PASS Information

Title	Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2018 Bi-annual assessment report. (B4Z-MC-B026)
Version identifier of the final study report	001
Date of last version of the final study report	N/A
EU PAS register number	EUPAS17371
Active substance	Atomoxetine hydrochloride
Medicinal product(s):	10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, 100 mg capsules, and 4 mg/ml oral solution
Product reference:	UK/H/0686/002-009
Procedure number:	Not applicable
Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	The objective of this study is to describe atomoxetine (Strattera) utilisation patterns for patients treated in Germany, United Kingdom (UK), Sweden, and the Netherlands
Country(-ies) of study	The United Kingdom, Germany, the Netherlands, and Sweden
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Signature of principal investigator	Signature on file/see approval date below

Approval Date: 12-Mar-2018 GMT

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1. Abstract

Title: Strattera patient exposures and adherence in the United Kingdom, Germany, the Netherlands, and Sweden: 2018 Bi-annual assessment report. (B4Z-MC-B026)

Keywords: Atomoxetine, ADHD, drug utilisation, Europe

Rationale and background: In 2003, Eli Lilly and Company (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 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 of ADHD medications in more recent years (Brett 2017). In 2014, the oral solution of atomoxetine was approved and marketing began in 2015 in various EU countries.

Research question and objectives: The main objective of this retrospective database study is to describe Strattera utilisation patterns for patients treated in the United Kingdom (UK), Germany, the Netherlands, and Sweden, by country and age group. This includes 1) estimating number of patients exposed to Strattera on years of available data, 2) estimating duration of exposure, medication possession ratio, and dose over the most recent 24 months of data available for capsules and 18 months for the oral solution, 3) for those who stopped taking Strattera, estimating the number that restarted, gap time between, and duration of use in additional exposures over the most recent 24 months for capsules and 18 months for the oral solution, and 4) describing the Strattera population in terms of common comorbidities and concomitant medications. Information on atomoxetine use patterns in the EU may have implications for the risk of increased blood pressure and increased heart rate, by virtue of dose/time on treatment and overall exposure/age. This report describes the updated and final drug utilisation study for the studies previously conducted in Europe (B4Z-MC-B019, submitted November 2011; B4Z-MC-B022, submitted April 2014; B4Z-MC-B025, submitted March 2016). New for the current study (B4Z-MC-B026 [B026]) is the inclusion of utilisation patterns for patients treated with the atomoxetine oral solution in Germany and Sweden.

Study design: Retrospective cohort study using secondary data.

Setting: This study included all patients, including children, adolescents, and adults, with prescriptions of Strattera in each selected database from the UK, Germany, the Netherlands, and Sweden.

Subjects and study size, including dropouts: Patients needed at least 2 consecutive prescriptions to be eligible for inclusion.

Variables and data sources: The data sources for this study included: the longitudinal prescription (LRx) data in Germany and the Netherlands; the Disease Analyser (DA) and the Clinical Practice Research Datalink (CPRD) datasets in the UK; and the National Drug and Patient Register in Sweden. Variables drawn from these data sources included those related to

Strattera exposure (dose, duration), outcomes related to patient counts and drug utilization measures of persistence, discontinuation and restarting patterns, mean daily dose (MDD), medication possession ratios, and length of therapy. Outcomes were assessed by various patient characteristics including country, age, and gender. Counts were also extracted for ADHD diagnoses, comorbidities, and concomitant medication usage.

Results: Among the cohort of prevalent Strattera capsule users from 2012 to 2016, the majority in each of the 4 countries were male and between 13 to 17 years old. Use among children 0 to 5 years old and adults 65+ years old was low (<1%) across countries in each year. There were trends showing gradually increasing use among adults and proportions of female users in all 4 countries. Among the cohort of new Strattera capsule users, the majority were male and <18 years old. The MDD ranged from 30.3 mg (Germany) to 50.7 mg (UK). As expected, the MDD was highest among patients ≥18 years old in all countries. The mean length of treatment supplied over 24 months ranged from 284 days (Netherlands) to 364 days (UK) and the medication possession ratio (MPR) ranged from 40% (Netherlands and Germany) to 50% (UK). The majority of new users in all countries had only 1 episode of treatment over the 24-month follow-up period. On average, persistence on treatment with Strattera capsules beyond 1 year was low.

Among the cohort of prevalent Strattera oral solution users in Germany and Sweden, the majority were male and aged between 6 to 9 years in both 2015 and 2016. Use among children aged 0 to 5 years was <5% of users in both countries in 2016 and use among patients ≥18 years of age was <8% in both countries in both 2015 and in 2016. Among the cohort of new Strattera oral solution users in both countries, the majority were male and less than 18 years of age. The highest proportion of new users in both countries were between 6 to 9 years of age. The MDD for Strattera oral solution was 24.8 mg in Germany and 35.5 mg in Sweden and MDD increased with increasing age in both countries. The mean length of treatment supplied over 18 months was 146 days in Germany and 440 days in Sweden while the MPR was 30% in Germany and 80% in Sweden. The majority of patients in both Germany and Sweden had only 1 episode of treatment with Strattera oral solution and on average, persistence on treatment with Strattera oral solution beyond 1 year was <50%. The most frequent diagnoses and medications listed among both Strattera capsule and oral solution users were not associated with cardiovascular disorders.

Discussion: This drug utilisation study found mean length of treatment episodes for Strattera capsule and oral solution patients in UK, Germany, the Netherlands, and Sweden varied, but were approximately 1 year, and majority of patients were male and treated with 1 episode. The overall Strattera persistence patterns in these EU countries are similar (<50% beyond 1 year) to those reported in the US (Winterstein et al. 2008). Taking into account the MDD, MPR, and mean days treated, even with persistence of more than 1 year, the patient is not necessarily being treated continuously during this period. Therefore, the Strattera utilisation patterns in the EU do not suggest any different potential risks of long-term severe cardiovascular outcomes related to Strattera treatment than would be expected from those reported in large cohort studies conducted in the US.

In regards to Strattera use among patients 0 to 5 years of age, the number of Strattera oral solution users in Germany and Sweden were approximately equal to the number of capsule users in this age group. Consistent with the previous drug utilization studies, the proportion of Strattera users (oral solution and capsule combined) 0 to 5 years of age in Germany and Sweden was less than 0.5% of all Strattera users. The MDD and mean days supplied by age group for oral solution were less than, or comparable to the mean days supplied for capsules. The availability of Strattera oral solution was limited (approximately 1600 and 1000 units of oral solution sold in Germany and Sweden, respectively) and it did not change the overall frequency of Strattera use or dosing regimens for children.

