PASS Information

Title	Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2014 Bi-annual assessment report
Version identifier of the final study report	B4Z-MC-B022
Date of last version of the final study report	Not Applicable
EU PAS register number	EU PAS register number ENCEPP/SDPP/6305
Active substance	Centrally acting sympathomimetics (ATC code: N06BA09)
Medicinal product(s):	Strattera10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100mg, hard capsules
Product reference:	UK/H/0686/002-008
Procedure number:	Not Applicable
Marketing authorisation holder(s)	Eli Lilly and Co.
Joint PASS	No
Research question and objectives	The objective of this drug utilization study is to describe atomoxetine (Strattera) utilization patterns for patients treated in the UK, Germany, the Netherlands, and Sweden by: • Estimating the number of patients exposed to Strattera, stratified by age group (paediatric, adolescent, adult and elderly) based on years of available data. • Estimating the duration of exposure, medication possession ratio, and dose over the most recent 24 months of data available. • Estimating the number of patients that restarted, the gap time in between, and duration of use in additional exposures over the most recent 24 months, for those patients who stopped taking Strattera. • Describing the population being treated with atomoxetine in terms of common comorbidities, and concomitant medications.
Country(-ies) of study	UK, Germany, Netherlands, and Sweden
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Approval Date: 09-Apr-2014 GMT

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1. Abstract

Title

Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2014 Bi-annual assessment report

Keywords

Atomoxetine, ADHD, Drug utilisation, Europe

Rationale and background

In 2003, Lilly launched Strattera (atomoxetine), which was the first attention-deficit/hyperactivity disorder (ADHD) medication indicated for adult use. The adult indication was approved in the European Union (EU) in May 2013. The patterns in ADHD medication use have changed over time and vary by country. The use of ADHD medications, including nonstimulant atomoxetine, has been increasing over time among children, adolescents, and among adults (Castle et al. 2007; Habel et al. 2011; Zoega et al. 2011). This database study analysed the unique patient exposures to atomoxetine for the period of 2008 to 2012 in each database. The analysis included an assessment of adherence patterns among users of atomoxetine and an evaluation of atomoxetine use patterns in the EU.

This report provides EU drug utilisation study results for the period of 2008 to 2012. The previously conducted drug utilization study in Europe (B4Z-MC-B019 [B019], submitted in November 2011) covered the period 2006 to 2011. Study B019 found the number of new Strattera users increased over time in the Netherlands and Sweden, and was relatively constant in the United Kingdom (UK). In each of the countries, a higher proportion of Strattera initiators were male and the drug was more commonly prescribed to persons 6 to 17 years old (73% to 83%) than adults 18 years or older (8% to 26%). The most common comorbid psychiatric condition in Sweden was depression (27%), and in UK was mental disturbance not otherwise specified (NOS; 30.1%). The most frequent diagnoses and medications listed among Strattera-treated patients were not associated with comorbid cardiovascular conditions. On average, children and adolescents used the drug for longer periods of time than adults. Persistence 1-year after drug initiation was low in each of the countries. Overall, adherence rates were lower than those reported in the United States (US) among stimulant and nonstimulant initiators (57% and 49%) respectively (Christensen et al. 2010). In conclusion, this drug utilization study of Strattera initiators found that usage appears to be confined to relatively short periods of time and with a low rate of treatment re-initiation. Overall, the measured key usage parameters were lower than those in the US (Winterstein et al. 2008; Christensen et al. 2010; Schellemen et al. 2011).

Research question and objectives

The objective of this drug utilization study is to describe atomoxetine (Strattera) utilization patterns for patients treated in the UK, Germany, the Netherlands, and Sweden.

Study design

This is a retrospective cohort database study looking at drug utilization among users of atomoxetine in the UK, Germany, the Netherlands, and Sweden.

Setting

This study included patients with filled prescriptions of Strattera for the longest available duration in each selected databases.

Subjects and study size, including dropouts

Patients needed at least 2 consecutive filled prescriptions to be eligible for inclusion. Patient discontinuation and adherence for a 24-month period (beginning at mid-year, July 1 through June 30) was estimated for each country. To estimate discontinuation and adherence for a 24-month period, a cohort of patients was identified using a 6-month window and all selected patients were time-aligned from the date of inclusion into the cohort. Each patient included in the cohort was considered persistent until it was estimated that the last day's supply of their last script had been exhausted. An allowable gap, or grace period of 90 days, due to drug holidays in this therapeutic area was incorporated.

Variables and data sources

The data sources for this study included: the LRx longitudinal prescription data in Germany and the Netherlands; the Disease Analyzer (DA) and the Clinical Practice Research Datalink (CPRD) datasets in the UK; and the National Drug and Patient Register in Sweden.

Results

The majority of patients treated with Strattera in each of the countries were 13 to 17 years old. Use among children 0 to 5 years old and adults 65+ years old is 0% to 1% across countries.

Among children younger than 18 years old, the majority of users are male and in some countries the gender distribution becomes more similar with increased age. The mean daily dose (MDD) between countries ranged from approximately 32 mg (Germany) to 49 mg (Sweden). In Sweden, the highest MDD was among patients 35 to 64 years old. The mean days supplied over 24 months ranged from approximately 280 days (Sweden) to 373 days (UK) and the medication possession ratio (MPR) ranged from 38% (Sweden) to 51% (UK). The findings for the Netherlands and Germany were very similar, where the MPR was approximately 40% and the mean days supplied was close to 300 days. Overall, the majority of patients were treated with one episode.

Discussion

Based on utilisation patterns in the EU, the potential risk of long-term severe cardiovascular outcomes related to atomoxetine treatment do not appear any different from those reported in large cohort studies conducted in the US. The most frequent diagnoses and medications listed among Strattera-treated patients were not associated with comorbid cardiovascular conditions. This drug utilisation study found mean treatment episodes for Strattera patients in the UK,

Germany, the Netherlands, and Sweden varied but were approximately 1 year and the majority of patients are treated with one episode. The overall Strattera persistence patterns in these EU countries are lower than those reported in the US.

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2. List of abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
AHRQ	Agency for Healthcare Research and Quality
CPRD	Clinical Practice Research Datalink
DA	Disease Analyzer
EU	European Union
GPRD	General Practice Research Database
HCPs	healthcare professionals
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
LOT	length of therapy
MDD	Mean daily dose
MHRA	Medicines and Healthcare Products Regulatory Agency
MPR	medication possession ratio
NOS	not otherwise specified
QA	quality assurance
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
SPDR	Swedish Patient and Drug Register
UK	United Kingdom
US	United States

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5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	02 Jan 2014	02 Jan 2014	None
End of data collection	31 Jan 2014	31 Jan 2014	None
Registration in the EU PAS register	04 Apr 2014	04 Apr 2014	None
Final report of study results	31 March 2014	11 April 2014	None

Abbreviations: EU = European Union; PAS = post-authorisation study.

6. Rationale and background

Strattera belongs to the class of selective norepinephrine reuptake inhibitors. The patterns in ADHD medication use have changed over time and vary by country. The use of ADHD medications, including nonstimulant atomoxetine has been increasing over time among children, adolescents, and among adults (Castle et al. 2007; Habel et al. 2011; Zoega et al. 2011). There has also been an increase in the duration of use over time (Castle et al. 2007).

IMS Healthcare performed the analysis of data assessing the utilisation of Strattera in this multicountry study in the UK, Germany, the Netherlands, and Sweden as requested by the Medicines and Healthcare Products Regulatory Agency (MHRA). The initial request was to ascertain how Strattera is used in everyday clinical practice in the UK, Germany, Sweden, Norway, Spain, and the Netherlands. During the initial assessment, it was found that data were unavailable for Spain and Norway. The current database study analysed the unique patient exposures to Strattera over the history available data in each database. The analysis included an assessment of adherence patterns among users of Strattera and obtained information on Strattera use patterns in the EU.

This study report describes EU drug utilisation study results for the period 2008 to 2012. The previously conducted drug utilization study in Europe (B4Z-MC-B019, submitted in November 2011) covered the period 2006 to 2011. This study assessed treatment patterns among users of Strattera with special attention to cardiovascular risks.

In addition to this follow up study, 2 additional biannual drug utilisation studies are planned, and study reports will be provided in early 2016 and early 2018.

7. Research question and objectives

The objective of this drug utilisation study was to describe Strattera utilisation patterns for patients treated in the UK, Germany, the Netherlands, and Sweden by:

- Estimating the number of patients exposed to Strattera, stratified by age group (paediatric, adolescent, adult, and elderly) based on years of available data.
- Estimating the duration of exposure, MPR, and dose over the most recent 24 months of data available.
- Estimating the number of patients that restarted, the gap time in between, and duration of use in additional exposures over the most recent 24 months, for those patients who stopped taking Strattera.
- Describing the population being treated with Strattera in terms of common comorbidities, and concomitant medications.

8. Amendments and updates

Not applicable.

9. Research methods

9.1. Study design

This is a retrospective cohort database study looking at drug utilisation among users of Strattera in the UK, Germany, the Netherlands, and Sweden.

9.2. Setting

This database study included patients with filled prescriptions of Strattera for the longest available duration in each selected databases.

9.3. Subjects

Patients needed at least 2 consecutive filled prescriptions to be eligible for inclusion. Patient discontinuation and adherence for a 24 month period (beginning at mid-year, July 1 through June 30) was estimated for each country. To estimate these measures, a cohort of patients was identified using a 6 month window and all selected patients were time-aligned from the date of inclusion into the cohort. Each patient included in the cohort was considered persistent until it was estimated that the last day's supply of their last script had been exhausted. The allowable time for utilisation of medication for each script included a grace period (allowable gap) to reduce the probability of misclassification of someone whose 30-day script lasts longer than 30 days. An allowable gap, or grace period of 90 days, due to drug holidays in this therapeutic area was incorporated.

9.4. Variables

Variable	Description
Treatment duration	the number of days between the date of the first and the last recorded prescription
Duration of exposure	percentage of patients remaining on therapy over time in monthly intervals
Total treatment dose	sum of the drug doses for all purchases (apart from the last purchase)
Daily average consumption	total treatment dose/treatment duration
Comorbid diagnoses	all ICD-10 diagnoses occurring during 24-month follow-up period
Length of therapy	time between episodes of treatment and restart of treatment
Mean daily dose	mean daily dose
Concomitant medication	concomitant medication
Medication possession ratio	number of days supply / number of days available
Moving annual total	annual estimation using midyear of most recent year available
Age	age at first prescription
Gender	gender
Year	year of treatment. Prevalent users can be represented across multiple years.

Abbreviation: ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th revision.

9.5. Data sources

IMS maintains different sets of longitudinal patient data in 11 countries around the world. For the purpose of this analysis, the following datasets were included:

1. The LRx longitudinal prescription data in Germany and the Netherlands
   - The LRx panel in Germany represents 60% of all retail scripts dispensed in the country. The LRx panel in the Netherlands represents 72% of all retail scripts dispensed in the country.
2. The Disease Analyzer (DA) and the Clinical Practice Research Datalink (CPRD) datasets in the UK.
   - DA is composed of electronic medical records gathered from physicians' office software. It also enables the tracking of patients longitudinally. In the UK, DA contains a panel of 630 general practitioners and 5 million patient records.
   - CPRD, formerly the General Practice Research Database (GPRD), is a generalisable UK-wide dataset covering about 8% of the population with 5.1 million currently active research quality patients. Participating practices use the InPractice software to record their clinical data, and thus there is no overlap with UK DA practices.
3. The National Drug and Patient Register in Sweden
   - The Swedish Patient and Drug Register (SPDR) is managed by the National Board of Health and Welfare and covers all drugs dispatched at pharmacies in Sweden from 01 July 2005 up to 31 December 2012. The register is updated in July every year. This data source contains information about unique patient identifiers for all prescriptions dispensed to the whole population of Sweden (9 million inhabitants) not including hospital data. For prescribed drugs, the register includes data on dispensed item, substance, brand name, formulation, package size, dispensed package count, strength, expenditure, and reimbursement. In order to evaluate the indication, the drug register data was linked to the Swedish patient register, which includes International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, also with national coverage.

