of atomoxetine versus placebo on ODD symptoms in children diagnosed with ADHD and ODD according to the DSM-IV, a sub-score ≥ 15 on the SNAP-IV scale[3] and an ADHD sub-score on the SNAP-IV scale higher than would be expected for an individual of the patient's age and gender.
The primary efficacy endpoint was the change in the "opposition" sub-score on the SNAP-IV scale after eight weeks of treatment.
The secondary endpoints included the percentage of responders, changes in the CGI-S and CGI-I score, and the ADHD sub-score on the SNAP-IN scale.

The children (average age 9.6 years, n=226) were randomised into two groups: placebo (n=70) or atomoxetine at a dosage of 0.8 mg/kg/day for three days, followed by 1.2 mg/kg/day in a single dose (n=156). This study protocol did not include any psychological measures. No adolescents were included.
Almost two-thirds of the children had previously been treated with a stimulant (69%) and 84.5% of them had a mixed form of ADHD (inattentive and impulsive).

[3] SNAP-IV scale evaluating ADHD and ODD symptoms. This scale includes 26 items (18 for the 18 ADHD symptoms referred to in the DSM-IV and 8 for the 8 ODD symptoms referred to in the DSM-IV). The items are scored from 0 (symptom not present) to 3 (symptom very frequent), producing a total score ranging from 0 to 78. The opposition sub-score measures opposition symptoms (items 19 to 26) and ranges from 0 to 24. The other sub-scores measure symptoms of inattention (items 1 to 9) and hyperactivity/impulsivity (items 10 to 18) in ADHD.

On inclusion, the average “opposition” sub-score of the children was 18.9 on the SNAP-IV scale.

The results of an analysis of repeated measurements of the “opposition” sub-score on the SNAP-IV scale (primary efficacy endpoints) showed that the overall effect of atomoxetine was greater than that of placebo after eight weeks of treatment (p=0.01). The difference observed for the « opposition » sub-score on the SNAP-IV scale was significant after 2 (p=0.003) and 5 weeks of treatment (p=0.043), but not after 8 weeks of treatment (NS).
The percentage of responders and changes in the CGI-S and CGI-I scores, and in the ADHD sub-score on the SNAP-IN scale, were higher in the atomoxetine group (secondary endpoints).
No information is available on the change in the total ADHDRS-IV-Parent:Inv score.

In absence of long-term data and robust proof that atomoxetine is effective in the short term in controlling ODD symptoms in children diagnosed with ADHD and ODD, it is difficult to determine the clinical relevance of the effect of the treatment. Furthermore, no data on adolescents is available.

N.B.:

The SPC for methylphenidate was harmonised following the EMA's assessment of the substance because of concerns about its safety (decision of the European Commission on 27 May 2009).
This harmonisation of the SPC is currently taking place at national level. From this point on (from 18/10/2010 for CONCERTA), a family history or diagnosis of Tourette's syndrome are no longer a contraindication but a warning.
Some contraindications have been reworded: “pronounced anxiety and tension, severe depression, psychotic symptoms or suicidal tendencies as the product can aggravate these pathologies” had been replaced by:
- “Diagnosis or history of severe depression, mental anorexia or anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic or borderline personality disorder.
- Diagnosis or history of episodic and severe (affective) bipolar disorder (type I) which is poorly controlled.”

New warnings have been added, particularly with regard to psychiatric disorders and anxiety, in order to mention the need for regular monitoring of the onset or worsening of these symptoms.

- **Children and adolescents with ADHD associated with anxiety disorders: LYBP**

Randomised, double-blind, placebo-controlled phase III study evaluating the effects of atomoxetine on ADHD and anxiety symptoms in children and adolescents with ADHD as defined by the DSM-IV and an anxiety disorder (generalised anxiety disorder, social phobia, etc.) confirmed by K-SADS-PL. The PARS[4] score had to be at least 15.
The primary efficacy endpoints were changes in the ADHDRS-IV-Parent:Inv and PARS[4] scores after 12 weeks of treatment.
The secondary endpoints included the percentage of responders defined by a reduction of ≥ 25% in the ADHDRS-IV-Parent:Inv score.

After initially taking placebo for 2 weeks, only qualified patients, observed to have a maximum decline of 25% in the PARS score, were randomised to two groups: placebo or atomoxetine at 1.2 to 1.8 mg/kg/day taken in two doses per day. 43 of the 176 children and adolescents who were randomised were excluded from the principal analysis.

[4] PARS (Pediatric Anxiety Rating Scale) evaluates the severity of anxiety among children and adolescents aged between 6 and 17 and is completed by the doctor during an interview with the parents and the child. It includes two parts: one part evaluating the anxiety symptoms presented by the child in the preceding week and seven severity items. The total score calculated on the basis of the severity items 2, 3, 5, 6 and 7 ranges from 0 to 25. Items 1 (total number of anxiety symptoms) and 4 (overall severity of physical symptoms) are not included in the total score.