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2. List of Abbreviations

Term	Definition
ADHD	attention-deficit/hyperactivity disorder
ATC	Anatomical Therapeutic Chemical
BNF	British National Formulary
CNS	central nervous system
CPRD	Clinical Practice Research Datalink, formerly the General Practice Research Database
DA	Disease Analyser
DSM	Diagnostic and Statistical Manual of Mental Disorders
EphMRA	European Pharmaceutical Market Research Association
EU	European Union
FDA	Food and Drug Administration
GPRD	General Practice Research Database
HCP	healthcare professional
ICD	International Classification of Diseases
LOT	length of therapy
MDD	Mean daily dose
MPR	medication possession ratio
SAP	statistical analysis plan
SPDR	Swedish Prescribed Drug Register
SmPC	Summary of Product Characteristics
UK	United Kingdom

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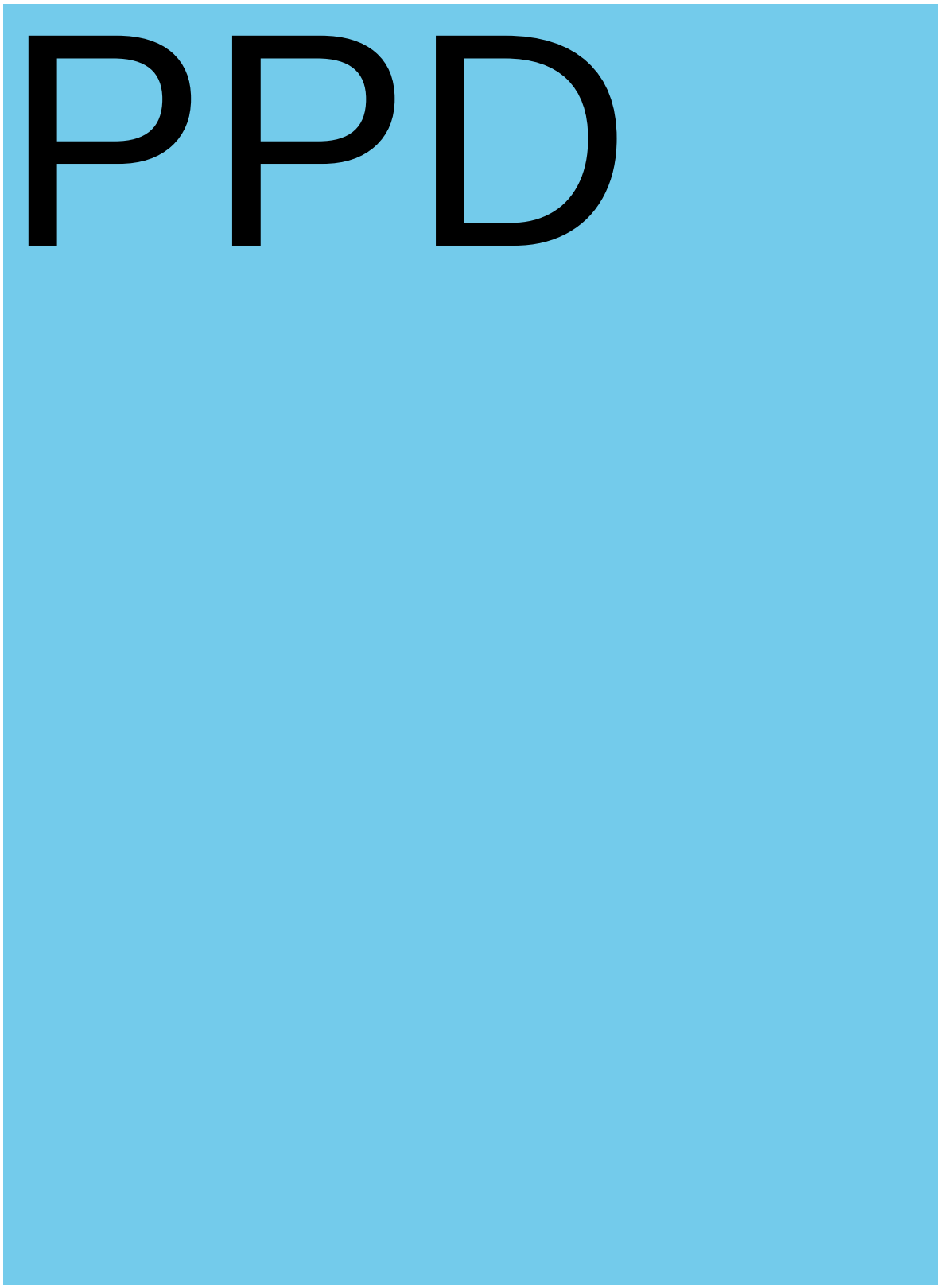
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4. Other Responsible Parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 April 2017	01 April 2017	
End of data collection	31 January 2018	15 January 2018	
<Registration in the EU PAS register>	31 March 2017	31 March 2017	
Final report of study results	31 March 2018	09 March 2018	

6. Rationale and Background

In 2003, Lilly launched Strattera (atomoxetine), which belongs to the class of selective norepinephrine reuptake inhibitors, in the EU. Strattera was the first ADHD medication indicated for adult use. The adult indication for Strattera capsule formulation was approved in the 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). There has also been an increase in the duration of use of ADHD medications in more recent years (Brett 2017). In 2014, an oral solution formulation of atomoxetine was approved and marketing began in 2015 in various EU countries.

IQVIA (formerly QuintilesIMS, IMS Health) executed the analysis of data assessing the utilisation of Strattera in a multi-country study, in the UK, Germany, the Netherlands, and Sweden. The initial request was to ascertain how atomoxetine is used in everyday clinical practice in the following countries: UK, Germany, Sweden, Norway, Spain, and the Netherlands. During the initial assessment it was found that data were unavailable for Spain and Norway. Therefore, the current database study will analyse the unique patient exposures to atomoxetine capsules available data in UK, Germany, Sweden, and the Netherlands.

From these 4 countries, data specific to the oral solution of atomoxetine is only available within Germany and Sweden; 2 of the highest use countries for Strattera oral solution. The Netherlands are not included as the oral solution is not available in the Netherlands. Oral solution data from the UK is also not included because a feasibility count in the UK data available to IQVIA was extremely low (<10 UK patients using the oral solution). Data from Lilly sales databases, as of April 2016, confirm low use in the UK (approximately 250 units since launch).

The Lilly sales database indicated the 3 EU countries with the highest sales of oral solution were Germany, Sweden and Hungary, with approximately 1600, 1000, and 750 units of oral solution sold respectively. Germany and Sweden are included in the current study and Hungary was considered for inclusion; however, the IQVIA dataset for Hungary did not have age and gender data, required data elements for inclusion in the analysis in this study.

The countries with the next highest sales are Austria and the UK, with approximately a quarter of the total sales as in Sweden and Germany (approximately 250 units sold in each country). IQVIA does not have access to data from Austria. Given the lack of feasibility demonstrated in the UK with similar sales of oral solution as Austria, lack of feasibly was expected in Austria and no additional data sources were sought for Austria.

The analysis included an assessment of adherence patterns among users of atomoxetine and obtained more information on atomoxetine use patterns in the EU, which may have implications for the risk of increased blood pressure and increased heart rate, by virtue of dose/time on treatment and overall exposure/age.

This is the updated and final drug utilisation study report for the studies previously conducted in Europe (B4Z-MC-B019 [B019], submitted November 2011; B4Z-MC-B022 [B022], submitted

April 2014; and B4Z-MC-B025 [B025], submitted March 2016), as requested by EU regulatory bodies.

7. Research Question and Objectives

The objective of this study was to describe atomoxetine (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) and formulation (capsule and oral solution) 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 for capsules and 18 months for the oral solution
- 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 capsules and 18 months for the oral solution, for those patients who stopped taking Strattera
- describing the population being treated with atomoxetine in terms of common comorbidities, and concomitant medications

This is a descriptive study and no formal hypotheses are being tested.

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 atomoxetine in the UK, Germany, the Netherlands, and Sweden.