9.6. Bias

The source of data for this data include the use of data from filled prescriptions as a proxy for actual medication use. As a result of the methodology used, it is possible to include persons not taking Strattera. In an effort to address this, inclusion criteria for this follow-up study was updated to 2 consecutive prescriptions rather than only 1 filled prescription to increase the probability that patients actually took the medication.

9.7. Study size

The study sample included all identified users of Strattera during the study time period with at least 2 consecutive Strattera prescriptions as inclusion criteria.

9.8. Data transformation

Persistence curves were calculated per month and patient from the index prescription up until the 24th month of follow-up. Re-initiation was also accounted for and separately reported. Follow-up time is normalized in relation to the index date of each patient; the total population size remained constant across the months. Persistence curves are reported, in addition to patient counts, on the number that discontinue and reinitiate. In the Sweden data, the number of days supplied is not included so persistence curves and length of therapy were calculated using a dispatch duration of 30 days and 90 day allowable gap. Any patient with a dispatch that is not preceded by a new dispatch within 120 days was considered discontinued. When a patient discontinued or reinitiated therapy, they were considered compliant during the period up until 120 days. The mean length of therapy (LOT) was used to calculate the patient years (# patients * mean LOT)/365.

9.9. Statistical methods

9.9.1. Main statistical methods

Patient counts

For each country, patient counts were provided for the most recent 5 full calendar years. Where data were unavailable, the number of unique Strattera patients were projected for each year and in each country. These projections were provided for Germany and the Netherlands.

Patient exposures

- Treatment duration, duration of exposure, daily average dose, and frequent comorbid diagnoses were estimated (where available).

Patient discontinuation and adherence

- The percentage of patients reinitiating therapy and persistence curves showing the percentage of patients remaining on therapy at monthly time intervals.
- A mean and median LOT, including the standard deviation. The mean LOT was used to calculate patient years (# patients * mean LOT)/365. The method for obtaining the standard deviation varied for each data source.
    - Note that the difference between persistence and LOT is that therapy gaps are counted in persistence and not LOT, where only the actual day's supply prescribed/dispensed are included.
- MDD. Within the CPRD database, the variables numeric daily dose were used to estimate the MDD. For each of the other databases, the MDD was estimated using the following formula (quantity dispensed/day's supply)*strength.
- A distribution of the percentage of patients having undergone 1 or more treatment episodes over the 24-month observation period.
- The percentage of Strattera patients who stopped taking Strattera and then reinitiated therapy, the gap in between, and the duration of the use in additional exposures.

- The MPR, a measure of patient compliance. The MPR was estimated by dividing the number of day's supply equivalent by the number of days available in a 24-month period.

Descriptive analysis

- Descriptive statistics including frequencies and proportions of patient count and demographics, such as age and gender, were provided for each 24-month period and for the total sample.
- Frequencies and proportions were provided for population characteristics such as common comorbidities and concomitant medication.

Treatment patterns

- Persistence curves showing the percentages of patients remaining on, or discontinuing, or restarting therapy in 1-month intervals. A 90-day gap (grace period) was used when determining persistence. The persistence curves show the patients who stopped taking Strattera, the patients that reinitiated therapy, the gap in between treatment episodes, and the duration.
- Treatment episodes over the 24-month observation period for each patient were reported by aggregating all prescriptions refilled with a 90-day allowable gap after exhausting days supplied in the prior prescription. Percentages of patients with number of treatment episodes are reported by age group. Mean, standard deviation, and median LOT for each treatment episode stratified by age group are provided.
- LOT was calculated by summing days supplied in each prescription in a given treatment episode. Mean, standard deviation, and median LOT are reported and stratified by age group.
- Notes:
    - If the days supplied was not available, the number of days supplied was calculated as the total dose (strength x package size x package count; where strength = medication strength; package size = number of pills in package, and package count = number of packages) contained in dispensed packages divided by the daily dose ordered in the prescription. If daily dose was not available, the strength prescribed was used instead based on the suggested dosing frequency of once-daily provided in the full prescribing information of Strattera. Patients were excluded from the analysis if they didn't have complete information on strength, package size, or package counts.
- MPR was used to measure patient compliance and calculated as the number of days supply equivalent divided by the number of days available in the 24-month period (730 days).
    - Note: In the Swedish prescription register, days supplied per dispatch is not available. Because the recommended dose for Strattera is weight-dependent (1.2 mg per kg and day), Swedish average weights were extracted across age groups. A weighted average weight was calculated for the age groups based on the representation across ages. A weighted average weight was used to

calculate the expected daily dose for the age group, which in turn is related to the total dose prescribed at the individual level, in order to calculate days supplied. Days supplied was calculated by the total dose (strength x package size x package count) dispensed in each dispatch divided by a patient's expected daily dose (1.2 x weighted average weight in Sweden nationally). Patients were excluded from the analysis if they didn't have complete information on strength, package size, or package count.

- MDD is defined as total treatment dose divided by treatment duration. Drug dose per prescription was calculated by multiplying package size by package dose in each prescription. Total treatment dose was calculated as the sum of drug doses in each prescription except the last prescription. Treatment duration was calculated as the number of days between the first and last recorded dispatch date. At least 2 prescriptions are required for the calculation of average daily dose. To avoid stochastic results, individuals that had fewer than 7 days between their first and last dispatch were excluded.
    - Note: Dosage was assumed to be once daily, therefore is strength used as daily dose for UK CPRD data and daily dosage is used for UK DA.

9.9.2. Missing values

Missing values were treated as unknown and were reported as such.

9.9.3. Sensitivity analyses

A sensitivity analysis was not completed for this study.

9.9.4. Amendments to the statistical analysis plan

This study included users of Strattera with 2 consecutive prescriptions as inclusion criteria. This is different from the initial study which included anyone with a filled prescription of Strattera. This method was selected to increase the probability that the patients included were actually taking the medication. A patient's refill is an indication the patient has exhausted their initial supply.

The data source for Sweden for this study included the National Drug and Patient Register rather than the Cebrxa data source used in the initial study. The inclusion of national prescription and healthcare data allowed for more complete coverage for the Swedish population.

9.10. Quality control

The study adhered strictly to standards consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (http://www.pharmacoepi.org). These standards include storage of sensitive data on a server with restricted access. Accuracy and completeness of study data were assessed by IMS and IMS followed its internal policies and procedures to ensure that all data and results were confirmed against the source and the final deliverables have been quality reviewed by a person external to the report author.

In addition to the standard quality assurance (QA) process, the programming of the study and selection criteria of patients were validated by a third consultant. IMS confirms the correctness of programming and cohort selection of the recent update and that the methodologies are aligned with the current statistical analysis plan (SAP).

10. Results

10.1. Participants

10.2. Descriptive data

Germany

In Germany, the number of patients treated with Strattera is declining (Table 1). The largest proportion of patients treated with Strattera was patients 13 to 17 years old (26.6% to 37.7%) annually and overall, the majority of Strattera-treated patients are 10 to 17 years old. Among adults 18 to 64, the proportion of users was low, 7.5% to 11.8% over time. Among Strattera-treated patients, fewer than 1% were 65 years and older. Overall, the data show a decline in the number of users of Strattera over time. In 2008, there were more than 31,000 patients treated with Strattera and in 2012, this decreased to approximately 22,500 users.

Table 1. Germany: Annual projected age distribution for all patients

Age in years	2008		2009		2010		2011		2012	
	N	%	N	%	N	%	N	%	N	%
0-5 years	308	0.99%	230	0.89%	195	0.77%	177	0.74%	149	0.66%
6-9 years	5511	17.77%	4582	17.66%	4458	17.57%	4119	17.30%	3548	15.74%
10-12 years	8118	26.17%	7596	29.27%	7938	31.29%	7527	31.62%	7470	33.15%
13-17 years	8239	26.56%	8120	31.29%	9102	35.88%	8673	36.43%	8505	37.74%
18-34 years	1793	5.78%	2238	8.62%	2445	9.64%	2148	9.02%	1813	8.04%
35-64 years	544	1.75%	573	2.21%	537	2.12%	403	1.69%	366	1.63%
65+ years	99	0.32%	97	0.37%	96	0.38%	85	0.36%	95	0.42%
Unknown	6412	71.48%	2515	79.10%	598	85.51%	676	86.09%	588	87.30%
<18 years	22176	7.53%	20528	10.83%	21693	11.76%	20496	10.72%	19672	9.67%
18-64 years	2337	20.67%	2810	9.69%	2982	2.36%	2551	2.84%	2179	2.61%
Total	**31024**	**100.00%**	**25951**	**100.00%**	**25370**	**100.00%**	**23808**	**100.00%**	**22534**	**100.00%**

In Germany, many patient records do not include gender or age information (Table 2). Overall, the majority of patients treated with Strattera with recorded gender are male. Strattera use among males is approximately 3 times higher than among females. This trend is consistent over time.

Table 2. Germany: Annual projected gender distribution for all patients

Gender	2008		2009		2010		2011		2012	
	N	%	N	%	N	%	N	%	N	%
Female	4049	13%	3399	13%	3265	13%	2986	13%	2612	12%
Male	14905	48%	12646	49%	11587	46%	9900	42%	8611	38%
Unknown	12070	39%	9906	38%	10517	41%	10923	46%	11311	50%
Total	**31024**	**100%**	**25951**	**100%**	**25370**	**100%**	**23808**	**100%**	**22534**	**100%**

The age and gender distribution among males and females for new users of Strattera is similar (Table 3). Overall the majority (62%) of initiators are aged 10 to 17 years old. Approximately 91.5% of male and 86% of female new users are younger than 18.

Table 3. Germany: Annual projected age and gender distribution for new users

	All		Female		Male	
Age in years	N	%	N	%	N	%
0-5 years	43	1.24%	2	0.42%	13	0.96%
6-9 years	842	24.43%	117	23.21%	334	25.12%
10-12 years	1142	33.15%	149	29.54%	486	36.48%
13-17 years	991	28.76%	168	33.33%	386	28.96%
18-34 years	247	7.17%	49	9.70%	92	6.88%
35-64 years	77	2.23%	17	3.38%	19	1.44%
65+ years	9	0.25%	0	0.00%	0	0.00%
<18 years	3017	87.57%	437	86.50%	1219	91.52%
18-64 years	324	9.40%	66	13.08%	111	8.32%
Unknown	96	2.78%	2	0.42%	2	0.16%
Total	**3445**	**100.00%**	**505**	**100.00%**	**1332**	**100.00%**

Netherlands

In the Netherlands, the largest portion of Strattera use is among adolescents 13 to17 years old (30.9% to 35.5%) (Table 4). This trend is consistent over time. The use of Strattera among adults (18 to 64 years old) has increased over time from 23.5% to 29.2% whereas the proportion of users under 18 has been gradually declining. Overall, the data show a decline in the number of Strattera users over time. In 2008, there were more than 7000 patients treated with Strattera and in 2012 this decreased to approximately 5700 users.

Table 4. Netherlands: Annual projected age distribution for all patients

	2008		2009		2010		2011		2012	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	25	0.36%	24	0.38%	36	0.60%	16	0.29%	21	0.37%
6-9 years	1441	20.54%	1081	17.04%	759	12.54%	693	12.16%	597	10.40%
10-12 years	1707	24.32%	1584	24.98%	1521	25.13%	1329	23.32%	1329	23.15%
13-17 years	2167	30.88%	2077	32.75%	1996	32.98%	1940	34.04%	2039	35.51%
18-34 years	1031	14.69%	992	15.65%	1083	17.90%	1091	19.14%	1050	18.29%
35-64 years	619	8.83%	569	8.98%	631	10.43%	610	10.71%	625	10.89%
65+ years	27	0.39%	13	0.20%	22	0.36%	20	0.35%	80	1.39%
<18 years	5340	76.10%	4765	75.14%	4313	71.26%	3980	69.81%	3986	69.43%
18-64 years	1650	23.51%	1562	24.63%	1714	28.33%	1701	29.84%	1676	29.18%
Unknown	0	0%	2	0.03%	3	0.05%	0	0%	0	0%
Total	**7017**	**100.00%**	**6341**	**100.00%**	**6052**	**100.00%**	**5701**	**100.00%**	**5741**	**100.00%**

The majority of patients treated with Strattera in the Netherlands, approximately 80%, are male (Table 5). This trend is consistent over time.