The average age of the patients was 12 years. More than half of the randomised patients had previously been treated with stimulants (61% in the atomoxetine group and 64% in the placebo group).

A significant reduction in the ADHDRS-IV-Parent:Inv and PARS scores compared to the baseline values was observed after 12 weeks of treatment between the atomoxetine and placebo groups (see table 3).

Table 3: Results for the primary efficacy endpoints in the LYBP study

LYBP study	**Average initial score**				**Average change at end of study**				p
Scores	N	Atomoxetine	N	Placebo	N	Atomoxetine	N	Placebo	
ADHDRS-IV-Parent:Inv									
Qualified patients (principal analysis)	55	33.9	58	34.2	55	-10.5	58	-1.4	<0.001
ITT	78	30.8	78	32.4	78	-9	78	-0.7	<0.001
PARS									
Qualified patients (principal analysis)	55	17.5	58	17	55	-5.5	58	-3.2	<0.01
ITT	78	15.6	78	15.3	78	-4.5	78	-2.4	<0.001

The percentage of responders (secondary endpoint) was higher in the atomoxetine group than in the placebo group (34/55 (61.8%) vs. 7/58 (12.1%)).
Contact was lost with 25% of participants.

- **Adolescents with ADHD associated with depression: LYAX**

Randomised, double-blind, placebo-controlled phase III study evaluating the effects of atomoxetine on symptoms of depression in adolescents with ADHD associated with depression (according to K-SADS-PL).
The CDRS-R[5] score had to be at least 40 and the ADHDRS-IV-Parent:Inv score had to be over 1.5 standard deviation for age, gender, and the attention, hyperactivity or mixed sub-types.
The primary efficacy endpoints were change in the total score on the ADHDRS-IV-Parent:Inv and CDRS-R scales after 9 weeks of treatment.

The study protocol provided for 240 patients. The study was stopped prematurely because recruitment was too slow. The results available were therefore taken from an analysis conducted on 142 children and adolescents with an average age of 14.4 years.
Patients were randomised to two groups: placebo (n=70) or atomoxetine at doses of 1.2 to 1.8 mg/kg/day taken once a day (n=72). The total ADHDRS-IV-Parent:Inv score on inclusion was 34.5 in the atomoxetine group and 33.7 in the placebo group, and the CDRS-R scores were 53.4 and 52 (moderate severity).
Most of the patients who were randomised had previously been treated with stimulants (81%).

A significant reduction in the ADHDRS-IV-Parent:Inv score compared to the baseline value was observed after 9 weeks of treatment between the atomoxetine and placebo groups (-13.3 vs. -5.1 points, p<0.001). However, there was no difference between the two groups in respect of change in the CDRS-R score (-14.8 vs. -12.8 points, NS).
The values observed for these two criteria are probably overestimates given the suspension of the study after an intermediate analysis.

[5] The CDRS-R scale allows doctors to evaluate the presence and severity of depressive symptoms. It is made up of 17 items, 14 of which are scored on the basis of the child's speech and 3 on his or her non-verbal behaviour. A score of < 20 indicates no depression; 20-30: borderline depression; 31-40: mild depression; 41-60: moderate depression and > 60: severe depression.

- **Children and adolescents with ADHD and tics: LYAS (non-inferiority)**

Randomised, double-blind, placebo-controlled phase III non-inferiority study evaluating the effects of atomoxetine on tics in children and adolescents with ADHD and tics (Tourette's syndrome or chronic motor tics).
The primary efficacy endpoint was change in the Yale tic severity scale (YGTSS[6]) after 18 weeks of treatment.
Non-inferiority was established if the lower limit of the 95% confidence interval (95% CI) of the difference between atomoxetine and placebo in the average changes in the YGTSS score after 18 weeks of treatment was above -3.7; this figure is equivalent to one-third of the average reductions in the YGTSS score observed in previous studies.
The secondary endpoints included the percentage of responders defined by a reduction of ≥ 25% in the YGTSS score and the change in the ADHDRS-IV-Parent:Inv score.

148 children and adolescents, average age 11.2, were randomised into two groups: placebo (n=72) or atomoxetine at doses of 0.5 to 1.5 mg/kg/day, in two doses per day (n=76).
Most of the patients who were randomised had previously been treated with stimulants (68.2%). The total YGTSS scores on inclusion were 21.7 in the atomoxetine group and 22.2 in the placebo group (mild to moderate severity).