9.2. Setting

This study included patients with at least two consecutive filled prescriptions of Strattera capsules in Germany, the Netherlands, and Sweden or prescriptions of Strattera in the UK from January 2012 through December 2016 and Strattera oral solution in Germany and Sweden from April 2015 through December 2016. These are the prevalent Strattera capsule and oral solution user cohorts. From these cohorts of prevalent users, incident (new) Strattera capsule and oral solution user cohorts were identified.

The difference in the time frame for identifying incident oral solution and capsule users was because the oral solution was not marketed in Germany and Sweden until April 2015 and May 2015, respectively. Also, a longer duration was allowed for oral solution incident user cohort identification to allow for increased uptake which is common when a new drug/formulation is approved.

9.3. Subjects

The source population for analyses of drug utilisation is the prevalent user cohort as defined above: patients with at least 2 consecutive dispensings of/prescriptions for Strattera in any calendar year from January 2012 through December 2016 in Germany, the Netherlands, UK, and Sweden. Prevalent use of the oral solution was available from April 2015 through December 2016 in Germany and Sweden. These prevalent user cohorts were used to assess patient counts, as well as for assessment of comorbidities and concomitant medication usage.

To estimate measures of patient utilisation and adherence for capsules and oral solution, incident user cohorts of patients were identified from the prevalent user cohorts. Incident users of Strattera capsules for each country were defined by the first of 2 consecutive prescriptions in the 6 month period between 01 January 2015 and 30 June 2015. Patients were excluded if any dispatches of Strattera were identified during the 6-month wash out period (01 July 2014 and 31 December 2014). Incident users of Strattera oral solution for Germany and Sweden were defined by a first of 2 consecutive prescriptions between 01 April 2015 and 31 December 2015. Because oral solution was not available prior to 2015, there was no need for a wash-out for oral solution dispensings in the 6-months prior. However, the incident users of oral solution may be previous users of capsules. New capsule users were followed for 24 months while new oral solution users were followed for 18 months to assess measures of drug utilisation including mean daily dose, treatment patterns (number of episodes, days between episodes), and persistence patterns.

9.4. Variables

Variable	Definition
Exposure	
Atomoxetine use	≥2 consecutive atomoxetine (Strattera) prescription dispatches, with a 90 day allowable gap between.
Outcomes	
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
Drug dose	package size multiplied by package dose **Please note, that in the database, package size can be a proportion of the package size. Thus, this proportion will also be used in the calculations
Total treatment dose	sum of the drug doses for all purchases (apart from the last purchase)
Mean daily dose	total treatment dose/treatment duration
Length of therapy	sum of days supplied in treatment episodes, not allowing for treatment gaps.
Other characteristics	
Comorbid diagnoses	ICD-10 diagnoses, at the four-digit level, which have been recorded in the database during follow-up
Concomitant medications	Anatomical Therapeutic Chemical (ATC) or British National Formulary (BNF) codes for medications reported during treatment period

Abbreviation: ICD = International Classification of Diseases

9.5. Data Sources

Data:

IQVIA (formerly QuintilesIMS, IMS health) maintains different sets of longitudinal patient data in over 15 countries around the world. For the purpose of this analysis, the datasets included were:

1. **The LRx longitudinal prescription data in Germany and the Netherlands**
    - LRx is gathered from pharmacy transactions through coding centers or directly from retail chains. This data source contains anonymised encrypted patient IDs that enable tracking of the patient over time. The LRx panel in Germany represents approximately 60% of all retail scripts dispensed in the country. The LRx panel in the Netherlands represents approximately 75% of all retail scripts dispensed in the country.
    - The LRx data for Germany and Netherlands utilise the European Pharmaceutical Market Research Association (EphMRA) Anatomical Therapeutic Chemical (ATC) coding scheme for medications.
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 physician office software and allows the tracking of patients longitudinally.

- CPRD, formerly the General Practice Research Database (GPRD) data set in the UK, is the new National Health Service observational data and interventional research service that provides large multi-linked observational datasets.
- Drugs are coded according to the British National Formulary (BNF) chapter in CPRD and EPhMRA ATC codes in the DA.

3. The Swedish Prescribed Drug Register and Swedish Patient Register

- The Swedish Prescribed Drug Register (SPDR) covers all drugs dispatched at pharmacies in Sweden dating back to 2005. The SPDR contains information for all prescriptions dispensed to the entire population of Sweden (approximately 9 million inhabitants). For prescribed drugs, the register includes data on dispensed item, substance, brand name, formulation, package size, dispensed package count, strength, date of prescribing and dispensing, as well as prescriber's profession and practice. All drugs are classified according to the ATC.
- In order to evaluate the indication, the SPDR data will be linked to the Swedish patient register, which includes 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis codes associated with all inpatient and outpatient (specialist) health care contacts, also with national coverage.

9.6. Bias

The study used dispensed prescriptions in Germany, the Netherlands, and Sweden, and written prescriptions in the UK as proxies for actual medication use. As a result of the methodology used, it is possible to include persons not actually taking Strattera. In an effort to address this source of potential bias, inclusion criteria required 2 consecutive dispensings/prescriptions rather than only 1, to increase the probability that patients actually took the medication. Henceforth, all data are described as dispensed medications, and the limitation of the UK and oral solution data and this potential source of bias is described again in Section 12.3.

9.7. Study Size

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

9.8. Data Transformation

Patient discontinuation and adherence for incident users of atomoxetine capsules within the most recent 24-month period (01 July 2015 to 30 June 2017) was estimated for each country. Discontinuation and adherence for incident users of atomoxetine oral solution within the most recent 18-month period (01 January 2016 to 30 June 2017) was estimated in Germany and Sweden. In order to estimate these measures, a cohort of patients was identified using a 3- or 6-month window and all patients selected 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 days' supply of their last script had been exhausted. The allowable time for utilisation of medication for each script included a grace period (allowable gap), in order to reduce the

probability of misclassification of someone whose 30-day script lasted longer than 30 days. An allowable gap, or grace period of 90 days, due to drug holidays in this therapeutic area was incorporated. The number of treatment episodes over the 24- (18 for oral solution) month period was described, as well as the percent reinitiating therapy, mean gap in between episodes, and the duration of use in the episodes.

Persistence curves were calculated per month from the index prescription up until the 24th month of follow-up. Reinitiation 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 were 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

9.9.1.1. Patient Counts and Descriptive Analyses

For each country, counts and proportions of prevalent Strattera capsule users were provided for the most recent 5 full calendar years. Counts and proportions were tabulated by country, year (2012 to 2016), age group (0 to 5, 6 to 9, 10 to 12, 13 to 17, 18 to 34, 35 to 64, 65+ years of age, as well as <18 or 18 to 64 years of age), gender (female/male) and formulation (capsules/oral). The observed numbers and age-gender proportions of Strattera patients in the LRx datasets from Germany and the Netherlands were used to estimate the projected counts of Strattera users weighted to the entire population of the respective country. These projected counts are provided for Germany and the Netherlands.

In addition to Strattera counts, frequencies and proportions were provided for ADHD diagnoses, 30 most common comorbidities (defined by 4 digit ICD-10 codes), and concomitant medication usage within 24 months of follow-up period for the capsule users, and up to an 18 month follow-up for the oral solution users.