Table 5. Netherlands: Annual projected gender distribution for all patients

	2008		2009		2010		2011		2012	
Gender	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Female	1494	21%	1418	22%	1421	23%	1322	23%	1337	23%
Male	5523	79%	4923	78%	4632	77%	4379	77%	4404	77%
Unknown	0	0	0	0	0	0	0	0	0	0
Total	**7017**	**100%**	**6341**	**100%**	**6052**	**100%**	**5701**	**100%**	**5741**	**100%**

Among females in the Netherlands, the largest proportion (26.7%) of patients initiating treatment are 18 to 34 years old and 51.8% are between 18 and 64 years old. Among males, the largest proportion of patients initiating treatment are 13 to 17 years old (26.1%) and 71.4% are younger than 18 (Table 6).

Table 6. Netherlands: Annual projected age and gender distribution for new users

	All		Female		Male	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	2	0.16%	0	0.00%	2	0.21%
6-9 years	263	20.72%	39	11.68%	224	23.96%
10-12 years	250	19.70%	52	15.57%	197	21.07%
13-17 years	314	24.74%	70	20.96%	244	26.10%
18-34 years	253	19.94%	89	26.65%	165	17.65%
35-64 years	182	14.34%	84	25.15%	98	10.48%
65+ years	5	0.39%	0	0.00%	5	0.53%
<18 years	829	65.33%	161	48.20%	668	71.44%
18-64 years	435	34.28%	173	51.80%	262	28.02%
Unknown	0	0%	0	0%	0	0%
Total	**1269**	**36.84%**	**334**	**100.00%**	**935**	**100.00%**

United Kingdom

In the UK, the majority of Strattera use is among adolescents 13 to 17 years old (34.9% to 43.9%). Over time, each year approximately 30% of users were 10 to 12 years old. Annually, the use among children 0 to 5 and the elderly 65+ years old was less than 1% and among users 35 to 64 years old, the proportion has increased from 1.8% to 3% (Table 7).

Table 7. UK: Annual age distribution for all patients

	2008		2009		2010		2011		2012	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	1	0.12%	2	0.24%	2	0.23%	2	0.21%	2	0.21%
6-9 years	134	16.11%	149	17.53%	169	19.31%	185	19.33%	191	20.41%
10-12 years	242	29.09%	236	27.76%	253	28.91%	280	29.26%	267	28.53%
13-17 years	365	43.87%	360	42.35%	345	39.43%	348	36.36%	327	34.94%
18-34 years	75	9.01%	81	9.53%	83	9.49%	115	12.02%	121	12.93%
35-64 years	15	1.80%	22	2.59%	23	2.63%	26	2.72%	28	2.99%
65+ years	0	0.00%	0	0.00%	0	0.00%	1	0.10%	0	0.00%
<18 years	742	89.18%	747	87.88%	769	87.89%	815	85.16%	787	84.08%
18-64 years	90	10.82%	103	12.12%	106	12.11%	141	14.73%	149	15.92%
Unknown	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%
Total	**832**	**100.00%**	**850**	**100.00%**	**875**	**100.00%**	**957**	**100.00%**	**936**	**100.00%**

The majority of patients treated with atomoxetine, more than 80%, in the UK are male (Table 8). This trend is consistent over time.

Table 8. UK: Annual gender distribution for all patients

	2008		2009		2010		2011		2012	
Gender	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Female	140	17%	145	17%	147	17%	173	18%	176	19%
Male	692	83%	705	83%	728	83%	784	82%	760	81%
Unknown	0	0%	0	0%	0	0%	0	0%	0	0%
Total	**832**	**100%**	**850**	**100%**	**875**	**100%**	**957**	**100%**	**936**	**100%**

Among males in the UK, the largest proportion (62%) of new atomoxetine users are 13 to 17 years old. Among females, the largest proportion of new atomoxetine users are 13 to 17 (50%). Among females, only 8% initiate Strattera treatment between ages 18 to 34. Among females, Strattera initiation is 92% in patients <18 years old and 8% from 18 to 64 years old whereas among males, 85% are <18 and 15% are 18 to 64 years old (Table 9).

Table 9. UK: Annual age and gender distribution for new users

	All		Female		Male	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	0	0.00%	0	0.00%	0	0.00%
6-9 years	3	5.08%	1	8.33%	2	4.26%
10-12 years	13	22.03%	4	33.33%	9	19.15%
13-17 years	35	59.32%	6	50.00%	29	61.70%
18-34 years	7	11.86%	1	8.33%	6	12.77%
35-64 years	1	1.69%	0	0.00%	1	2.13%
65+ years	0	0.00%	0	0.00%	0	0.00%
<18 years	51	86.44%	11	91.67%	40	85.11%
18-64 years	8	13.56%	1	8.33%	7	14.89%
Unknown	0	0.00%	0	0.00%	0	0.00%
Total	**59**	**100.00%**	**12**	**100.00%**	**47**	**100.00%**

Sweden

In Sweden, a large proportion of Strattera use is among adolescents 13 to 17 years old (30.7% to 36%). Approximately 20% of users were 10 to 12 years old and approximately 11% of users were 6 to 9 years old. Strattera use among the elderly 65+ and children 0 to 5 years old is less than 1%. The majority of patients treated with Strattera are 6 to 18 years of old (Table 10).

Table 10. Sweden: Annual age distribution for all patients

	2008		2009		2010		2011		2012	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	N<10	-	14	0.25%	14	0.20%	26	0.31%	18	0.20%
6-9 years	465	10.88%	564	10.14%	731	10.47%	931	11.00%	933	10.44%
10-12 years	798	18.68%	984	17.69%	1211	17.35%	1476	17.44%	1605	17.95%
13-17 years	1546	36.18%	1924	34.60%	2279	32.65%	2652	31.34%	2748	30.73%
18-34 years	947	22.16%	1320	23.74%	1751	25.09%	2147	25.37%	2331	26.07%
35-64 years	517	12.10%	742	13.34%	983	14.08%	1210	14.30%	1284	14.36%
65+ years	N<10	-	13	0.23%	11	0.16%	21	0.25%	22	0.25%
<18 years*	2809	65.74%	3486	62.69%	4235	60.67%	5085	60.09%	5304	59.32%
18-64 years	1464	34.26%	2062	37.08%	2734	39.17%	3357	39.67%	3615	40.43%
Unknown	0	-	0	-	0	-	0	-	0	-
Total*	**4273**	**100.00%**	**5561**	**100.00%**	**6980**	**100.00%**	**8463**	**100.00%**	**8941**	**100.00%**

* Excludes rows with N<10. Numbers less than 10 are not reported, as required by the National Prescription and Drug Register.

The majority of patients in Sweden treated with Strattera, 66% to 72%, are male. Over time, the proportion of female users is gradually increasing (Table 11).

Table 11. Sweden: Annual gender distribution for all patients

	2008		2009		2010		2011		2012	
Gender	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Female	1218	28%	1681	30%	2181	31%	2808	33%	3035	34%
Male	3072	72%	3880	70%	4799	69%	5655	67%	5906	66%
Unknown	0	0%	0	0%	0	0%	0	0%	0	0%
Total	**4290**	**100%**	**5561**	**100%**	**6980**	**100%**	**8463**	**100%**	**8941**	**100%**

In Sweden, more than half of new Strattera users are 13 to 34 years old. Among females, 56.4% of new Strattera users were 18 to 64, whereas among male new Strattera users, 61.8% were younger than 18 (Table 12).

Table 12. Sweden: Annual age and gender distribution for new users

	All		Female		Male	
Age in years	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	N<10	-	0	-	N<10	-
6-9 years	242	12.87%	51	7.99%	191	15.38%
10-12 years	277	14.73%	60	9.40%	217	17.47%
13-17 years	527	28.03%	167	26.18%	360	28.99%
18-34 years	528	28.09%	229	35.89%	299	24.07%
35-64 years	306	16.28%	131	20.53%	175	14.09%
65+ years	N<10	-	N<10	-	N<10	-
<18 years*	1046	55.64%	278	43.57%	768	61.84%
18-64 years	834	44.36%	360	56.43%	474	38.16%
Unknown	0	0.00%	0	0.00%	0	0.00%
Total*	**1880**	**100.00%**	**638**	**100.00%**	**1242**	**100.00%**

* Excludes rows with N<10. Numbers less than 10 are not reported, as required by the National Prescription and Drug Register.

10.3. Outcome data

Germany

Overall, the MDD among new Strattera users in the German population is 32.3 mg. The highest MDD was recorded among patients treated with Strattera 18 to 34 years old (45.41 mg). Among new users 35 to 64 years old, the MDD was reduced to 39.09 mg and among adults 65 and older, the MDD was reduced to 31.45 mg. Overall, the mean days supplied is 314 days within a 24-month window. The overall MPR was 0.43 or 43% of days within a 24-month period (Table 13).

Table 13. Germany: Mean daily dose and medication possession ratio in new users

		Mean Daily Dose (mg)			Days Supplied		MPR Proportion of days supplied		
Age in years	N	Mean	SD	Median	Mean	Median	MPR	SD	Median
0-5 years	20	28.89	16.21	22.85	290.7	196.5	0.40	0.32	0.27
6-9 years	395	24.88	12.94	23.11	304.0	252.0	0.42	0.31	0.35
10-12 years	536	28.88	15.95	25.41	336.1	324.5	0.46	0.30	0.45
13-17 years	465	38.59	25.04	34.03	301.4	248.0	0.41	0.28	0.34
18-34 years	116	45.41	25.26	46.46	311.2	245.5	0.43	0.31	0.34
35-64 years	36	39.09	22.96	32.69	258.3	168.0	0.35	0.27	0.23
65+ years	4	31.45	11.38	29.75	202.5	147.0	0.28	0.16	0.21
<18 years	1416	30.95	19.58	26.35	315.1	273.5	0.43	0.30	0.38
18-64 years	152	43.91	24.81	44.22	298.7	240.0	0.41	0.30	0.33
Unknown	45	36.94	17.98	33.61	358.4	343.0	0.49	0.30	0.47
Total	**1617**	**32.34**	**20.42**	**27.58**	**314.5**	**270.0**	**0.43**	**0.30**	**0.37**

Abbreviations: MPR = medication possession ratio (days supplied /730 days – days in 24 month period); SD = standard deviation.

Of the 1617 new Strattera users, 1271 (79%) were treated with 1 episode and 272 (17%) were treated with 2 episodes. Only 63 of the patients were treated with 3 episodes and 11 (0.7%) of 1671 patients had 4 episodes of treatment. In Germany, the mean number of days for the patients treated was 314.5 days (Table 14).

Table 14. Germany: Length of treatment and number of episodes in new users

		Treatment Episodes					Cumulative length of treatment (Days)	
		One	Two	Three	Four	Five+	Patient-Level	
Age in years	N	n(%)	n(%)	n(%)	n(%)	n(%)	Mean days(sd)	Median
0-5 years	20	19(1)	1 (0)	0(0)	0(0)	0(0)	290.7(234)	196.5
6-9 years	395	321(26)	59(23)	12(22)	3(20)	0(0)	304.0(223)	252.0
10-12 years	536	417(33)	96(33)	19(36)	4(40)	0(0)	336.1(221)	324.5
13-17 years	465	356(27)	80(30)	25(31)	4(40)	0(0)	301.4(207)	248.0
18-34 years	116	88(7)	25(8)	3(7)	0(0)	0(0)	311.2(226)	245.5
35-64 years	36	29(2)	4(2)	3(3)	0(0)	0(0)	258.3(201)	168.0
65+ years	4	4(0)	0(0)	0(0)	0(0)	0(0)	202.5(114)	147.0
<18 years	1416	1113(88)	236(87)	56(88)	11(100)	0(0)	315.1(218)	273.5
18-64 years	152	117(9)	29(10)	6(10)	0(0)	0(0)	298.7(220)	240.0
Unknown	45	37(3)	7(3)	1(2)	0(0)	0(0)	358.4(220)	343.0
Total	**1617**	**1271(100)**	**272(100)**	**63(100)**	**11(100)**	**0(0)**	**314.5(218)**	**270.0**

Abbreviation: sd = standard deviation.

Netherlands

Overall, the MDD among users of Strattera is 41.9 mg (Table 15). The highest MDD was recorded among patients treated with atomoxetine 65+ years old. This may not be representative as only 2 treated patients were included. Overall, the mean days supplied is 303 days within a 24-month window. The overall MPR was 0.42 or 42% of days within a 24-month period.