The average change in the YGTSS score was -5.5 in the atomoxetine group and -3 in the placebo group after 18 weeks of treatment.
The lower limit of the 95% CI of the difference in the average changes in the YGTSS score between atomoxetine and placebo [-0.13; 4.88] after 18 weeks of treatment was greater than -3.7. Consequently, the non-inferiority of atomoxetine to placebo in reducing the severity of tics was demonstrated.

The percentage of responders on the YGTSS score was not different between the atomoxetine and placebo groups (50% vs. 33.8%; NS). The reduction of the ADHD-RS score was higher with atomoxetine (10.9 points) than with placebo (4.9 points); p=0.002.

B. Maintenance treatment

The efficacy of maintenance treatment was evaluated in one phase II study (HFBE) and one phase III study (LYAF).
The pharmaceutical company did not present the HFBE study in its dossier as it was an inconclusive placebo-controlled phase II study.

A randomised, double-blind phase III study (LYAF) compared the efficacy and tolerance of atomoxetine to those of placebo over the course of nine months in preventing relapse in patients with ADHD according to the DSM-IV criteria and who responded to atomoxetine treatment in an open-label 10-week phase.
During the open-label phase, patients were treated with atomoxetine at a starting dosage of 0.5 mg/kg/day, taken twice a day. The target dosage was 1.2 mg/kg/day, taken twice a day, up to a maximum of 1.8 mg/kg/day.
The inclusion and non-inclusion criteria were identical to those of the short-term studies.

Among the 604 patients included in the open-label phase, 416 patients who had responded to atomoxetine after 10 weeks (69%) were randomised to receive either atomoxetine (292 patients) or placebo (124 patients) during a nine-month double-blind phase. The responders were defined by a CGI-ADHD-S score of < 2 and a 25% decline in the total ADHD-RS score compared to baseline.

[6] The YGTSS scale allows doctors to evaluate the severity of motor and vocal tics and is comprised of five items: the number, frequency, intensity, complexity and interference of tics. Each symptom is scored from 0 (non) to 5 (severe/always) for motor and vocal tics, allowing a motor sub-score and a vocal sub-score to be calculated. Each of these sub-scores ranges from 0 to 25. The total score is the sum of the two sub-scores and ranges from 0 to 50.

After the nine months of double-blind treatment with atomoxetine or placebo, patients who maintained their response to atomoxetine (163/292) were re-randomised to receive either atomoxetine (81 patients) or placebo (82 patients) on a double-blind basis for a further six months.

The primary efficacy endpoint was the average time to relapse during the double-blind phase, defined as an increase in the CGI-ADHD-S score of ≥ 2 points compared to the score at the end of the open-label phase and a total ADHDRS-IV-Parent:Inv score of ≥ 90% of the initial score at two successive visits in the qualified population, defined as patients:
- who did not experience relapse at the randomisation visit or the preceding visit,
- or whose CGI-ADHD-S score was stable compared to the score observed at randomisation.

Results:
The average age on inclusion was 10.2 years. Almost half of the patients had previously been treated with a stimulant, and almost two-thirds of them had a mixed form of ADHD.
Among the 416 patients who were randomised to receive either atomoxetine or placebo for nine months, only 295 were analysed (qualified population). This means that 121 patients were excluded from the principal analysis (83 in the atomoxetine group and 38 in the placebo group).

After 10 weeks of open-label treatment and nine months of double-blind treatment, the average time to relapse was longer in the atomoxetine group than in the placebo group (227.7 days vs. 158.1 days; p=0.013 in the qualified population and 217.7 days vs. 146.1 days for all randomised patients, p<0.001). The percentage relapse was 19.0% in the atomoxetine group and 36.9% in the placebo group (p<0.001).

After approximately one year of treatment, the following results were obtained for patients who continued treatment with atomoxetine for a further six months:
- in the qualified population (61 patients having been excluded from this principal analysis): the average time to relapse (160.2 days vs. 130.8 days, NS) and the percentage of relapse (4.2% vs. 13%, NS) were not different between the atomoxetine and placebo groups;
- for all the patients who were randomised: the average time to relapse was 160.5 days in the atomoxetine group and 130.8 days in the placebo group (p<0.008), and the percentage of relapse was 2.5% in the atomoxetine group and 12.2% in the placebo group.