9.9.1.2. Patient Exposures, Discontinuation, Adherence

Within the incident user cohorts, the following measures of drug utilization were estimated:

- Treatment duration, duration of exposure, daily average dose were estimated (where available) stratified by formulation (capsules/oral solution).
- 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.
- Mean daily dose (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. A single episode was defined as the aggregate of all prescriptions refilled, with a 90-day allowed gap after exhausting days supplied in prior prescription.
- 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.

9.9.1.3. 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 who 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. The number of treatment episodes in the 24-month period, as well as the 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 day's supply equivalent divided by the number of days available in the 24-month period (24-month period defined as 30 day month * 12 months in a year * 2 years = 720 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 was 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 were 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 strength was used as daily dose for UK CPRD data and daily dosage was used for UK DA.

- In the SPDR, the days supplies per dispatch is not available. MDD was calculated based on text regarding the dose recorded in the SPDR. The unique dose texts were extracted and summarized. A daily intake was defined based on a substring of the dose text, corresponding to the number of tablets per day, for approximately 40 unique combinations of the dose text substring. Code was developed to test the dose text against those 40 hard coded combinations. If the dose text in question contained a substring that matched one of the 40 defined substrings, the daily intake was defined accordingly. If the dose text did not match one of the approximately 40 hard coded combinations, the daily dose was assumed to be 1 tablet. Duration was defined as the size of the package multiplied by the number of packages dispensed and divided by the daily intake. The patient level daily dose over the analysis period was defined as the total mg dispensed during the period divided by the total duration estimated for the period (that is, the sum of the volume of atomoxetine dispensed divided by the sum of the duration of the dispensations within the analysis period). MDD was defined as the mean of the patient level daily dose
- For the German oral solution analyses, since the recommended dose for oral solution atomoxetine is weight-dependent (1.2 mg per kg and day), German average weights across age groups were extracted and a weighted average weight was calculated for each age group based on the representation across ages. The weighted average weight was then used to calculate the expected daily dose for the age group, which in turn was used to calculate the total dose prescribed and days' supply at the individual level.

9.9.2. Missing Values

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

9.9.3. Sensitivity Analyses

Sensitivity analyses were not completed for this study.

9.9.4. Amendments to the Statistical Analysis Plan

In the SPDR, MDD was calculated based on text regarding the dose recorded rather than extracting average weights across age groups and calculating a weighted average weight for each age group based on the representation across ages then using the weighted average weight to calculate the expected daily dose for the age group, and the total dose prescribed and days' supply at the individual level.

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 IQVIA

(formerly QuintilesIMS, IMS Health) which followed internal policies and procedures to ensure that all data and results were confirmed against the source and the final deliverables were quality reviewed by a person external to the report author.

IQVIA confirmed the correctness of programming and cohort selection of the recent update and that the methodologies were aligned with the current statistical analysis plan (SAP).

10. Results

10.1. Capsule Use Results

10.1.1. Descriptive Data Among Prevalent and New Users of Strattera Capsules from 2012 to 2016

Counts of patient users of Strattera capsules were estimated among prevalent users between 2012 through 2016, stratified by country, age group, and gender. Counts were also estimated among incident users (that is, new users) of Strattera capsules. Incident users were those initiating their first prescription sometime between 1 January 2015 and 30 June 2015.

10.1.1.1. Germany

Overall, the projected number of patients treated with Strattera capsules in Germany declined from 22,113 in 2012 to 18,754 in 2016 (Table 1). Annually, from 2012 to 2016, the largest proportion of patients treated with Strattera were 13 to 17 years of age. The numbers and proportions of patients treated with Strattera capsules in the 18 to 34 years and 35 to 64 years age groups increased steadily between 2012 and 2016 from 1,308 (5.92%) in 2012 to 4,339 (23.13%) in 2016 in the 18 to 34 years age group and from 206 (0.93%) in 2012 to 2,369 (12.63%) in 2016 in the 35 to 64 years age group. The proportion of very young (0 to 5 years of age) or the very old (65 years of age and older) users was consistently less than 1%, in each year between 2012 and 2016.

In Germany, many patient records (32.41% in 2016) did not include gender information (Table 2). For those with the recorded information, the majority of patients treated with Strattera capsules were male. Strattera capsule use was consistently approximately 2 times higher among males than females throughout the follow up period.

Among incident Strattera capsule users, majority were less than 18 years of age (59.3%) and among those with available gender data, majority were male (46.90%) compared to 22.73% females (Table 3).

10.1.1.2. Netherlands

In the Netherlands, the data show a gradual decrease in the number of Strattera capsule users from 5,531 in 2012 to 4,498 in 2016 (Table 4). Annually, between 2012 and 2016, the largest proportion of patients treated with Strattera capsules were 13 to 17 years of age. The proportion of adult (18 to 64 years of age) Strattera capsules users gradually increased over time from 29.16% in 2012 to 40.31% in 2016 whereas the proportion of users under 18 years of age gradually declined from 69.59% in 2012 to 59.07% in 2016. Annually, use among children 0 to 5 years of age and adults 65 years of age and older was less than 1% in each age group.

Annually, from 2012 to 2016, more than 70% of patients treated with Strattera capsules in the Netherlands were male (Table 5). However, the proportion of female users gradually increased slightly from 22.55% in 2012 to 25.79% in 2016.

Among new users of Strattera capsules in the Netherlands, the majority (55.46%) were less than 18 years of age and the highest proportion of new users were 18 to 34 years of age (27.43%) (Table 6). The proportion of new users 0 to 5 years of age and 65 years of age and older was 0.2% and 0.4%, respectively. The majority of new users (69.97%) were male. Among female new users, majority (56.33%) were 18 to 64 years of age while among male new users majority (61.37%) were less than 18 years of age.

10.1.1.3. UK

Overall, the number of Strattera capsule users in the UK increased annually from 767 in 2012 to 804 in 2014 then decreased gradually to 682 in 2016 (Table 7). Annually, from 2012 through 2016, the largest proportion of Strattera capsule users in the UK were between 13 to 17 years of age; however, while the proportion of users 13 to 17 years of age gradually decreased from 43.70% in 2012 to 34% in 2016, the proportion of users 18 to 34 years of age gradually increased from 17.9% in 2012 to 30.4% in 2016. There were no users 0 to 5 years of age in 2012 and 2015 in the UK and because of very low numbers, the 0 to 5 years age group was combined with the 6 to 9 years age group in 2013, 2014 and 2016. The proportion of users in the other age groups remained relatively consistent from 2012 to 2016.

Annually from 2012 to 2016, the majority (>78%) of patients treated with Strattera capsules in the UK were male and Strattera capsule use was consistently approximately 2 times higher among males than females (Table 8).

Among new Strattera capsule users in the UK, the majority (57.5%) were less than 18 years of age (Table 9). However, the highest proportion of new users were 18 to 34 years of age (31.7%). The majority (80.83%) of new Strattera capsule users in the UK were male. Among both male and female new Strattera capsule users in the UK, the highest proportion were 13 to 17 years of age (28.9% of males and 34.8% of females).

10.1.1.4. Sweden

The number of Strattera capsule users in Sweden increased annually from 8,964 in 2012 to 11,522 in 2015 then decreased slightly to 11,213 in 2016 (Table 10). Use among patients aged 18 to 34 years and 35 to 64 years gradually increased between 2012 and 2016, while use among patients aged 6 to 9, 13 to 17, and 10 to 12 years gradually decreased. Strattera capsule use among patients aged 0 to 5 years and 65 years of age and older was consistently less than 0.5% annually between 2012 and 2016.