Table 15. Netherlands: Mean daily dose and medication possession ratio in new users

		Mean Daily Dose (mg)			Days Supplied		MPR Proportion of days supplied		
Age in years	**N**	**Mean**	**SD**	**Median**	**Mean**	**Median**	**MPR**	**SD**	**Median**
0-5 years	1	16.00	-	16.00	22.0	22.0	0.03	0.00	0.03
6-9 years	110	29.56	13.80	26.47	338.1	166.5	0.46	0.44	0.23
10-12 years	110	33.76	12.75	32.51	361.5	257.0	0.50	0.41	0.35
13-17 years	135	43.45	16.01	40.75	293.2	178.5	0.40	0.38	0.24
18-34 years	110	52.21	18.82	53.88	251.1	134.0	0.34	0.34	0.18
35-64 years	78	53.16	17.17	52.36	276.2	167.0	0.38	0.36	0.23
65+ years	2	72.21	6.66	72.21	63.0	19.8	0.09	0.03	0.09
<18 years	356	36.09	15.55	34.36	327.4	201.5	0.45	0.41	0.28
18-64 years	188	52.60	18.11	53.04	261.5	152.5	0.36	0.35	0.21
Unknown	0	0	0	0	0	0	0	0	0
Total	**546**	**41.91**	**18.30**	**40.00**	**303.8**	**180.5**	**0.42**	**0.38**	**0.25**

Abbreviations: MPR = medication possession ratio (days supplied /730 days – days in 24 month period); SD = standard deviation.

Of the 546 patients treated, 497 (91%) had 1 episode of treatment, 40 (7%) were treated with 2 episodes, 7 (1%) were treated with 3 episodes and 2 (0.4%) had 4 episodes of treatment (Table 16). The mean number of days for the patients treated was 304 days. Children 10 to 12 years old had the highest mean length of treatment (361 days) followed by children 6 to 9 years old (338 days). The lowest mean days of treatment was among children 0 to 5 (22) and adults 65 and older (63 days). The number of users in these 2 groups was small so this may not be representative of treatment episodes for new users 0 to 5 and 65 years and older.

Table 16. Netherlands: Length of treatment and number of episodes in new users

		Treatment Episodes					Cumulative length of treatment (Days)	
		One	Two	Three	Four	Five+	Patient-Level	
Age in years	N	n(%)	n(%)	n(%)	n(%)	n(%)	Mean days(sd)	Median
0-5 years	1	1(0)	0	0	0	0	22.0(0)	22.0
6-9 years	110	104(21)	5(13)	1(14)	0	0	338(319)	167
10-12 years	110	104(21)	4(10)	1(14)	1(50)	0	361(300)	257
13-17 years	135	121(24)	12(30)	1(14)	1(50)	0	293(277)	179
18-34 years	110	97(20)	11(28)	2(29)	0	0	251(245)	134
35-64 years	78	68(14)	8(20)	2(29)	0	0	276(263)	167
65+ years	2	2(0)	0	0	0	0	63(20)	63
<18 years	356	330(66)	21(53)	3	2(100)	0	327(298)	202
18-64 years	188	165(33)	19(48)	4	0	0	261(255)	153
Unknown	0	0	0	0	0	0	0(0)	0
Total	**546**	**497(100)**	**40(100)**	**7(100)**	**2(100)**	**0**	**304(281)**	**181**

Abbreviation: sd = standard deviation.

United Kingdom

Overall, the MDD among users of Strattera is 46 mg (Table 17). The highest MDD was recorded among patients treated with Strattera 35 to 64 years old. This may not be representative as only 1 treated patient was included. These data reflect no new users of Strattera under 6 and over 64 years old. Overall, the mean days supplied is 372.7 days within a 24-month window. The overall medication possession ratio was .51 or 51% of days within a 24-month period.

Table 17. UK: Mean daily dose and medication possession ratio in new users

		Mean Daily Dose (mg)			Days Supplied		MPR Proportion of days supplied		
Age in Years	**N**	**Mean**	**SD**	**Median**	**Mean**	**Median**	**MPR**	**SD**	**Median**
0-5 years	0	-	-	-	-	-	-	-	-
6-9 years	3	21.61	3.67	22.11	495.7	500.0	0.68	0.24	0.68
10-12 years	13	33.10	15.87	40.00	324.2	196.0	0.44	0.48	0.27
13-17 years	35	51.00	18.99	50.00	351.3	226.0	0.48	0.37	0.31
18-34 years	7	50.34	19.92	47.27	494.1	730.0	0.68	0.42	1.00
35-64 years	1	80.00	-	80.00	532.0	532.0	0.73	.	0.73
65+ years	0	-	-	-	-	-	-	-	-
<18 years	51	44.70	20.02	45.00	352.9	308.0	0.48	0.39	0.42
18-64 years	8	54.05	21.22	53.64	498.9	631.0	0.68	0.39	0.86
Unknown	0	-	-	-	-	-	-	-	-
Total	**59**	**45.97**	**20.26**	**46.15**	**372.7**	**315.0**	**0.51**	**0.40**	**0.43**

Abbreviations: MPR = medication possession ratio (days supplied /730 days – days in 24 month period); SD = standard deviation.

Of the 59 new users treated with Strattera, 45 (76%) patients were treated with 1 episode. A total of 11 (19%) were treated with 2 episodes and 2 (3%) patients were treated with 3 episodes. One patient (2%) went on to be treated with 4 episodes. The mean number of days for the patients treated was approximately 373 days. The total number of new users included in this table limit the ability to interpret the findings within each age strata (Table 18).

Table 18. UK: Length of treatment and number of episodes in new users

		Treatment Episodes					Cumulative length of treatment (Days)	
		One	Two	Three	Four	Five +	Patient-Level	
Age in years	**N**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**Mean days(sd)**	**Median**
0-5 years	0	0(0)	0(0)	0(0)	0(0)	0(0)	-	-
6-9 years	3	3(7)	0(0)	0(0)	0(0)	0(0)	495.7(179)	500.0
10-12 years	13	11(24)	1(9)	0(0)	1(100)	0(0)	324.2(353)	196.0
13-17 years	35	27(60)	7(64)	1(50)	0(0)	0(0)	351.3(271)	226.0
18-34 years	7	4(9)	3(27)	0(0)	0(0)	0(0)	494.1(304)	730.0
35-64 years	1	0(0)	0(0)	1(50)	0(0)	0(0)	532.0(-)	532.0
65+ years	0	0(0)	0(0)	0(0)	0(0)	0(0)	-	-
<18 years	51	41(91)	8(73)	1(50)	1(100)	0(0)	352.9(288)	308.0
18-64 years	8	4(9)	3	1(50)	0(0)	0(0)	498.9(281)	631.0
Unknown	0	0(0)	0(0)	0(0)	0(0)	0(0)	-	-
Total	**59**	**45**	**11(100)**	**2**	**1**	**0**	**372.7(289)**	**315.0**

Abbreviation: sd = standard deviation.

Sweden

Overall, the MDD among users of Strattera was approximately 49 mg (Table 19). The highest MDD was recorded among patients treated with Strattera 35 to 64 years old. Under the age of 6 and 65+ years old, there were fewer than 10 patients per group treated with Strattera and, therefore, the numbers could not be reported. Overall, the mean days supplied is 279.5 days within a 24-month window. Users 6 to 9 years old had the largest mean days supplied (401.1) and 18 to 34-year-olds had the smallest mean days supplied, 89 days. The overall MPR was 0.38 or 38% of days within 24-month period.

Table 19. Sweden: Mean daily dose and medication possession ratio in new users

		Mean Daily Dose (mg)			Days Supplied		MPR Proportion of days supplied		
Age in Years	**N**	**Mean**	**SD**	**Median**	**Mean**	**Median**	**MPR**	**SD**	**Median**
0-5 years	N<10	-	-	-	-	-	-	-	-
6-9 years	238	33.41	14.23	32.85	456.0	401.1	0.62	0.50	0.55
10-12 years	269	42.39	18.27	42.08	399.4	355.3	0.55	0.44	0.49
13-17 years	518	50.63	26.68	49.87	291.7	217.4	0.40	0.34	0.30
18-34 years	509	52.11	36.78	46.67	175.0	89.0	0.24	0.27	0.12
35-64 years	296	58.01	46.00	50.77	187.1	91.7	0.26	0.31	0.13
65+ years	N<10	-	-	-	-	-	-	-	-
<18 years*	1025	44.43	23.27	41.91	359.5	264.2	0.49	0.42	0.36
18-64 years	805	54.27	40.49	48.53	179.5	90.0	0.25	0.28	0.12
Unknown	0	-	-	-	-	-	-	-	-
Total*	**1830**	**48.74**	**32.33**	**44.50**	**279.5**	**159.8**	**0.38**	**0.39**	**0.22**

Abbreviations: MPR = medication possession ratio (days supplied /730 days – days in 24 month period); SD = standard deviation.

* Excludes rows with N<10. Numbers less than 10 are not reported, as required by the National Drug and Prescription Register.

Of the 1857 treated patients, 1514 (82%) patients were treated with 1 episode. A total of 308 (17%) were treated with 2 episodes. A total of 35 (2%) of the patients were treated with 3 episodes and a low number of the new Strattera-treated patients went on to be treated with 4 episodes. The mean number of days for the patients treated with Strattera was 410.7 days (Table 20).

Table 20. Sweden: Length of treatment and number of episodes in new users

		Treatment Episodes					Cumulative length of treatment (Days)	
		One	Two	Three	Four	Five +	Patient-Level	
Age in years	N	n(%)	n(%)	n(%)	n(%)	n(%)	Mean days(sd)	Median
0-5 years	N<10	N<10	N<10	0(0)	0(0)	0(0)	-	-
6-9 years	236	203(13)	33(11)	N<10	N<10	0(0)	516.3(277)	558.0
10-12 years	272	230(15)	42(14)	N<10	0(0)	0(0)	485(272)	457.0
13-17 years	524	396(26)	104(34)	24(69)	N<10	N<10	431(244)	344.0
18-34 years	526	428(28)	87(28)	11(31)	N<10	0(0)	341.5(226)	264.5
35-64 years	299	257(17)	42(14)	N<10	N<10	0(0)	343.4(237)	239.0
65+ years	N<10	N<10	N<10	0(0)	0(0)	0(0)	-	-
<18 years	1032	829(55)	179(58)	24(69)	N<10	N<10	465.4(262)	397.0
18-64 years	825	685(45)	129(42)	11(31)	N<10	0(0)	342(230)	254.5
Unknown		0	0(0)	0(0)	0(0)	0(0)	-	-
Total*	**1857**	**1514**	**308**	**35**	**-**	**-**	**410.7(256)**	**315.0**

Abbreviation: sd = standard deviation.

* Excludes rows with N<10. Numbers less than 10 are not reported, as required by the National Drug and Prescription Register.

10.4. Main results

Germany

After 24 months, approximately 31% of patients are still being treated with Strattera (Table 21). Of the patients that discontinued, approximately 8% restarted therapy. In general, persistence on Strattera therapy upon initiation is 100% up until 6 months. After 6 months, there is a gradual increase in Strattera treatment discontinuation over time (Figure 1).