3.1.2 Non-inferiority studies versus methylphenidate: LYBI and LYBR

Table: Results of the two non-inferiority studies (PP)

Studies	Treatment	Length of treatment	N	% of responders	95% CI
LYBI N=516 Phase III	Atomoxetine 0.8 mg/kg/day 1.2 mg/kg/day 1.8 mg/kg/day in 2 doses	6 weeks	213	44.6% * (95/213)	[-21.2; -2.3]
	methylphenidate LP 18 mg/day 36 mg/day 54 mg/day in 1 dose		211	56.4% ** (119/211)	
	placebo		74	23.5% (16/68)	
LYBR N=330 Phase III	Atomoxetine 0.8 mg/kg/day to 1.8 mg/kg/day in 1 dose	8 weeks	164	77.4% (123/159)	[-11.7; not provided]
	methylphenidate 0.2 mg/kg/day to 0.6 mg/kg/day in 2 doses		166	81.5% (128/157)	

* p vs. placebo ≤ 0.001; ** p vs. placebo = 0.003

- **Study LYBI**

Randomised, double-blind, non-inferiority study conducted over six weeks, with the primary objective of comparing the efficacy of atomoxetine with that of methylphenidate LP (and placebo) in 516 children aged between 6 and 16 suffering from ADHD.
This study was carried out in the United States.

Main inclusion criteria:
- ADHD diagnosed according to DSM-IV, documented by a clinical assessment and confirmed by a structured psychiatric interview (K-SADS-PL[7]) ;
- severe symptoms, defined by a score of >1.5 standard deviation for age, gender and clinical sub-type on the ADHDRS-IV-Parent:Inv scale and a score of ≥ 4 on the CGI-ADHD-S scale.

Main exclusion criteria:
- methylphenidate or amphetamines not tolerated or ineffective;
- comorbidities: anxiety disorder (diagnosed by the K-SADS-PL interview), motor tics and Tourette's syndrome;
- the following psychiatric history: risk of suicide, bipolar disorder, psychosis, pervasive developmental disorder, treatment with MAOI in the 14 days prior to inclusion, concomitant psychotropic treatment;
- patient likely to start on structured psychotherapy, or has started such treatment within the month prior to inclusion;
- past or present abuse of psychogenic substances (alcohol, illegal drugs or medication);
- the following medical history: epilepsy (except for febrile convulsions), sympathicomimetic treatment, arterial hypertension, cardiovascular disease, glaucoma, severe gastrointestinal occlusion (chronic inflammatory intestinal disease, Meckel's diverticulum, etc.).

Treatment: see table
The patients were randomised to one of three treatment groups:
- atomoxetine group: 0.8 mg/kg/day, 1.2 mg/kg/day or 1.8 mg/kg/day, taken twice a day;
- methylphenidate LP group (CONCERTA): 18 mg/day, 36 mg/day or 54 mg/day, taken once a day;
- placebo group.

Primary efficacy endpoint: percentage of responsive patients, defined as a reduction of ≥ 40% in the total ADHDRS-IV-Parent:Inv score after six weeks of treatment.
Non-inferiority was established if the lower limit of the 95% confidence interval (95% CI) of the difference between the average percentages of responsive patients after six weeks of treatment in the atomoxetine and methylphenidate LP groups was less than -15%.

Results:
The average age of the children was 10.3 years. Approximately 60% of the children had previously been treated with stimulants, and almost 70% had a mixed form. The average CGI-ADHD-S score on inclusion was 5.
The percentage of responders after six weeks of treatment was 44.6% in the atomoxetine group, 56.4% in the methylphenidate group and 23.5% in the placebo group. The percentage of responders was significantly higher in the atomoxetine and methylphenidate groups than in the placebo group.
The lower limit of the 95% CI of the difference of the average percentages of responders between atomoxetine and methylphenidate LP (95% CI [-21.2; -2.3]) after six weeks of treatment was greater than -15%. Consequently, the non-inferiority of atomoxetine and methylphenidate LP in terms of the percentage of responders was not demonstrated (see table).

[7] K-SADS-PL : Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version

- **Study LYBR**

Randomised, double-blind, non-inferiority study conducted over eight weeks, with the primary objective of comparing the efficacy of atomoxetine with that of methylphenidate LP in 330 children and adolescents aged between 6 and 16 suffering from ADHD.

Main inclusion criteria:
- ADHD diagnosed according to DSM-IV, documented by a clinical assessment and confirmed by a semi-structured psychiatric interview (K-SADS-PL);
- ADHDRS-IV-Parent:Inv score of ≥25 for boys and ≥22 for girls, or score of >12 for one of the sub-types and score of ≥ 4 on the CGI-ADHD-S scale.

Main exclusion criteria:
- subjects who have already taken part in a study evaluating atomoxetine;
- methylphenidate or amphetamines not tolerated or ineffective in a well-conducted prior study;
- comorbidities: anxiety disorder (DSM IV and K-SADS-PL), tics and personal or family history of Tourette's syndrome;
- the following psychiatric history: risk of suicide, bipolar disorder, psychotic disorder, pervasive developmental disorder, concomitant psychotropic treatment.