Annually, from 2012 to 2016, the majority of Strattera capsule users in Sweden were male and the number of male users was consistently approximately 2 times higher than the number of female users (Table 11). However, there was a slight gradual increase in the proportion of female users from 34.04% in 2012 to 37.67% in 2016.

Among new Strattera capsule users in Sweden, majority (53.49%) were 18 to 64 years of age. The highest proportion of new users were 18 to 34 years of age (33.31%) (Table 12). Majority of new years in Sweden were male (58.87%) and among both male and female new users, the majority were 18 to 34 years of age (40.59% of females and 28.22% of males).

10.1.2. Mean Daily Dose, Length of Therapy, and Number of Treatment Episodes in New Users of Strattera Capsules

Drug utilisation measures including MDD, average length of therapy and the number of treatment episodes were estimated within the incident capsule user cohort, also referred to as the new user cohort. These were users of Strattera capsules initiating their first prescription sometime between 01 January 2015 and 30 June 2015. Data for drug utilisation were then estimated from a 24-month period of follow-up after initiation, for a last possible date of follow-up of 30 June 2017.

10.1.2.1. Germany

Overall, the MDD among new Strattera capsule users in the German population was 30.3 mg (Table 13). The highest MDD was among Strattera-treated patients 18 to 34 years of age (35.9 mg) and the lowest was among patients 0 to 5 years of age (9.4 mg). MDD was higher among patients 18 to 64 years of age (35.6 mg) than among patients <18 year of age (27.0 mg).

Overall, the mean days supplied was 314 days within a 24-month window. Mean days supplied was highest among patients 0 to 5 years of age (564 days) and lowest among patients 65 years of age and older (124.8 days).

The overall MPR was 0.4 or 40% of days within a 24-month period and was highest among patients 0 to 5 years of age (0.8) and lowest among patients 65 years of age and older (0.2).

Overall, the number of treatment episodes ranged from 1 to 4 (Table 14). Of the 1,473 new users, the majority (1,177 or 79.9%) had only 1 treatment episode while 250 (16.97%) had 2 treatment episodes, 45 (3.05%) had 3 treatment episodes and 1 patient had 4 treatment episodes.

Overall, the mean duration of treatment episode was 314 days. The mean duration of treatment episodes was highest in PPD 0 to 5 years of age (564 days) and lowest among patients PPD 65 years of age and older (124.8 days). The mean duration of treatment episodes was relatively similar in the 6 to 9 years, 10 to 12 years, 13 to 17 years, and 18 to 34 years age groups.

10.1.2.2. Netherlands

Overall, the MDD among users of Strattera capsules was 41.8 mg (Table 15). The highest MDD was recorded among patients 35 to 64 years of age (57.9 mg) and the lowest MDD was recorded among patients 6 to 9 years of age (22.2 mg). Overall, the mean days supplied was 284 days within a 24-month window and was highest among patients 10 to 12 years of age (336.9 days) and lowest among patients 0 to 5 years of age (45 days, PPD). The overall MPR was 0.40 or 40% of days within a 24-month period and MPRs ranged from 0.1 among patients 0 to 5 years of age and 65 years of age and older to 0.5 among patients 10 to 12 years of age.

Of the 458 new users of Strattera capsules in the Netherlands, majority of patients (430 or 93.89%) only had 1 treatment episode while 24 (5.24%) had 2 treatment episodes and 4 (0.87%) had three treatment episodes (Table 16). The mean duration of treatment was 284 days and was

highest among patients 10 to 12 years of age (336.9 days) and lowest among patients 0 to 5 years of age (45.0 days; PPD).

10.1.2.3. UK

The overall MDD among Strattera capsules users in the UK was 50.7 mg (Table 17). The highest MDD (76.1 mg) was recorded among patients 35 to 64 years of age while the lowest MDD (34.8 mg) was recorded among patients 6 to 9 years of age. Overall, the mean days supplied was 363.9 days within a 24-month window and mean days' supply by age group ranged from 307.3 days among patients 13 to 17 years of age to 423.2 days among patients 6 to 9 years of age. The overall MPR was 0.50 or 50% of days within a 24-month period and MPRs by age group ranged from 0.4 among patients 13 to 17 years age to 0.6 among patients 6 to 9 years of age.

In the UK, of the 120 incident Strattera users, the majority (109 or 90.8%) of patients had only 1 treatment episode, while 8 (6.7%) had 2 episodes and 3 (2.5%) had 3 or 4 episodes (Table 18). The mean duration of treatment was 356.9 days and the mean duration of treatment by age group ranged from 302.4 days among patients 13 to 17 years of age to 415.3 days among patients 6 to 9 years of age.

10.1.2.4. Sweden

The overall MDD among Strattera capsule users in Sweden was approximately 47.9 mg (Table 19). MDD by age group ranged from 31.8 mg among patients 6 to 9 years of age to 54.9 mg among patients 35 to 64 years of age. Overall, the mean days supplied was 359.6 days within a 24-month window. The mean days supplied by age group ranged from 291.9 days among patients 18 to 34 years of age to 448.1 days among patients 10 to 12 years of age. The overall MPR was 49.9% of days within 24-month period and MPRs by age group ranged from 40.5% of days among patients 18 to 34 years of age to 62.2% of days among patients 10 to 12 years of age.

Of the 2,492 new users of Strattera capsules in Sweden, majority (2,204 or 88.4%) had only 1 treatment episode while 277 (11.1%) had 2 and 11 (0.44%) had 3 (Table 20). The mean duration of treatment was 359.6 days and the mean duration of treatment by age group ranged from 291.9 days among patients 18 to 34 years of age to 448.1 among patients 10 to 12 years of age.

10.1.3. Persistence and Mean Gap Between Episodes in New Users of Strattera Capsules

Similar to measures of MDD, average length of therapy and the number of treatment episodes, measures of persistence and gaps between episodes were estimated within the incident capsule user cohort. These were users of Strattera capsules initiating their first prescription sometime between 01 January 2015 and 30 June 2015. Data for drug utilisation were then estimated from a 24-month period of follow-up after initiation, for a last possible date of follow-up being 30 June 2017.

10.1.3.1. Germany

Overall, persistence on Strattera therapy in Germany was 100% up to 3 months of follow up then gradually decreased (Table 21 and Figure 1). After 24 months of follow up, 31.5% of patients were still being treated with Strattera, 58.93% had discontinued treatment while 9.57% discontinued then restarted treatment. Of the 296 patients who restarted therapy, majority (250 or 84.46%) had only 2 treatment episodes, 45 (15.2%) had 3, and 1 (0.34%) patient had 4 episodes of treatment (Table 22).

In Germany, the mean gap between treatment episodes was approximately 106.2 days (Table 23). The mean length of treatment gaps according to age group ranged from 8.0 days among patients 0 to 5 years of age PPD to 123.2 days among patients 35 to 64 years of age. Overall, the mean length of treatment gap decreased with increasing number of treatment episodes.

10.1.3.2. Netherlands

In general, persistence on Strattera therapy upon initiation in the Netherlands was nearly 100% up to 3 months then gradually decreased over time (Table 24 and Figure 2). After 24 months of follow up, approximately 24.02% of patients were still being treated with Strattera in the Netherlands, 72.93% had discontinued treatment while 3.06% discontinued then restarted treatment. Of the 28 patients who restarted treatment, the majority (24 or 85.71%) had 2 treatment episodes while 4 (14.29%) had 3 (Table 25).