Table 21. Germany: Patient persistence by month over a 24-month period (percent)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100%	100%	100%	100%	100%	96%	88%	81%	74%	68%	63%	59%
Discontinuation	0%	0%	0%	0%	0%	4%	12%	19%	26%	31%	35%	38%
Re-initiation	0%	0%	0%	0%	0%	0%	0%	0%	1%	1%	2%	2%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	56%	53%	49%	47%	44%	42%	40%	38%	36%	34%	33%	31%
Discontinuation	41%	43%	46%	49%	51%	53%	55%	57%	57%	59%	60%	61%
Re-initiation	3%	4%	5%	5%	5%	5%	5%	6%	6%	7%	7%	8%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

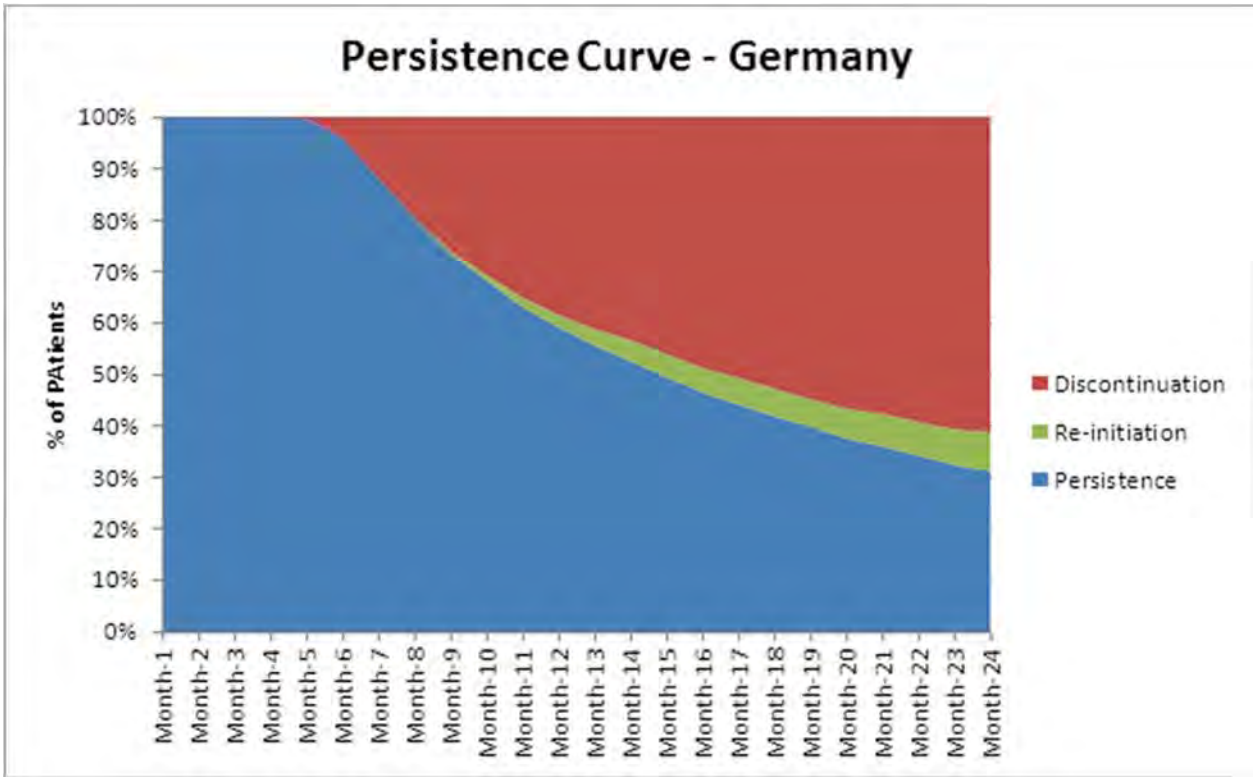

Figure 1. Persistence over a 24-month period among patients in Germany

In Germany, the mean gap between episodes is approximately 256 days. The largest gap between episodes was found among patients 35 to 64 years old and 0 to 5 years old. Although, this estimate is based on 1 patient. Overall, the mean days between episodes decreases with each episode treatment group (Table 22).

Table 22. Germany: Mean gap (in days) between treatment episodes

	Episode Gaps All ≥2 Episodes		Gap between Episode 1 and 2 ≥2 Episodes		Gap between Episode 2 and 3 ≥3 Episodes		Gap between Episode 3 and 4 ≥4 Episodes	
	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)
0-5 years	1	727.0 (-)	1	727.0 (-)	0	-	0	-
6-9 years	74	272.3 (168)	74	277.2 (171)	15	260.9 (168)	3	208.0 (64)
10-12 years	119	253.7 (133)	119	254.8 (138)	23	246.8 (113)	4	260.3 (71)
13-17 years	109	238.8 (139)	109	244.9 (149)	29	224.8 (101)	4	175.5 (55)
18-34 years	28	264.8 (161)	28	247.3 (156)	3	428.7 (113)	0	-
35-64 years	7	311.9 (182)	7	340.6 (194)	3	245.0 (162)	0	-
65+ years	0	-	0	-	0	-	0	-
<18 years	303	253.9 (146)	303	258.3 (153)	67	240.4 (122)	11	215.2 (69)
18-64 years	35	276.3 (165)	35	265.9 (166)	6	336.8 (160)	0	-
Unknown	8	245.2 (129)	8	257.0 (132)	1	151.0 (-)	0	-
Total	**346**	**255.8 (148)**	**346**	**259.0 (153)**	**74**	**247.0 (126)**	**11**	**215.2 (69)**

Abbreviation: sd = standard deviation.

Netherlands

After 24 months, approximately 22% of patients are still being treated with Strattera in the Netherlands (Table 23). Of the patients that discontinued, approximately 2% restarted Strattera therapy. In general, persistence on Strattera therapy upon initiation is 100% up until 3 months. After 3 months there is a gradual increase in treatment discontinuation over time (Figure 2).

Table 23. **Netherlands: Patient persistence by month over a 24-month period (percent)**

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100%	100%	100%	94%	82%	71%	61%	54%	49%	46%	42%	39%
Discontinuation	0%	0%	0%	6%	18%	29%	39%	45%	49%	53%	57%	60%
Re-initiation	0%	0%	0%	0%	0%	0%	0%	1%	1%	1%	1%	1%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	36%	35%	32%	30%	29%	27%	27%	25%	25%	24%	23%	22%
Discontinuation	62%	64%	67%	68%	70%	72%	73%	73%	74%	75%	75%	76%
Re-initiation	1%	1%	2%	1%	1%	1%	1%	1%	1%	2%	2%	2%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

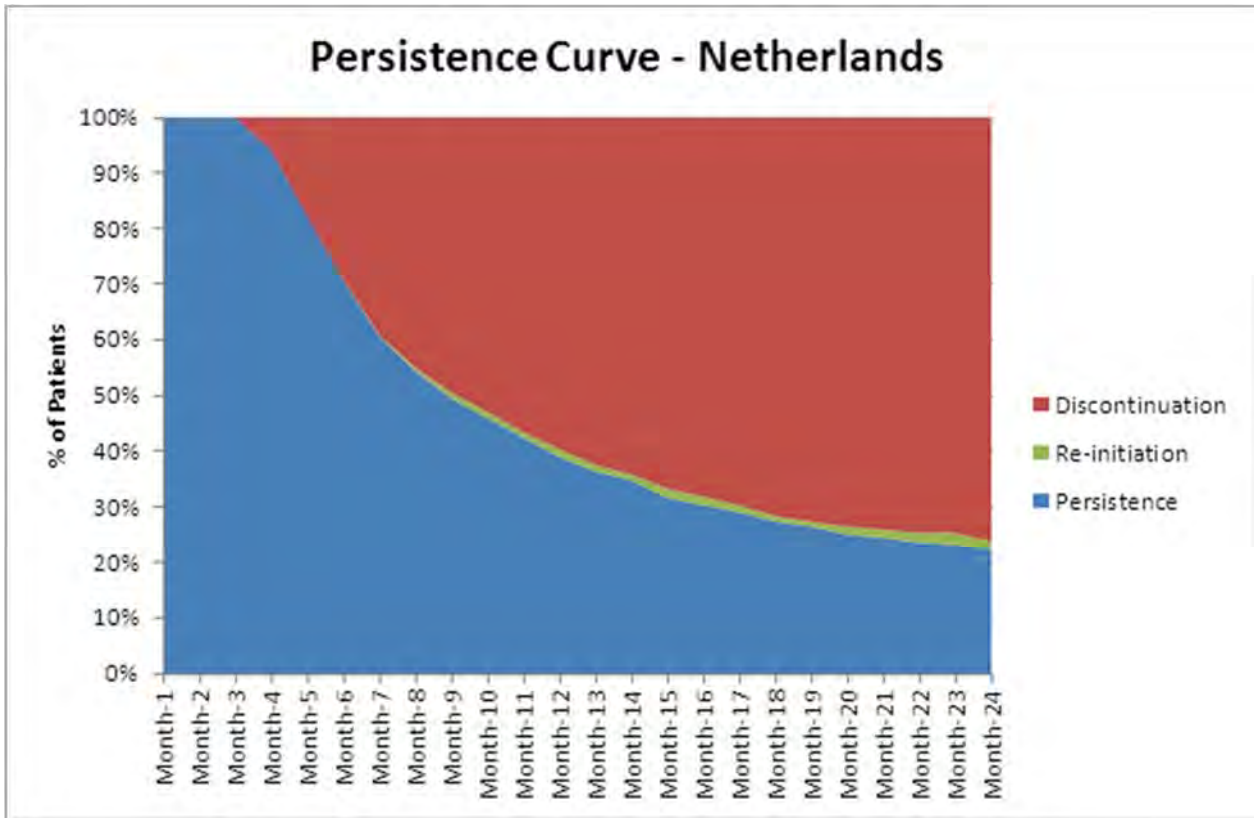

Figure 2. **Persistence over a 24-month period among patients in the Netherlands**

In the Netherlands, the mean gap between episodes is approximately 202 days (Table 24). The largest gap between episodes was found among patients 18 to 34 years old. There is no pattern in the gap between treatment as the number of episodes increases, as the mean days for 2 episodes or more is 202, the mean gap for 3 episodes or more is 204 days, and the mean gap between episodes 3 and 4 is 188 days.

Table 24. Netherlands: Mean gap (in days) between treatment episodes

	Episode Gaps All ≥2 Episodes		Gap between Episode 1 and 2 ≥2 Episodes		Gap between Episode 2 and 3 ≥3 Episodes		Gap between Episode 3 and 4 ≥4 Episodes	
	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)
0-5 years	0	(-)	0	(-)	0	-	0	-
6-9 years	6	202.4 (172)	6	221 (180)	1	91.0 (-)	0	-
10-12 years	6	200.1 (126)	6	173.2 (50)	2	305.0 (293)	1	152.0 (-)
13-17 years	14	192.8 (119)	14	196.0 (130)	2	155.0 (79.2)	1	223.0 (-)
18-34 years	13	212.3 (120)	13	215.0 (127)	2	194.5 (100)	0	-
35-64 years	10	202 (176)	10	198.5 (190)	2	219.5 (121)	0	-
65+ years	0	-	0	-	0	-		-
<18 years	26	196.8 (129)	26	196.5 (126)	5	202.2 (180)	2	187.5 (50)
18-64 years	23	207.7 (145)	23	207.8 (154)	4	207.0 (92)	0	-
Unknown	0	0	0	-	0	- (-)	0	-
Total	**49**	**201.7 (135)**	**49**	**201.8 (138)**	**9**	**204.3 (139)**	**2**	**187.5 (50)**

Abbreviation: sd = standard deviation.

United Kingdom

In the UK, 19% of patients in this study are treated past 23 months and reinitiation past 23 months is 5% (Table 25). At 16 months, discontinuation is greater than 60%. Reinitiation is the highest between 18 and 20 months. In general, persistence on therapy upon initiation is 100% until 3 months. After 3 months, there is a gradual increase in discontinuation over time (Figure 3).