Treatment: see table

The patients were randomised to one of two treatment groups:
- atomoxetine group: 0.8 mg/kg/day to 1.8 mg/kg/day taken in one dose a day (n=164);
- methylphenidate group: 0.2 mg/kg/day to 0.6 mg/kg/day taken in two doses a day (n=166);

N.B.: the validated dosage of methylphenidate in France is: 0.3 mg/kg/day to 1 mg/kg/day taken in two or three doses, up to a maximum dose of 60 mg/day.

Primary efficacy endpoint: percentage of responsive patients, defined as a reduction of ≥ 40% in the total ADHDRS-IV-Parent:Inv score after eight weeks of treatment.

Non-inferiority was established if the lower limit of the 95% confidence interval (95% CI) of the difference between the average percentages of responsive patients after six weeks of treatment in the atomoxetine and methylphenidate LP groups was less than -18%.

N.B.: justification of the non-inferiority threshold being set at -18% (protocol, page 43)

The secondary endpoints included: change in ADHDRS-IV-Parent:Inv, CGI-ADHD-S and CPRS-R:S scores between inclusion and the end of the study.

Results:

The average age of the children was 9.7 years.

N.B.: As most of the patients taking part were of Asian (91.5%) or Mexican origin, the results of this study cannot be fully extrapolated to the use of atomoxetine in Europe.

Approximately 24% of the children had previously been treated with methylphenidate, and almost 60% had a mixed form. The average CGI-ADHD-S score on inclusion was 5.3.

The percentage of responders was 77.4% in the atomoxetine group and 81.5% in the methylphenidate group after eight weeks of PP treatment.

The lower limit of the 95% CI of the difference of the average percentages of responders between atomoxetine and methylphenidate LP (95% CI [-11.7; not provided]) after eight weeks of treatment was less than -18%. Consequently, the non-inferiority of atomoxetine and methylphenidate LP in terms of the percentage of responders was demonstrated (see table).

The ITT results were similar (75.9% vs. 81.1%; 95% CI [-12.8; not provided]).

The change in the ADHDRS-IV-Parent:Inv, CGI-ADHD-S and CPRS-R:S scores between inclusion and the end of the study (secondary endpoints) were not different between the atomoxetine and methylphenidate groups.

3.1.3 Other data

- **Study LYAV**

Randomised, double-blind, cross-over phase III study (atomoxetine or methylphenidate) evaluating the time to achieve sound sleep in 85 children and adolescents with ADHD according to the DSM-IV criteria. The ADHDRS-IV-Parent:Inv score had to be > 1 standard deviation for age, gender and sub-type.
The primary efficacy endpoint was the change in time to achieve sound sleep (measured by actimetry) between inclusion and the end of treatment.
The children and adolescents (average age 10.1 years) were randomised into two groups: atomoxetine taken twice daily (0.5 to 1.8 mg/kg/day up to a maximum dose of 120 mg/day) or methylphenidate taken three times daily (0.45 to 1.35 mg/kg/day up to a maximum dose of 60 mg/day) for six to seven weeks. After 10 to 20 treatment-free days, the patients randomised to the atomoxetine group underwent treatment with methylphenidate for six to seven weeks, and vice versa.
The time to achieve sleep was shorter in the atomoxetine group than in the methylphenidate group. The increase in the average time to achieve sleep compared to baseline was 12.06 minutes in the atomoxetine group versus 39.24 minutes in the methylphenidate group ($p<0.001$).
The change in the ADHDRS-IV-Parent:Inv score (-13.31 vs. -11.79) (secondary endpoint) between inclusion and the end of the study was not different between the atomoxetine and methylphenidate groups.

- **Study LYCC**

Randomised, double-blind, placebo-controlled phase III study evaluating the efficacy of atomoxetine taken once daily (in the morning) with that of placebo after six weeks treatment on children aged 6 to 12 years suffering from ADHD according to the DSM-IV criteria. The ADHDRS-IV-Parent:Inv score had to be > 1.5 standard deviation for age, gender and sub-type.
The primary efficacy endpoints were the change in the total ADHDRS-IV-Parent:Inv and Conners-parents-evening[8] scores between inclusion and the end of the study.
Children and adolescents with an average age of 8.9 years were randomised into two groups: placebo (n=93) or atomoxetine (n=195) once daily (0.8 to 1.4 mg/kg/day with a maximum dose of 100 mg/day).
After six weeks of treatment, the reduction in the total ADHDRS-IV-Parent:Inv score (-17.76 vs. -9.51; $p<0.001$) and the Conners-Parents-Evening score (-5.82 vs. -2.03; $p<0.001$) was greater with atomoxetine taken once a day in the morning than with placebo.