The mean gap between treatment episodes was approximately 131.9 days (Table 26). The mean length of treatment gap according to age group ranged from 62.9 days among patients 13 to 17 years of age to 399 days among patients 35 to 64 years of age.

10.1.3.3. UK

In general, persistence on Strattera therapy upon initiation in the UK was 100% through 4 months then gradually decreased over time (Table 27 and Figure 3). After 24 months of follow up, 25.83% of patients were still being treated with Strattera in the UK while 66.67% had discontinued treatment and 7.50% discontinued then restarted treatment. Of the 11 patients who restarted treatment, 8 (72.7%) had only 2 episodes of treatment (Table 28).

The mean gap between treatment episodes was approximately 178.1 days (Table 29); however, age-specific data could not be calculated due to limited number (<6) of patients in each strata.

10.1.3.4. Sweden

In general, persistence on Strattera therapy upon initiation was 100% through 3 months and then gradually decreased over time (Table 30 and Figure 4). After 24 months of follow up, 20.30% of patients were still being treated with Strattera in Sweden, 68.14% had discontinued treatment and 11.56% discontinued then restarted treatment. Of the 288 patients who restarted treatment, the majority (277 or 96.2%) had 2 treatment episodes while 11 (3.8%) had 3 treatment episodes (Table 31).

The mean gap between episodes was approximately 231.3 days (Table 32) and the gap was relatively consistent across age groups ranging from 219.3 days among patients 18 to 34 years of age to 262 days among patients 6 to 9 years of age.

10.1.4. Diagnoses and Concomitant Medication Use Among Prevalent Strattera Capsule Users

Diagnoses and concomitant medications were assessed from a 24-month period of follow-up among the prevalent capsule users of Strattera in the UK and in Sweden. Germany and the Netherlands' LRx data are only pharmacy claims data and do not have medical claims data. Due to the lack of medical claims data, it was not possible to provide information on ADHD diagnosis and comorbidities for patients in these 2 countries.

10.1.4.1. Presence of ADHD Diagnosis (ICD-10 F90*), Most Frequent Diagnosis Codes, and Concomitant Medications

10.1.4.1.1. United Kingdom

Among patients in the UK using Strattera, 21.04% had an ADHD diagnosis recorded within 24-months of follow-up (Table 33). The proportions of Strattera users having an ADHD diagnosis by age group ranged from 16.31% among patients 13 to 17 years of age to 29.91 among patients 18 to 34 years of age.

The 30 most frequent ICD-10 diagnostic codes recorded for a 24-month follow-up period among all Strattera patients in the UK (CPRD and DA) included 4 codes for mental, behavioural, and neurodevelopmental disorders (F900, F909, F990, F840) (Table 34). Excluding ADHD diagnosis (F900), cases with unspecified diagnosis (R693), and codes for health care service encounters (Z518, Z519, Z408, Z000, Z718, Z138, Z017), the top 5 comorbidities included acute upper respiratory infection (J069), and acne vulgaris (L700), asthma unspecified (J459), pain in limb (M796) and acute tonsillitis unspecified (J039).

Table 35 shows the 30 most frequent drug/treatment ATC codes recorded for a 24-month follow-up period among Strattera patients in the UK DA database, while Table 36 shows the 30 most frequent drug/treatment BNF codes recorded for a 24-month follow-up period among Strattera patients in the UK CPRD database. The 5 most frequent concomitant drug/treatment ATC codes included all other central nervous system (CNS) drugs, psychostimulants, non-barbiturate, broad spectrum penicillin and non-narcotic analgesics while the 5 most frequent drug/treatment BNF codes included CNS stimulants and drugs used for ADHD, hypnotics, broad spectrum penicillin, selective beta 2 agonists and second-generation antipsychotics.

10.1.4.1.2. Sweden

Among patients in Sweden using Strattera, 88.43% had an ADHD diagnosis recorded within 24-months of follow-up (Table 37). The proportions of Strattera users having an ADHD diagnosis by age group ranged from 59.68% among patients 65 years of age and older to 90.29% among patients 13 to 17 years of age.

Table 38 shows the 30 most frequent ICD-10-SE diagnosis codes recorded for a 24-month follow-up period among all patients in Sweden. Of the 30 most frequent diagnoses among patients prescribed Strattera in Sweden, 12 were codes for mental, behavioural, and neurodevelopmental disorders including F900, F419, F329, F412, F845, F321, F100, F909, F192, F840, F430, and F331. Not considering an ADHD diagnosis (F900), and codes for unspecified illness (R699) and health care service encounters (Z0xx) the top 5 comorbidities among patients using Strattera in Sweden included pain in the abdomen (R104), anxiety disorder unspecified (F419), major depressive disorder (F329), generalized anxiety disorder (F412), and Asperger's syndrome (F845).

Table 39 shows the 30 most frequent drug/treatment ATC codes recorded for a 24-month follow-up period among Strattera-treated patients in Sweden. Of these, the 5 most frequent drug/treatment ATC codes included centrally acting sympathomimetics, beta-lactamase sensitive penicillins, melatonin receptor agonists, selective serotonin reuptake inhibitors, and diphenylmethane derivatives.

10.2. Oral Solution Results

10.2.1. Descriptive Data Among Prevalent and New Users of Strattera Oral Solution Between 2015 and 2016

Counts of patient users of oral Strattera solution were estimated among prevalent users between 2015 through 2016, stratified by country, age group, and gender. Counts were also estimated among incident users (that is, new users) of Strattera oral solution. Incident users were those initiating their first prescription sometime between 1 April 2015 and 31 December 2015.

10.2.1.1. Germany

Overall, the projected number of patients treated with Strattera oral solution in Germany increased from 241 in 2015 to 568 in 2016 (Table 40). The largest proportion of patients treated with Strattera oral solution in Germany were 6 to 12 years of age in both 2015 (81.13%) and 2016 (74.80%). The proportions of patients 0 to 5 years of age treated with Strattera oral solution were PPD in 2015 PPD, and 4.40% (n=25) in 2016. The proportion of users 18 to 34 years of age and 35 to 64 years of age increased from PPD to 4.80% and 0% to 2.40%, respectively from 2015 to 2016. There was no oral solution use recorded among patients 65 years of age and older in both 2015 and 2016.

Majority of patients treated with Strattera oral solution were male (Table 41). Strattera oral solution use among males was approximately 2 times higher than among females in both 2015 and 2016.

Among new Strattera oral solution users, majority were less than 18 years of age (n=193 or 96.59%) (Table 42). Only PPD were 18 years of age or older. The highest proportion of new users were 6 to 9 years of age (56.82%). There were no new oral solution users 35 years of age or older. In addition, majority of new oral solution users were male (45.5%) compared to 24.0% female.

10.2.1.2. Sweden

Overall, the number of Strattera oral solution users in Sweden increased from 165 in 2015 to 299 in 2016 (Table 43). Majority of Strattera oral solution users in Sweden were less than 18 years of age both in 2015 (96.97%) and in 2016 (94.98%). The largest proportion of Strattera oral solution users in Sweden were 6 to 9 years of age in both 2015 (46.67%) and 2016 (46.49%). There were 14 (8.48%) Strattera oral solution users 0 to 5 years of age in 2015 and 13 (4.35%) in 2016.