Table 25. UK: Patient persistence by month over a 24-month period (percent)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100%	100%	100%	86%	78%	69%	61%	56%	51%	49%	42%	42%
Discontinuation	0%	0%	0%	14%	22%	31%	36%	39%	41%	41%	49%	44%
Re-initiation	0%	0%	0%	0%	0%	0%	3%	5%	8%	10%	8%	14%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	41%	36%	34%	29%	29%	29%	29%	24%	24%	20%	20%	19%
Discontinuation	51%	56%	59%	63%	61%	58%	59%	64%	66%	69%	73%	76%
Re-initiation	8%	8%	7%	8%	10%	14%	12%	12%	10%	10%	7%	5%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

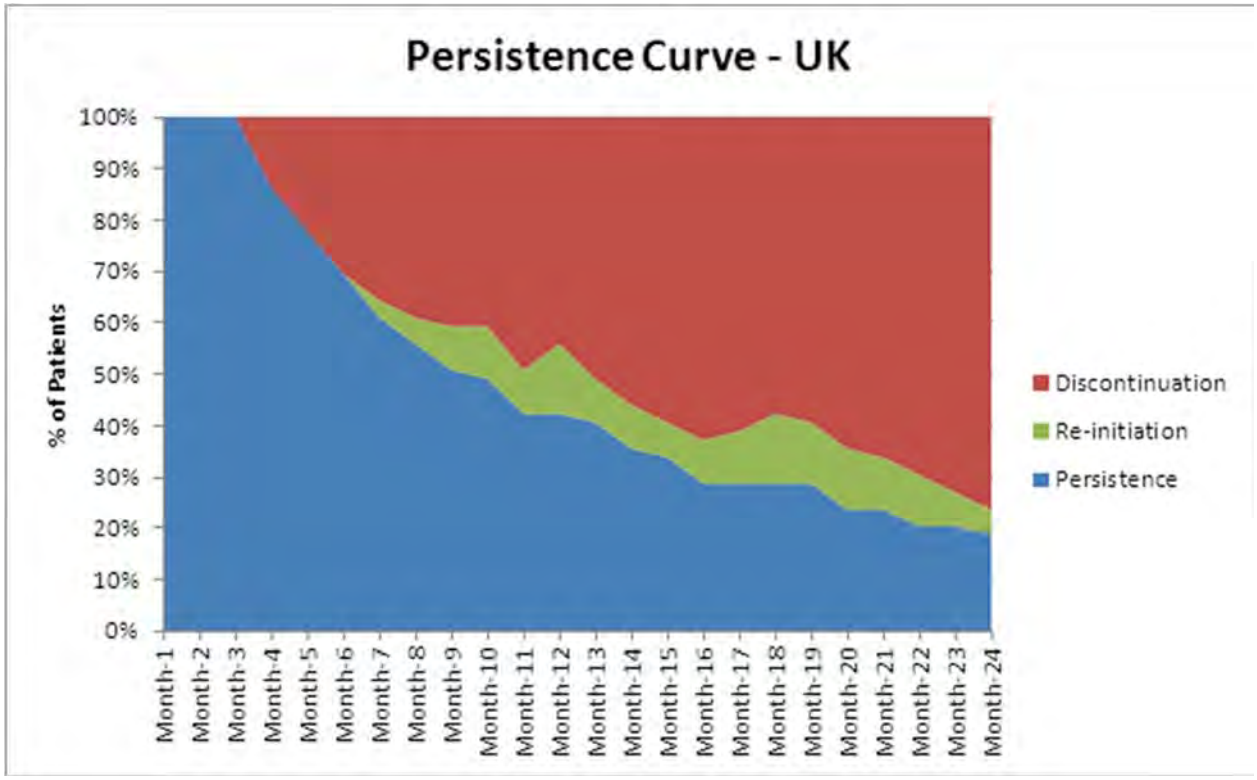

Figure 3. Persistence over a 24-month period among patients in the UK

In the UK, the mean gap between episodes is approximately 180 days (Table 26). The largest gap between episodes was found among patients 10 to 12 years old. The mean days for 2 episodes or more is 192, the mean gap for 3 episodes or more is 150 days, and the mean gap between episodes 3 and 4 is 107 days.

Table 26. UK: Mean gap (in days) between treatment episodes

	Episode Gaps All ≥2 Episodes		Gap between Episode 1 and 2 ≥2 Episodes		Gap between Episode 2 and 3 ≥3 Episodes		Gap between Episode 3 and 4 ≥4 Episodes	
	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)
0-5 years	0	-	0	-	0	-	0	-
6-9 years	0	-	0	-	0	-	0	-
10-12 years	2	223 (164)	1	339 (-)	0	-	1	107 (-)
13-17 years	8	164.6 (56)	7	164.0 (61)	1	169 (-)	0	-
18-34 years	3	209.3 (138)	3	209.3 (138)	0	-	0	-
35-64 years	1	130 (-)	0	-	1	130 (-)	0	-
65+ years	0	-	0	-	0	-	0	-
<18 years	10	176.3 (78)	8	185.9 (83)	1	169 (-)	1	107 (-)
18-64 years	4	189.5 (119)	3	209.3 (138)	1	130 (-)	0	-
Unknown	0	-	0	-	0	-	0	-
Total	**14**	**180.1 (87)**	**11**	**192.3 (94)**	**2**	**149.5 (28)**	**1**	**107 (-)**

Abbreviation: sd = standard deviation.

Sweden

In Sweden, 19% of patients were persistent after 24 months and reinitiation within 24 months is 4% (Table 27). At 13 months, discontinuation is greater than 60%. Reinitiation of Strattera is consistent over time. In general, persistence on Strattera therapy upon initiation is 100% until 4 months. After 4 months, there is a gradual increase in treatment discontinuation over time (Figure 4).

Table 27. Sweden: Patient persistence by month over a 24-month period (percent)

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100%	100%	100%	100%	84%	70%	61%	54%	49%	45%	41%	38%
Discontinuation	0%	0%	0%	0%	16%	30%	38%	44%	48%	52%	55%	57%
Re-initiation	0%	0%	0%	0%	0%	0%	1%	2%	3%	4%	4%	4%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	36%	34%	32%	30%	28%	26%	24%	23%	22%	21%	20%	19%
Discontinuation	61%	63%	64%	66%	68%	69%	71%	72%	74%	75%	76%	77%
Re-initiation	4%	4%	4%	5%	4%	4%	4%	5%	4%	4%	4%	4%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

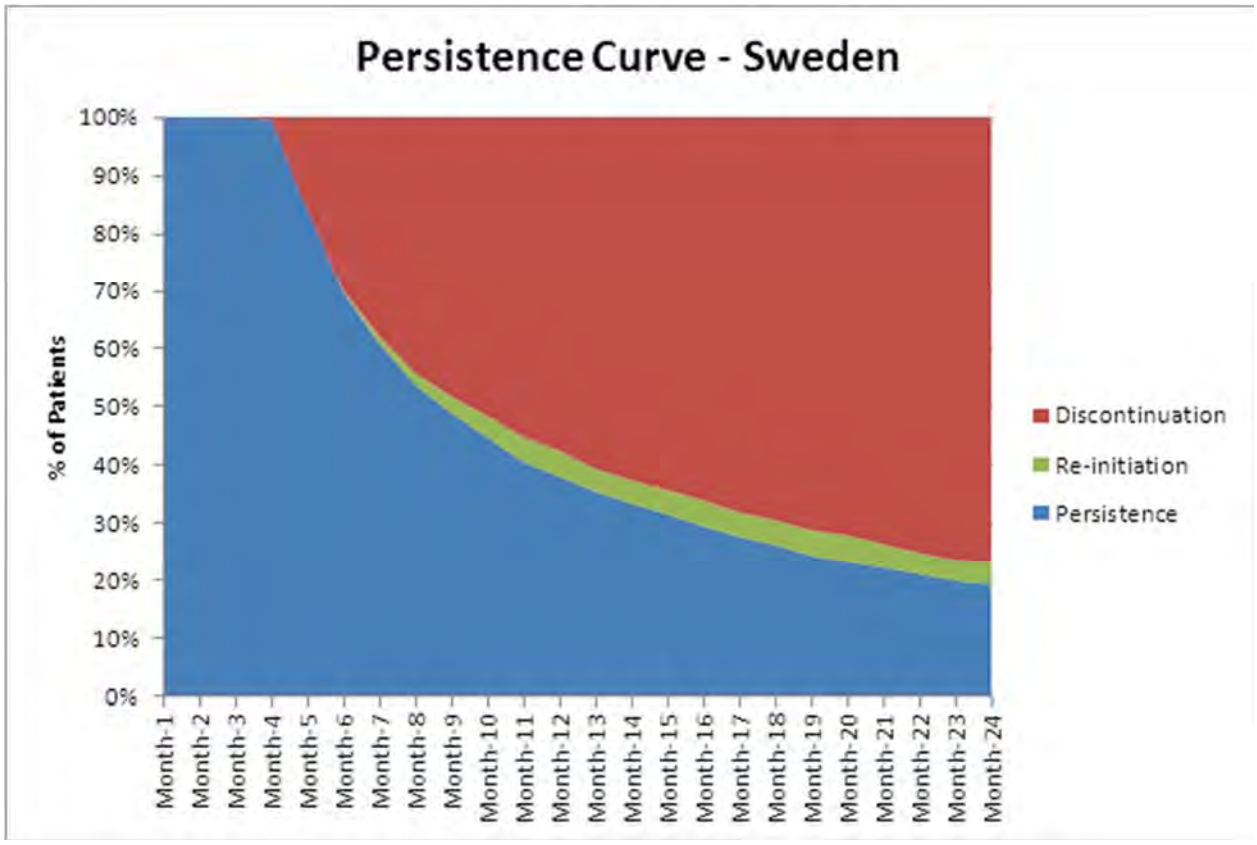

Figure 4. Persistence over a 24-month period among patients in Sweden

In Sweden, the mean gap between episodes is approximately 87 days (Table 28). The largest gap between episodes was found among patients 35 to 64 years old. The mean days for 2 episodes or more is approximately 94 days and the mean gap for 3 episodes or more is 53 days. In Sweden, numbers <10 cannot be reported so the data are not available for patients treated with 4 or more episodes.

Table 28. Sweden: Mean gap (in days) between treatment episodes

	Episode Gaps All ≥2 Episodes		Gap between Episode 1 and 2 ≥2 Episodes		Gap between Episode 2 and 3 ≥3 Episodes		Gap between Episode 3 and 4 ≥4 Episodes	
	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)	N	Mean days (sd)
0-5 years	N<10	-	N<10	-	-	-	-	-
6-9 years	33	78.6 (126)	33	85.9 (136)	N<10	-	N<10	-
10-12 years	42	75.4 (115)	42	81.1 (120)	N<10	-	N<10	-
13-17 years	128	79.2 (106)	128	84.0 (114)	24	62 (62)	N<10	-
18-34 years	98	98.7 (120)	87	107.6 (126)	11	42.9 (24.3)	N<10	-
35-64 years	42	104.9 (105)	42	111.7 (111)	N<10	-	N<10	-
65+ years	-	-	-	-	-	-	-	-
<18 years	203	77.9 (111)	203	83 (119)	24	53.2 (58)	N<10	-
18-64 years	140	100.8 (115)	140	109 (121)	11	53.9 (39)	N<10	-
Unknown	-	-	-	-	-	-	-	-
Total*	**343**	**87 (113)**	**343**	**93.6 (120)**	**35**	**53.4 (52)**	**N<10**	**-**

Abbreviation: sd = standard deviation.

* Excludes rows with N<10. Numbers less than 10 are not reported, as required by the National Drug and Prescription Register.

10.5. Other analyses

Percentages of patients with ADHD diagnosis (ICD-10 F90) during 24 months of follow-up

German and Netherlands' LRx data, which are pharmacy claims data, do not have medical claims data. We are not able to provide the information of ADHD diagnosis and comorbidities for patients in these 2 countries as we do not have the medical claims data.

Table 29 shows that among patients in the UK new to Strattera, 31% have an ADHD diagnosis recorded within the 24-month follow-up. This low percentage can be attributed to many causes, such as differences in the way ADHD is coded and treated in the UK, and that the actual diagnosis may have occurred outside the 24-month observation window.

Table 29. Proportion of ADHD diagnoses among Strattera users during a 24-month follow-up in UK

	Strattera	Patients w/ ADHD	Proportion ADHD
Age in years	N	N	%
0-5 years	2	1	50%
6-9 years	300	101	34%
10-12 years	474	155	33%
13-17 years	766	215	28%
18-34 years	213	81	38%
35-64 years	46	14	30%
65+ years	0	0	0%
<18 years	1542	472	31%
18-64 years	259	95	37%
Unknown Age	0	0	0%
Total	**1801**	**567**	**31%**

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; UK = United Kingdom.

Table 30 includes the 30 most frequent ICD – 10 diagnosis codes recorded for a 24-month follow-up period among all patients in the UK. These are the most common diagnoses found in the data among patients treated with Strattera in both the CPRD and DA databases.