- **Study LYBG**

Randomised, double-blind, placebo-controlled phase III study evaluating the efficacy over 24 hours of atomoxetine taken once daily with that of placebo after eight weeks treatment in children aged 6 to 12 years suffering from ADHD according to the DSM-IV criteria. The ADHDRS-IV-Parent:Inv score had to be > 1.5 standard deviation for age, gender and sub-type.
The primary efficacy endpoint was the change in the total ADHDRS-IV-Parent:Inv score between inclusion and the end of the study.
Children and adolescents with an average age of 9.5 years were randomised into two groups: placebo (n=64) or atomoxetine (n=133) once daily (0.8 to 1.8 mg/kg/day with a maximum dose of 120 mg/day).
After eight weeks of treatment, the reduction in the total ADHDRS-IV-Parent:Inv score was greater with atomoxetine taken once daily than with placebo (-16.75 vs. -7.03; $p<0.001$).

[8] The Conners-parents-evening score evaluatees ADHD symptoms in the evening and includes 10 items, each scored from 0 (not at all true/never) to 3 (very true/very often), giving a total score of between 0 and 30. Parents respond indicating their child's behaviour in the evening prior to taking the treatment.

3.2. Tolerance

The tolerance data was obtained from clinical studies versus placebo and methylphenidate and the European Risk Management Plan (especially PSUR 11 and PSUR 12).

3.2.1 Data obtained from studies

A- Placebo-controlled studies

According to the SPC, the most frequently reported adverse events during studies were gastrointestinal complaints and disorders of the central nervous system:

- very common (≥ 1/10): headache (19%), abdominal pain (18%), loss of appetite (16%) and vomiting, nausea, somnolence (10 to 11%),
- common (≥ 1/100 and <1/10): anorexia, irritability, mood swings, insomnia, sensations of vertigo, constipation, dyspepsia, dermatitis, skin eruption, fatigue, lethargy, weight loss, increase in blood pressure.

An average increase in the heart rate of approximately five beats per minute and an increase in systolic blood pressure (approximately 2 mmHg) and diastolic blood pressure (approximately 1 mmHg) were observed compared to placebo.
Some patients taking atomoxetine were observed to have orthostatic hypotension (0.2%) or to faint (0.8%). This is because of the effect which atomoxetine has on the noradrenergic system.

In 2005 the CHMP evaluated various selective serotonin and noradrenalin reuptake inhibitors, including atomoxetine, because of the risk of suicidal behaviour (including attempted suicide, suicidal thoughts and/or self-harming behaviour), hostility and emotional lability among children and adolescents.
A meta-analysis of 12 studies (after excluding patients with a bipolar disorder or a history of risk of suicide) identified an increased risk of suicidal thoughts and behaviour in children being treated with atomoxetine compared with those in the placebo group.
The CHMP concluded that there was no indication of an increased risk of suicidal behaviour in the clinical studies which evaluated atomoxetine, but that there was an increased risk of abnormal behaviour (aggression and hostility).
Consequently, a warning was added: “During clinical trials, hostility (particularly aggression, oppositional behaviour and anger) and emotional lability have been observed more frequently in children and adolescents being treated with STRATTERA than in those being treated with placebo. Patients must be closely monitored for the onset or worsening of aggressive behaviour, hostility or emotional lability".

B- Methylphenidate-controlled studies

- **Study LYBI**

2.3% (12/515) of patients (atomoxetine: 5/221, methylphenidate: 5/220 and placebo: 2/74) stopped treatment because of adverse events.
Five serious adverse events were reported: four in the atomoxetine group and one in the methylphenidate group.
The frequency of adverse events was similar in the atomoxetine and methylphenidate groups (67.4% vs. 66.7% vs. 54.1%).
Among the most frequent adverse events, those reported most frequently were:

- in the atomoxetine group (vs. methylphenidate and placebo): headaches (17.6% vs. 11.4% vs. 9.5%), vomiting (6.8% vs. 3.7% vs. 5.4%), irritability (6.3% vs. 5.9% vs. 1.4%) and somnolence (6.3% vs. 1.8% vs. 4.1%);
- in the methylphenidate group (vs. atomoxetine vs. placebo): loss of appetite (16.9% vs. 14% vs. 2.7%), nausea (5.9% vs. 4.1% vs. 8.1%) insomnia (7.8% vs. 4.1% vs. 1.4%) and insomnia in the early stages of treatment (5.5% vs. 2.7% vs. 0).

- **Study LYBR**

18 patients in the atomoxetine group (11%) and 6 in the methylphenidate group (3.6%) were reported as having stopped treatment because of adverse events.