Majority of Strattera oral solution users in Sweden were male in both 2015 (69.70%) and 2016 (73.24%) and Strattera oral solution use among males was approximately 2 times higher than among females in both 2015 and 2016 (Table 44).

Of the 162 new Strattera oral solution users in Sweden, majority were less than 18 years of age (97.53%) and the highest proportion of new users were 6 to 9 years of age (46.91%) (Table 45). In addition, majority of new Strattera oral solution users in Sweden were male n=115 (70.99%) compared to 47 (29.01%) females.

10.2.2. Mean Daily Dose, Length of Therapy, and Number of Treatment Episodes in New Users of Strattera Oral Solution

Drug utilisation measures including MDD, average length of therapy and the number of treatment episodes were estimated within the oral solution incident user cohort, also referred to as the new user cohort. These were users of Strattera oral solution initiating their first prescription sometime between 01 April 2015 and 31 December 2015. Data for drug utilisation were then estimated from an 18-month period of follow-up after initiation, for a last possible date of follow-up being 30 June 2017.

10.2.2.1. Germany

Overall, the MDD among the 88 new Strattera oral solution users in the German population was 24.8 mg (Table 46). The MDD among new Strattera oral solution users in the Germany increased with increasing age ranging from 8.7 mg among patients 0 to 5 years of age PPD to 48.4 mg among patients 18 to 34 years of age PPD. The MDD among new users 6 to 9 years of age (the most frequent age group; n=50, 56.8% of new users), was 19.7 mg.

Overall, the mean days supplied was 146.1 days within an 18-month window. Mean days supplied was highest among the PPD patients 0 to 5 years of age (240.4 days) and lowest among the PPD patients 18 to 34 years of age (16.2 days). The overall MPR was 0.3 or 30% of days within a 18-month period and was highest among patients 0 to 5 years of age (0.4) and lowest among among patients 18 to 34 years of age (0).

Majority of new Strattera oral solution users (90.91%) had only one treatment episode while 7 (7.95%) had 2, and 1 patient had 3 (Table 47). Overall, the mean duration of treatment episodes was 146.1 days and mean duration of treatment episodes gradually decreased with increasing age ranging from 240.4 days among patients 0 to 5 years of age to 16.2 days among patients 18 to 34 years of age.

10.2.2.2. Sweden

The overall MDD among the 162 new users of Strattera oral solution in Sweden was approximately 35.5 mg (Table 48). The MDD increased with increasing age from 19.0 mg among patients 0 to 5 years of age (n=14) to 51.5 mg among patients 13 to 17 years of age (n=20).

The overall mean days supplied among new Strattera oral solution users in Sweden was 440.4 days. Mean days supplied ranged from 376.6 days among patients 13 to17 years of age to 493 days among patients 6 to 9 years of age.

The overall MPR was 0.8 or 80% of days within the 18-month follow up period. MPR by age group ranged from 0.7 among patients 10 to 12 years and 13 to17 years of age to 0.9 among patients 6 to 9 years of age.

Majority of new Strattera oral solution users in Sweden had only one treatment episode (89.51%) while 17 patients (10.49%) had 2 (Table 49). The mean duration of treatment was 440.4 days and the mean treatment duration of treatment by age group ranged from 376.3 days among patients 13 to 17 years of age to 493 days among patients 6 to 9 years of age.

10.2.3. Persistence and Mean Gap Between Episodes in New Users of Strattera Oral Solution

Similar to measures of MDD, average length of therapy and the number of treatment episodes, measures of persistence and gaps between episodes were estimated within the incident user cohort. These were users of Strattera initiating their first prescription sometime between 01 April 2015 and 31 December 2015. Data for drug utilisation were then estimated from a 18-month period of follow-up after initiation, for a last possible date of follow-up being 30 June 2017.

10.2.3.1. Germany

Persistence on Strattera oral solution therapy in Germany upon initiation was 100% up to 4 months of follow up then gradually decreased (Table 50 and Figure 5). After 18 months of follow up 17.05% of patients were still being treated with Strattera oral solution in Germany, 78.41% had discontinued treatment while 4.55% discontinued then restarted treatment. Of the 8 patients who restarted Strattera oral solution treatment in Germany, 7 had 2 treatment episodes while 1 patient had 3 treatment episodes (Table 51).

The mean gap between treatment episodes was approximately 132.6 days (Table 52). The mean gap between treatment episodes according to age group ranged from 119.9 days among patients 6 to 9 years of age PPD to 191.4 days among patients 10 to 12 years of age.

10.2.3.2. Sweden

In general, persistence on Strattera oral solution therapy in Sweden upon initiation was 100% through 3 months and then gradually decreased over time (Table 53 and Figure 6). After 18 months of follow up, 37.04% of Strattera oral solution users were still being treated while

52.7% had discontinued treatment and 10.49% discontinued then restarted treatment. All 17 patients who restarted therapy had only 2 episodes of treatment (Table 54).

The mean gap between episodes was approximately 195.2 days Table 55). Low patient counts precluded calculation of mean gap between treatment episodes by age group.

10.2.4. Diagnoses and Concomitant Medication Use Among Prevalent Strattera Oral Solution Users

Diagnoses and concomitant medications were assessed from an 18-month period of follow-up among the prevalent users of Strattera oral solution in Sweden. Germany LRx data are only pharmacy claims data and do not have medical claims data. Due to the lack of medical claims data, it was not possible to provide information on ADHD diagnosis and comorbidities for Strattera oral solution users in Germany.

10.2.4.1. Presence of ADHD Diagnosis (ICD-10 F90*), Most Frequent Diagnosis Codes, and Concomitant Medications

10.2.4.1.1. Sweden

Among Strattera oral solution users in Sweden, 83.33% had an ADHD diagnosis recorded within 18-months of follow-up (Table 56). The proportions of Strattera users having an ADHD diagnosis by age group was highest (92.86%) among patients 0 to 5 years of age and lowest (75%) among patients 13 to 17 years. There were less than 10 patients in each age group for patients 18 years of age and older hence, the proportions were not calculated.

The 30 most frequent ICD-10-SE diagnosis codes recorded for a 18-month follow-up period among Strattera oral solution users in Sweden included 6 for mental, behavioural, and neurodevelopmental disorders (that is, F900, F840, R418, F909, F913, F849) while 9 were for health care service encounters (Table 57). Not considering an ADHD diagnosis (F900), and codes for health care service encounters (Z0xx and Z711) the top 5 comorbidities among patients using Strattera in Sweden included autistic disorder (F840), acute upper respiratory infection unspecified (J069), constipation (K590), other and unspecified asthma (J459), and viral infection unspecified (B349).

Table 58 shows the most frequent drug/treatment ATC codes recorded for a 18-month follow-up period among Strattera oral solution users in Sweden. Of these codes, the 5 most frequent included centrally acting sympathomimetics, beta-lactamase sensitive penicillins, melatonin receptor agonists, mucolytics, and osmotically acting laxatives.

11. Adverse Events/Adverse Reactions

No adverse events were reported in this analysis.