Table 30. 30 most frequent diagnosis codes during a 24-month follow-up for all patients in the UK

ICD10 Level 4	Description	N	%
F900	DISTURBANCE ACTVTY/ATTEN	425	35%
R694	DIOC ADMIN CODES	329	27%
J069	AC UPP RESP INFECT UNSP	173	14%
F909	HYPERKINETIC DIS UNSP	122	10%
L700	ACNE VULGARIS	112	9%
R698	ILL DEFINED DIAG	91	7%
M796	PAIN IN LIMB	90	7%
J039	ACUTE TONSILLITIS UNSP	88	7%
J459	ASTHMA UNSPECIFIED	86	7%
B070	VIRAL WARTS	85	7%
J220	UNSP AC LOW RESP INFECT	82	7%
H920	OTALGIA	68	6%
T149	INJURY UNSPECIFIED	63	5%
F990	Mental disorder NOS	61	5%
L989	DIS SKN/SUBCUT TISS UNSP	52	4%
F840	CHILDHOOD AUTISM	51	4%
J301	ALLERG RHINITIS-POLLEN	49	4%
M255	PAIN IN JOINT	49	4%
R688	OTHER GENERAL SYMPTOMS AND SIGNS	48	4%
L010	IMPETIGO-ANY ORGNISM/STE	45	4%
H103	AC CONJUNCTIVITIS UNSP	44	4%
L209	ATOPIC DERMATITIS UNSP	42	3%
H669	OTITIS MEDIA UNSP	41	3%
J029	ACUTE PHARYNGITIS UNSP	41	3%
F845	ASPERGER'S SYNDROME	40	3%
L089	LOC INF SKN/SC TISS UNSP	40	3%
L600	INGROWING NAIL	40	3%
F919	CONDUCT DISORDER UNSP	37	3%
R104	OTH AND UNSP ABDO PAIN	35	3%
R210	RASH/OTH UNSP SKIN ERUPT	34	3%
Total	**Total**	**1231**	**100%**

Table 31 includes the 30 most frequent drug/treatment codes recorded for a 24-month follow-up period among all patients in the UK DA database. This list includes the most common drugs/treatments found in the data among patients treated with Strattera. The tables that follow not only include specific drugs or treatments but also related procedures used for billing

purposes. The nature of using these types of codes allows for inclusion of codes that do not always describe specific drugs or treatments.

Table 31. 30 most frequent ICD-10 codes during a 24-month follow-up for all patients in the UK using Disease Analyser

UK - DA			
ATC Level 4		**N**	**%**
N07X0	ALL OTHER CNS DRUGS	225	100%
N06B0	PSYCHOSTIMULANTS	87	39%
J01C1	BROAD SPECT PENICILL ORAL	52	23%
J01H1	MED/NARROW SPECT PEN PLAI	37	16%
N02B0	NON-NARCOTIC ANALGESICS	36	16%
N05A1	ATYPICAL ANTIPSYCHOTICS	36	16%
R03A4	SHORT-ACT B2-STIM,INHAL	34	15%
R06A0	ANTIHISTAMINES SYSTEMIC	31	14%
D02A0	EMOLLIENTS & PROTECTIVES	30	13%
Z98A0	SPEC DUMMY NON VET	30	13%
J01F0	MACROLIDES & SIMILAR TYPE	23	10%
M01A1	ANTIRHEUMATICS NON-S PLN	23	10%
D07A0	TOP CORTICOSTEROIDS PLAIN	21	9%
N05B1	NON-BARBITURATE PLAIN	21	9%
D06A0	TOPICAL ANTIBACTERIALS	19	8%
R03D1	CORTICOIDS INHALANTS	17	8%
D01A1	TOPICAL DERMAT ANTIFUNGAL	14	6%
D11A0	OTHER DERMATOLOGICAL PREP	14	6%
S02C0	STEROID ANTI-INFECT EAR	14	6%
S01A0	ANTI-INFECTIVES-EYE	13	6%
A06A9	OTHER LAXATIVES	12	5%
D10A0	TOPICAL ANTI-ACNE PREPS	11	5%
Y19A0	SPACERS	11	5%
N02C9	ALL OTH A-MIGRAINE PREPS	10	4%
H02A2	ORAL CORTICOSTEROID PLAIN	9	4%
J01A0	TETRACYCLINES & COMBS	9	4%
N06A4	SSRI ANTIDEPRESSANTS	9	4%
R01A1	NASAL CORTIC W/O ANTI-INF	9	4%
D07B2	TOP STEROIDS+ANTI-FUNG	8	4%
N01B3	ANAESTH LOCAL TOPICAL	8	%
Total		**225**	**100%**

Table 32 includes the 30 most frequent drug/treatment codes recorded for a 24-month follow-up period among all patients in the UK CPRD database. This list includes the most common drugs/treatments found in the data among patients treated with Strattera. As with the DA data source, the nature of using these codes allows for inclusion of codes that do not describe specific drugs but also describe procedures used for billing purposes.

Table 32. 30 most frequent medications in a 24-month follow-up for all patients in the UK using CPRD

UK - CPRD		
	N	%
CNS Stimulants And Drugs Used For Attention Deficit Hyperactivity Disorder	1576	100%
Broad-spectrum Penicillins	349	22%
Hypnotics	341	22%
Selective Beta 2 Agonists	221	14%
Non-opioid And Compound Analgesics	206	13%
Antipsychotic Drugs	198	13%
Non-steroidal Anti-inflammatory Drugs	191	12%
Non-sedating Antihistamines	190	12%
Penicillinase-resistant Penicillins	174	11%
Corticosteroids (for Respiratory Conditions)	148	9%
Topical Corticosteroids	130	8%
Benzylpenicillin And Phenoxymethylpenicillin	128	8%
Corticosteroids Used In Nasal Allergy	105	7%
Selective Serotonin Re-uptake Inhibitors	102	6%
Topical Corticosteroids With Antimicrobials	84	5%
Bronchodilators	82	5%
Sedating Antihistamines	81	5%
Emollient Bath Additives And Shower Preparations	79	5%
Antibacterial Preparations Only Used Topically/Antibacterial Preparations Also Used Systemically (for Skin Conditions)	77	5%
Emollient Skin Preparations	77	5%
Macrolides	74	5%
Antibacterials (in Eye Preparation)	72	5%
Sulphonamides And Trimethoprim	66	4%
Control Of Epilepsy	63	4%
Topical Antibacterials For Acne	61	4%
Emollients	56	4%
Macrolides/Oral Antibacterials For Acne	55	3%
Proton Pump Inhibitors	55	3%
Unknown	55	3%
Osmotic Laxatives	51	3%
Total	**1576**	**100%**

Table 33 describes the proportion of ADHD diagnoses captured in the 24-month follow-up period among new users of Strattera in Sweden. Among patients in Sweden new to Strattera, 71% have an ADHD diagnosis recorded within the 24-month follow-up.

Table 33. Proportion of ADHD diagnoses among Strattera users during a 24-month follow-up in Sweden

	Straterra	Patients w/ ADHD	Proportion ADHD
Age in years	N	N	%
0-5 years	33	16	48%
6-9 years	993	726	73%
10-12 years	2192	1550	71%
13-17 years	3521	2445	69%
18-34 years	2676	1949	73%
35-64 years	1592	1089	68%
65+ years	21	N<10	-
<18 years	6739	4737	70%
18-64 years	4268	3038	71%
Unknown Age	0	0	0%
Total	**11007**	**7775**	**71%**

Abbreviation: ADHD = attention-deficit/hyperactivity disorder.

Table 34 includes the 30 most frequent diagnosis codes recorded for a 24-month follow-up period among all patients in the Sweden. These are the most common diagnoses found in the data among patients treated with atomoxetine.

Table 34. 30 most frequent ICD-10 codes during a 24-month follow-up for all patients in Sweden

ICD10 Level 4	Description	N	%
F900	Disturbance of activity and attention	7566	85%
R104	Other and unspecified abdominal pain	746	8%
F845	Asperger syndrome	714	8%
F419	Anxiety disorder, unspecified	632	7%
F329	Depressive episode, unspecified	480	5%
Z004	General psychiatric examination, not elsewhere classified	449	5%
F412	Mixed anxiety and depressive disorder	440	5%
F909	Hyperkinetic disorder, unspecified	422	5%
F192	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances, Dependence syndrome	422	5%
F952	Combined vocal and multiple motor tic disorder [de la Tourette]	370	4%
F840	Childhood autism	323	4%
Z038	Observation for other suspected diseases and conditions	325	4%
F849	Pervasive developmental disorder, unspecified	295	3%
F319	Bipolar affective disorder, unspecified	289	3%
B182	Chronic viral hepatitis C	290	3%
Z090	Follow-up examination after surgery for other conditions	263	3%
F603	Emotionally unstable personality disorder	265	3%
F100	Mental and behavioural disorders due to use of alcohol, Acute intoxication	255	3%
F321	Moderate depressive episode	248	3%
F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	247	3%
T509	Other and unspecified drugs, medicaments and biological substances	248	3%
F102	Mental and behavioural disorders due to use of alcohol, Dependence syndrome	238	3%
F191	Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances, Harmful use	235	3%
J459	Asthma, unspecified	224	3%
F101	Mental and behavioural disorders due to use of alcohol, Harmful use	225	3%
F913	Oppositional defiant disorder	218	2%
Z032	Observation for suspected mental and behavioural disorders	212	2%
F609	Personality disorder, unspecified	214	2%
R074	Pain in throat and chest	200	2%
F700	Family history of mental retardation	203	2%
Total		**8887**	**100%**

Table 35 includes the 30 most frequent drug/treatment codes recorded for a 24-month follow-up period among all patients in Sweden. This list includes the most common drugs/treatments found in the data among patients treated with Strattera. As with the UK data sources, the nature of using these codes allows for inclusion of codes that do not describe specific drugs but also describe procedures used for billing purposes.

Table 35. 30 most frequent medications in a 24-month follow-up for all patients in Sweden

ATC Level 4	Description	N	%
N06BA	Centrally acting sympathomimetics	11028	100%
N06AB	Selective serotonin reuptake inhibitors	2442	22%
J01CE	Beta-lactamase sensitive penicillins	2349	21%
N05CH	Melatonin receptor agonists	2315	21%
R06AD	Phenothiazine derivatives	2004	18%
N05CF	Benzodiazepine related drugs	1777	16%
N06AX	Other antidepressants	1508	14%
N05BB	Diphenylmethane derivatives	1475	13%
R03AC	Selective beta-2-adrenoreceptor agonists	1337	12%
N05BA	Benzodiazepine derivatives	1278	12%
N03AX	Other antiepileptics	1254	11%
N05CM	Other hypnotics and sedatives	1239	11%
N02BE	Anilides	1226	11%
A02BC	Proton pump inhibitors	1213	11%
M01AB	Acetic acid derivatives and related substances	1187	11%
R01AD	Corticosteroids	1168	11%
N05AX	Other antipsychotics	1089	10%
R05CB	Mucolytics	1057	10%
R06AX	Other antihistamines for systemic use	988	9%
J01CF	Beta-lactamase resistant penicillins	959	9%
N05AH	Diazepines, oxazepines, thiazepines and oxepines	927	8%
A01AA	Caries prophylactic agents	921	8%
R05FA	Opium derivatives and expectorants	864	8%
M01AE	Propionic acid derivatives	836	8%
J01AA	Tetracyclines	790	7%
R03BA	Glucocorticoids	782	7%
N02AA	Natural opium alkaloids	775	7%
J01CA	Penicillins with extended spectrum	767	7%
G03AC	Progestogens	708	6%
D07AC	Corticosteroids, potent (group III)	651	6%
Total		**11028**	

The following tables describe trends among new users that restart therapy.

Table 36 describes the number of new users in Germany restarting therapy over a period of 24 months of follow-up. In Germany, a total of 346 new users restarted therapy over the 24-month follow-up period. A total of 272 new users had 2 episodes of treatment.

Table 36. Germany: Patients restarting therapy over a 24-month period (new users)

	Total			Number of Restarters by episodes					
Age in years	**New Users**	**Restarters**		**2 episodes**		**3 episodes**		**4 episodes**	
	N	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	20	1	0%	1	0%	0	0%	0	0%
6-9 years	395	74	21%	59	22%	12	19%	3	27%
10-12 years	536	119	34%	96	35%	19	30%	4	36%
13-17 years	465	109	32%	80	29%	25	40%	4	36%
18-34 years	116	28	8%	25	9%	3	5%	0	0%
35-64 years	36	7	2%	4	1%	3	5%	0	0%
65+ years	4	0	0%	0	0%	0	0%	0	0%
<18 years	1416	303	88%	236	87%	56	89%	11	100%
18-64 years	152	35	10%	29	11%	6	10%	0	0%
Unknown	45	8	2%	7	3%	1	2%	0	0%
Total	**1617**	**346**	**100%**	**272**	**100%**	**63**	**100%**	**11**	**100%**

Table 37 describes the number of new users in the Netherlands restarting therapy over a period of 24 months of follow-up. In the Netherlands, a total of 49 new users restarted therapy over the 24-month follow-up period. A total of 40 restarters had 2 episodes of treatment. Among this group of new users, only 7 had 3 episodes of treatment and 2 had 4 episodes of treatment.