One severe adverse event (focal motor convulsion) was reported in the atomoxetine group (1/164), leading to discontinuation of treatment.
Adverse events occurred more frequently in the atomoxetine group (86.6% vs. 67.5%).
Among the most frequent adverse events, those reported most frequently in the atomoxetine group (vs. methylphenidate) were: anorexia (37.2% vs. 25.3%), loss of appetite (28% vs. 19.3%), nausea (20.1% vs. 10.2%), somnolence (26.2% vs. 3.6%), headache (15.2% vs. 9.6%), vertigo (15.2% vs. 7.2%), vomiting (11.6% vs. 3.6%).
The CHMP was asked by the European Commission on 22 June 2007 to evaluate the tolerance of methylphenidate-based proprietary drugs, with particular emphasis on the cardiovascular risk.
It has been recognised that additional data on long-term use is still needed so that the potential effect of methylphenidate on cardiovascular and cerebrovascular events can be evaluated. Additional data is also needed to evaluate the psychiatric risk and effects on the growth and development of children. Clinical studies on these problems and on puberty are currently taking place. With regard to the risk of suicide, the marketing authorisation holders have undertaken to use their current knowledge and to conduct a meta-analysis on the results of the various clinical studies that are available.
The SPCs were harmonised following this assessment, and information was strengthened and brought up to date (pre- and post-treatment monitoring, contraindications, warnings, adverse reactions, dosage).

3.2.2 Data obtained from post-marketing experience

According to PSUR 12 (covering the period from 27/11/2008 to 26/5/2009), the adverse events most frequently reported were of a psychiatric nature (30.7%), mainly aggression and suicidal thoughts, central nervous system disorders including headache and somnolence (11.3%) or of a gastrointestinal nature, including nausea and vomiting (11.9%).

In view of the risks identified with atomoxetine, the European Risk Management Plan includes several ongoing studies or analyses:

- PEM (Prescription Events Monitoring) study evaluating the risk of suicide/suicidal thoughts, hepatotoxicity, cardiovascular events, aggression/hostility and convulsions in a cohort of 5,000 patients being treated with atomoxetine.
- retrospective study (covering the period from 2002 to 2006) evaluating signals using the "i3 Aperio" tool to analyse reports of adverse events (suicidality/suicidal thoughts, cardiovascular events, convulsions) which occurred after starting hyperactivity treatment (first 30 days) and comparing 68,273 patients on atomoxetine vs. amphetamines and 68,343 patients on atomoxetine vs. methylphenidate.
  Subject to the methodological shortcomings of this study, no increase in the risk of suicide, convulsions or cardiovascular events were detected in comparison with methylphenidate and amphetamines in the first month of treatment.
- periodic meta-analyses of placebo-controlled studies in paediatric medicine: assessment of the risk of suicide/suicidal thoughts and aggression/hostility.
- retrospective paediatric cohort comparing a population of hyperactive children treated with atomoxetine to a population of hyperactive children treated with stimulants and to a population receiving no treatment: assessment of the risk of convulsions.

A national pharmacovigilance monitoring programme is to be set up in France, and AFSSAPS asked the pharmaceutical firm to conduct a study on use and proper usage in March 2010.

The adverse events most closely monitored and detected during clinical studies or from post-marketing data (PSUR 11 or 12) are:

- confirmed risks:

- risk of suicide (attempted suicide and suicidal thoughts): among self-harming and suicidal behaviour, suicidal thoughts were the elements reported most often.

- risk of liver damage: spontaneous reports show that the risk of severe liver damage is very rare and idiosyncratic. Atomoxetine treatment can be associated with slight to moderate increases in liver enzymes.
- risk of Raynaud's syndrome.
    - potential risks:
- cardiovascular and cerebrovascular risk (increased QT interval, myocardial ischaemia, tachyarrhythmia, CVA/TIA): no causal link between these events and atomoxetine has yet been demonstrated. Additional data is needed, in particular a study to evaluate whether atomoxetine prolongs the QT/QTc interval.
- risk of aggression/hostility: a meta-analysis showed that adverse events relating to aggression and hostility were slightly more common in patients treated with atomoxetine compared to placebo (RR=1.15 95% CI [0.66; 2.02] at the most recent update in November 2008). No data comparing atomoxetine with other treatments is available.
- risk of convulsions: the data available does not allow it to be concluded that atomoxetine is associated with an increased risk of convulsion.

These risks are referred to in the SPC (Special warnings and precautions for use) and type II variations were requested during the assessment of PSUR 11 in order to add other potential risks: anxiety, depression and tics in some patients being treated with atomoxetine and to highlight the risk of suicide.

3.3. Conclusion

Atomoxetine administered once or twice daily has been found by short-term studies (six to 12 weeks) to be more effective than placebo in controlling the symptoms of attention deficit and hyperactivity disorder (ADHD). The ADHD-RS score fell by 7 to 10 points more in patients taking atomoxetine compared with those taking placebo. The subjects were children aged over six or adolescents with no psychiatric comorbidity (non-inclusion criteria) who may or may not have been previously treated with stimulants.
During a 9-month period of treatment the time to relapse observed with atomoxetine (1.2 to 1.8 mg/kg/day) was increased in comparison with that observed with placebo in patients who had responded to 10 weeks of open-label treatment with atomoxetine.