Table 37. Netherlands: Patients restarting therapy over a 24-month period (new users)

	Total			Number of Restarters by episodes					
Age in years	New Users	Restarters		2 episodes		3 episodes		4 episodes	
	N	N	%	N	%	N	%	N	%
0-5 years	1	0	-	0	-	0	-	0	-
6-9 years	110	6	12%	5	13%	1	14%		
10-12 years	110	6	12%	4	10%	1	14%	1	50%
13-17 years	135	14	29%	12	30%	1	14%	1	50%
18-34 years	110	13	27%	11	28%	2	29%	0	-
35-64 years	78	10	20%	8	20%	2	29%	0	-
65+ years	2	0	-	0	-	0	-	0	-
<18 years	356	26	53%	21	53%	3	43%	2	100%
18-64 years	188	23	47%	19	48%	4	57%	0	-
Unknown	0	-	0	-	0	-	0	-	0
Total	**546**	**49**	**100%**	**40**	**100%**	**7**	**100%**	**2**	**100%**

Table 38 describes the number of new users in the UK restarting therapy over a period of 24 months of follow-up. In the UK, a total of 14 new users restarted therapy over the 24-month follow-up period. A total of 11 restarters had 2 episodes of treatment. Among this group of new users, only 2 had 3 episodes of treatment and 1 had 4 episodes of treatment.

Table 38. UK: Patients restarting therapy over a 24-month period (new users)

	Total			Number of Restarters by episodes					
Age in years	New Users	Restarters		2 episodes		3 episodes		4 episodes	
	N	N	%	N	%	N	%	N	%
0-5 years	0	0	0%	0	0%	0	0%	0	0%
6-9 years	3	0	0%	0	0%	0	0%	0	0%
10-12 years	13	2	15%	1	8%	0	0%	1	8%
13-17 years	35	8	23%	7	20%	1	3%	0	0%
18-34 years	7	3	43%	3	43%	0	0%	0	0%
35-64 years	1	1	100%	0	0%	1	100%	0	0%
65+ years	0	0	0%	0	0%	0	0%	0	0%
<18 years	51	10	20%	8	16%	1	2%	1	2%
18-64 years	8	4	50%	3	38%	1	13%	0	0%
Unknown	0	0	0%	0	0%	0	0%	0	0%
Total	**59**	**14**	**24%**	**11**	**19%**	**2**	**3%**	**1**	**2%**

Table 39 describes the number of new users in Sweden restarting therapy over a period of 24 months of follow-up. In Sweden, a total of 343 new users restarted therapy over the 24-month follow-up period. A total of 308 restarters had 2 episodes of treatment. Among this group of new users, 35 had 3 episodes of treatment. The numbers were too small to report among the users with 4 episodes of treatment.

Table 39. Sweden: Patients restarting therapy over a 24-month period (new users)

	Total			Number of Restarters by episodes					
Age in years	**New Users**	**Restarters**		**2 episodes**		**3 episodes**		**4 episodes**	
	N	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
0-5 years	**N<10**	N<10	-	N<10	-	-	-	-	-
6-9 years	**242**	33	14%	33	14%	N<10	-	N<10	-
10-12 years	**277**	42	15%	42	15%	N<10	-	-	-
13-17 years	**527**	128	24%	104	20%	24	5%	N<10	-
18-34 years	528	98	19%	87	16%	11	2%	N<10	-
35-64 years	306	42	14%	42	14%	N<10	-	N<10	-
65+ years	**N<10**	N<10	-	-	-	N<10	-	-	-
<18 years	1046	203	19%	179	17%	24	2%	N<10	-
18-64 years	834	140	17%	129	15%	11	1%	N<10	-
Unknown		-	-	-	-	-	-	-	-
Total	**1880**	**343**	**18%**	**308**	**16%**	**35**	**2%**	**N<10**	**-**

10.6. Adverse events/adverse reactions

No adverse events were reported in this analysis.

11. Discussion

11.1. Key results

Age

In general, in each of the countries, the majority of patients treated with Strattera are between 13 and 17 years old. Strattera use among children 0 to 5 years old and adults 65 and older is 0 to 1% across countries. The age distribution in the current study was more granular and included greater stratification of the adult-treated population. The current study added the following age strata: 35 to 64, 65+, <18, 18 to 64. This information is especially important given the recent approval of an indication for treatment among adults. Over time, subsequent drug utilisation studies will provide important information on any changes in the adult population treated with Strattera. In Sweden, the data source for this study allowed for greater population-based coverage, which allowed for better assessment of treatment trends in this country. Even with the change in the data source, the overall trends observed were similar.

Gender

The majority of Strattera users are male, particularly for users younger than 18. In some countries, the gender distribution becomes more similar with increased age. This trend was also observed in the original Study B019.

Mean daily dose

Overall, the MDD between countries ranged from approximately 32 mg (Germany) to 49 mg (Sweden). When age group is taken into consideration, the highest MDD in Germany (45 mg) was among patients 18 to 34 years old and the UK (50 mg) was among patients 13 to 17 years old (51 mg). In the Netherlands, the highest MDD was recorded among patients treated with Strattera who were 65 and older. This estimate in the Netherlands may not be representative as only 2 treated patients were included. In Sweden, the highest MDD (58 mg) was among patients 35 to 64 years old. Overall, for a pediatric population, these mean doses could be appropriate for patients with lower weight and may be low for patients that weigh approximately 50 kg. For the adult population, the observed MDD seems to be below the recommended target dose.

Mean days supplied over 24 months, the medication possession ratio, and persistence

The mean days supplied ranged from approximately 280 days (Sweden) to 373 days (UK), and the MPR ranged from 38% (Sweden) to 51% (UK). The findings for the Netherlands (304 days) and Germany (314 days) were very similar. Overall, the MPR was approximately 40% and the mean days supplied was close to 300 days. The MPR is the proportion of days during the treatment period (24 months) that the patient is considered persistent. In Sweden, on average, patients were treated for 280 days, which translates to 38% treated days over a 24-month period (730 days). The country with the largest number of treatment days was the UK. In the UK, on average, patients were treated 373 days, which translates to 51% treated days over a 24-month period (730 days).

Treatment episodes and length of treatment

Overall, the majority of patients were treated with 1 episode and the mean number of days treated ranged from 304 in the Netherlands to 411 in Sweden.

Recorded medication use and medical conditions

In the UK, between the 2 databases (CPRD and DA) used to assess medication use among Strattera-treated patients, many of the listed drugs are associated with treatment of psychiatric disorders. Many others include treatment for infections and various common conditions. Neither cardiovascular conditions nor medication for cardiovascular disease were listed among the 30 most common conditions/medications. Of the 30 most common conditions, several were related to psychiatric disorders, such as disturbance activity/attention (35%), mental disorder NOS (5%), and conduct disorder (3%). Table 29 shows that in the UK, among patients new to atomoxetine, 30% have a recorded ADHD diagnosis within the 24-month follow-up period. One can speculate that this low percentage can be attributed to many causes such as differences in the way ADHD is coded and treated in the UK, and that the actual diagnosis may have occurred outside the 24-month observation window.

In Sweden, a high proportion of medications listed are for treating psychiatric disorders. All patients in the cohort were taking centrally acting sympathomimetics. Many other medications for treating psychiatric conditions were listed, including: SSRI (22%); melatonin receptor agonists (21%); benzodiazepine-related drugs (16%). Of the listed medical conditions, 85% of the Strattera-treated patients had a recorded diagnosis of disturbance of activity and attention and 5% listed hyperkinetic disorder, unspecified. Neither cardiovascular conditions nor medication for cardiovascular disease were listed among the 30 most common conditions/medications. Table 33 shows that among patients new to Strattera, 70% have a recorded ADHD diagnosis within the 24-month follow-up period. This proportion is notably higher than the findings in the UK. One can speculate that these findings could also be attributed to differences in the way ADHD is coded and treated in Sweden. It is also possible that in the Swedish cohort, the actual diagnoses may have occurred outside of the 24-month observation window.

11.2. Limitations

Limitations to the methodology used for this study include:

- The types of data sources used for each country varied. Germany and the Netherlands used claims data, whereas Sweden used the most comprehensive combined pharmacy data with national healthcare data. The UK combined CPRD clinical data with disease analyser patient database. Care should be taken when comparing the data from these different data sources.
- The sample size in the UK was notably smaller than the other countries and, as a result, the findings may not be representative of the entire country.
- ADHD diagnoses from claims and encounter databases is limited (Habel et al. 2011). In this report, this is apparent for the UK and Sweden in the effort to identify the common comorbidities as administrative and procedural codes are included.

11.3. Interpretation

This study assessed drug utilisation patterns of Strattera initiators in the UK, Germany, the Netherlands, and Sweden. Patterns of treatment assessed with MPR, mean days treated, discontinuation, and persistence show that, on average, persistence past 1 year is approximately 50% overall. Among users in the UK and Sweden, neither cardiovascular outcomes nor use of medication for the treatment of cardiovascular outcomes were listed among the 30 most common conditions/medications. This is reassuring and may be the result of appropriate assessment for preexisting cardiovascular conditions, as recommended in the Summary of Product Characteristics (SmPC), among patients being assessed for ADHD treatment with Strattera. These findings are consistent with the literature and findings from a recent risk minimisation assessment survey (B4Z-MC-B024) conducted in Europe among healthcare professionals (HCPs). This survey found that the majority of physicians participating in the survey are aware of and adhere to the recommendation to monitor blood pressure and heart rate in all patients at baseline and during treatment with Strattera, indicating that core risk minimisation activities, particularly appropriate labeling, are effective in managing these cardiovascular risks.

Overall, duration of treatment is relatively short (1 year on average), patients receive 1 episode of treatment, and the MPR show that treatment is generally not continuous over time. Additionally, data from short-term and long-term Strattera clinical trials show that the increases in blood pressure and heart rate observed during treatment with Strattera do not persist after the drug is discontinued. This may explain the fact that studies conducted in the US have reported no significant difference in cardiovascular outcomes among ADHD medication users versus nonusers (Cooper et al. 2011; Schelleman et al. 2011). One study comparing the rate of severe cardiovascular events and death in children 3 to 17 years old treated with ADHD medications compared to nonusers found the rate of cardiovascular events in exposed children was, in general, no higher than among controls (Schelleman et al. 2011). A retrospective cohort study, conducted by Agency for Healthcare Research and Quality (AHRQ) and FDA funded, using data from 4 health plans assessed the risk of serious cardiovascular events (sudden cardiac death, acute myocardial infarction, and stroke) in children and young adults between the ages of 2 and 24 (Cooper et al. 2011). This study did not find evidence that current use of an ADHD medication was associated with an increased risk of serious cardiovascular events (Cooper et al. 2011).

11.4. Generalisability

The countries included in this study represent a large market share of Strattera use in the EU. As a result these study findings should be representative of patients and treatment patterns in the EU, however sample sizes should be considered.

12. Other information

Not applicable.

13. Conclusion

In conclusion, the potential risk of long-term severe cardiovascular outcomes related to Strattera treatment do not appear any different from those reported in large pharmacoepidemiological cohort studies conducted in the US. The most frequent diagnoses and medications listed among Strattera-treated patients were not associated with cardiovascular conditions. This drug utilisation study found mean treatment episodes for Strattera patients in UK, Germany, the Netherlands, and Sweden varied, but were approximately 1 year and the majority of patients are treated with 1 episode. The overall Strattera persistence patterns in these EU countries are lower than those reported in the US. Patterns of usage show that, on average, persistence past 1 year is low. Taking into account MPR and mean days treated, even with persistence of more than 1 year, the patient is not necessarily being treated continuously during this period.

14. References

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Annex 1. List of standalone documents

Not applicable.

Annex 2. Additional information

Not applicable.