Comparative studies versus methylphenidate which included a placebo arm, in particular study LYBI, indicate that atomoxetine seems to be less effective than methylphenidate.

In a non-inferiority study versus placebo, it was shown that atomoxetine did not aggravate tics in children and adolescents with ADHD (chronic motor tics or Tourette's syndrome).
Two short-term studies versus placebo have been conducted on children or adolescents with ADHD and co-morbidities (moderate anxiety and depression). Most of the patients randomised had previously been treated with stimulants (60 to 80%). These studies showed atomoxetine to be effective versus placebo but do not show atomoxetine to be more beneficial than the reference treatment.
Furthermore, in the context of post-marketing monitoring (PSUR 11), changes to the SPC were requested in the form of the addition of potential risks, especially anxiety, depression and tics in some patients treated with atomoxetine.

Regarding tolerance, the adverse events most often reported were of a psychiatric nature (mainly aggression and suicidal thoughts), headaches, somnolence, nausea and vomiting.
The adverse events most closely monitored are, in the case of confirmed risks, suicidal risk, liver damage and Raynaud's syndrome, and in the case of potential risk, cardiovascular and cerebrovascular events, aggression/hostility and convulsions.

Since atomoxetine was first put on the market, the SPC for this proprietary drug has been revised several times, particularly in order to reflect concerns over tolerance including psychiatric problems (suicidal behaviour, psychosis and hostility).

A national pharmacovigilance monitoring programme is to be set up in France, and AFSSAPS asked the pharmaceutical firm to conduct a study on use and proper usage in March 2010.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Attention deficit and hyperactivity disorder (ADHD) is defined primarily by signs of lack of attention, hyperactivity and impulsiveness. Other (related) disorders such as oppositional defiance disorder, learning difficulties, anxiety, depression, tics and Tourette's syndrome, can be associated with the condition. It significantly impairs patients' emotional lives and school performance.

These proprietary medicinal products are intended for use as part of symptomatic therapy.

As the prevalence of this condition is estimated at 2% for children of school age,[9] and given the impact it can have on family life, education and social life, the public health burden caused by attention deficit and hyperactivity disorder (AHDH) can be regarded as moderate.Improving the management of children suffering from this disorder, which is commonly associated with other co-morbidities (language disorders, psychiatric disorders, sleep disorders, etc.) is a public health need that is part of established priorities (Public Health Act 2004, Psychiatry and Mental Health Plan).
In view of the clinical data available and the findings of studies versus active comparators, (STRATTERA appears to be less effective than methylphenidate), STRATTERA is not expected to have any additional impact on the morbidity or quality of life of patients undergoing treatment.
Consequently, if the response to the identified public health need is not to be limited to a medication-based approach (psychological, educational and family measures), where drug treatment is recommended, STRATTERA is unable to offer an additional response to this need.
Furthermore, there is no guarantee that these results will be transposed into actual practice because of:
- difficulties in diagnosing these disorders and in the clinical evaluatement of patients requiring treatment,
- uncertainty as to the long-term effects of STRATTERA (lack of data).

Consequently, in the light of the other treatments that are available, STRATTERA is not expected to benefit public health in this indication.

In view of:
- the fact that STRATTERA has been shown to be effective versus placebo but that its non-inferiority versus the reference treatment (methylphenidate) in children or adolescents with ADHD has not been demonstrated
- the fact that STRATTERA was not shown to be more beneficial than the reference treatment in studies carried out on children or adolescents with ADHD and comorbidities
- its toxicity, in particular with regard to psychiatric effects (risk of suicide, aggression/hostility), liver damage, effects on the cardiovascular system (Raynaud's syndrome, prolongation of the QT interval, tachyarrhythmia) and cerebrovascular system (CVA), the short-term efficacy/adverse effects ratio is poor in the context of overall

[9] Troubles mentaux: Dépistage et prévention chez l'enfant et l'adolescent. INSERM expert group review. Les Editions INSERM 2002

therapeutic management (psychological, educational and social measures). The long-term efficacy/adverse effects ratio remains to be determined.

There is a treatment alternative (immediate-release or prolonged-release methylphenidate) which has been found to be effective in children or adolescents with ADHD.

The transparency Committee considers therefore that, in the light of the information provided in the current dossier, the actual benefit of these ~~proprietary~~ drugs is insufficient to be refundable by public funds, in view of the efficacy data and the concerns over tolerance and in the light of the reference treatment that is available.

4.2. Transparency Committee recommendations

The transparency Committee does not recommend inclusion on the list of medicines refundable by National Health Insurance or on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.