12. Discussion

12.1. Key Results: Strattera Capsules

12.1.1. Age

Overall, from 2012 to 2016, the number of prevalent Strattera capsule users in Germany and the Netherlands gradually decreased while the number of prevalent Strattera users in UK and Sweden initially increased then decreased. A universal trend among all 4 countries was gradually increasing use among adults (18 to 64 years of age) and decreasing use among patients less than 18 years of age. The increasing use among adults is a trend that was observed in previous Studies B022 and B025 and it is expected due to the EU ADHD indication approval in adult patients in 2013. Other contributing factors could include persistence of ADHD into adulthood. For example, in a long-term follow-up study of children with ADHD, 40 to 60% of ADHD persisted into adulthood (Volkow and Swanson 2013). Therefore, increasing use among adults may in part be due to the transition of adolescent users into adult users. Additionally, changes to the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM) update (DSM-5) for diagnosing adult ADHD led to more inclusive criteria, requiring symptoms be present prior to 12 years of age instead of 7 years of age in the DSM-IV (APA 2013). Furthermore, the number of symptoms for a reliable diagnosis in adults changed to 5, instead of 6. Lastly, examples of ADHD presentation were added to improve the diagnosis across the different ages. These considerations, alongside the EU ADHD indication approval in adult patients in 2013, could contribute to the trends observed towards increasing use among adults.

Other universal trends noted included 1) use in adults 65 years of age and older and children 0 to 5 years of age remained consistently low in all 4 countries (<1% of Strattera users) and 2) in Germany, the Netherlands, and the UK, the majority of patients treated with Strattera were between 13 and 17 years of age. These findings are consistent with results from European and worldwide epidemiological studies that indicate higher incidence and/or prevalence of ADHD among children and adolescents (6 to 17 years of age) and very low incidence and or prevalence among children 0 to 5 years of age (Erskine et al. 2013; Holden et al. 2013).

12.1.2. Gender

In all 4 countries, the majority of prevalent Strattera users were male each year throughout the study period and the numbers of male users were consistently approximately 2 times higher than the numbers of female users. Similarly, majority of new users in all four countries were male. Among the new users in Germany and the Netherlands, the gender difference was most prominent in patients less than 34 years of age with almost no gender difference in the numbers of patients 35 years of age and older. Among new users in Sweden, the gender difference was most prominent among users less than 17 years of age with almost no gender difference among new users 18 years of age and older. These findings are consistent with the results from previous reports (B022 and B025). The results are also consistent with findings from epidemiological studies that show a higher prevalence of ADHD among males compared to females in European countries (Erskine et al. 2013; Holden et al. 2013) and worldwide (Erskine et al. 2013).

Epidemiological studies also show that adulthood prevalence rates of ADHD diagnosis are actually similar across genders (Marraccini et al. 2017). Although the exact reason for the gender discrepancy in ADHD prevalence remains undetermined, differences in clinical presentation might contribute to the discrepancy. Females with ADHD have been found to predominantly manifest the inattentive type of the disorder symptoms with more internalizing comorbid disorders such as depression and anxiety, which are more difficult to detect than the hyperactivity, and externalizing symptoms among males (Biederman and Faraone 2004). In addition, there are general public, teacher, and parent misconceptions about the prevalence and diagnosis of ADHD among females, difficulty in recognizing ADHD among females by teachers, and females are more likely to be diagnosed and treated for comorbid psychiatric disorders before diagnosis and treatment of their ADHD (Quinn and Wigal 2004). The increase in ADHD prevalence among adult women may reflect higher self-referral rates, because women may be more likely to recognize ADHD symptoms and seek help compared to men (Marraccini et al. 2017).

Consistent with the findings from previous studies B022 and B025, there were gradual increases in the proportion of female users in all 4 countries during the study period. Increasing ADHD medication use among females has been reported in epidemiological studies in Europe (McCarthy et al. 2012), and US (Collins and Cleary 2016). Although the exact reason for the increasing use among females remains undetermined, it is possible that the increase in use among females could be due to increasing acceptance and recognition of the presence of ADHD in females.

12.1.3. Mean Daily Dose

The overall MDD between countries ranged from approximately 30.3 mg in Germany to 50.7 mg in the UK. Generally, MDD increased with increasing age in all 4 countries then decreased among patients 65 years of age and older in Germany and the Netherlands, while in UK and Sweden there were insufficient counts of patients aged 65 years and older.

Among users less than 18 years of age, MDD by country ranged from 27.0 mg in Germany to 43.8 mg in Sweden while among users 18 to 64 years of age, MDD by country ranged from 35.6 mg in Germany to 62.5 mg in the UK.

Overall, for both paediatric and adult populations, the observed MDD seems to be below the recommended target dose. However, the overall MDDs were generally consistent with those reported in the previous studies (B022 and B025).

12.1.4. Mean Days Supplied over 24 Months, the MPR, and Persistence

The mean days supplied ranged from 284 days in the Netherlands to 363.9 days in the UK. Mean days supplied was higher among users less than 18 years of age than among users 18 to 64 years of age in all countries except the UK. The mean days supplied among those less than 18 years of age by country ranged from 314.9 days in the Netherlands to 414 days in the Sweden. Among users 18 to 64 years of age, the mean days supplied ranged from 252.9 days in the

Netherlands to 377.2 days in the UK. The overall MPR by country ranged from 40% of days in Germany and the Netherlands to 50% of days in the UK.

12.1.5. Treatment Episodes and Length of Treatment

Overall, in all 4 countries, the majority of patients received only 1 episode of treatment. The mean number of days of treatment ranged from 284 in the Netherlands to approximately 360 days in Sweden. The mean range of treatment duration is similar but slightly less and narrower than the range observed in the previous studies 262 days to 405 days in B025 and 304 days to 411 days in B026. The mean duration of treatment was higher among users less than 18 years of age than among users 18 to 64 years of age in all countries except UK, where mean duration of treatment was higher among users 18 to 64 years of age than among users less than 18 years of age. These findings are consistent with the results from previous studies B022 and B025.

12.1.6. ADHD Diagnosis

In the UK, only 21.04% of users had a recorded ADHD diagnosis while in Sweden, 88.43% of users had a recorded ADHD diagnosis. The low percentage of ADHD diagnoses in the UK database has been observed in previous reports (B022 and B025) and could be attributed to various causes, 1 of which is that the diagnosis may have occurred outside of the 24-month observation window for collecting the data. For example, a diagnosis of ADHD prior to a patient receiving the first Strattera prescription would not have been captured in the data. This may be particularly true within the CPRD, which is an electronic health record and unlike a claims database tied to billing, a diagnosis does not necessarily occur again when a prescription occurs. The higher proportion of users with an ADHD diagnosis in Sweden could be due to differences in the way ADHD is coded and treated in Sweden. However, even in Sweden, it is possible that some diagnoses may have occurred outside of the 24-month observation window.

12.1.7. Recorded Medication Use and Medical Conditions

In the UK, the majority of concomitant medications used among patients treated with Strattera capsules were those associated with the treatment of psychiatric disorders, infections, and various common conditions. The codes for the 30 most frequent comorbidities included neuropsychiatric disorders, health care service encounters, and common conditions such as upper respiratory tract infections, acne vulgaris, asthma, pain in limb, and acute tonsillitis.

In Sweden, concomitant medications used among patients treated with Strattera capsules were also mainly those associated with the treatment of psychiatric disorders, infections and various common conditions. Majority (86.74%) of patients in the cohort were taking centrally acting sympathomimetics; a drug class that includes other medications used for the treatment of ADHD such as amphetamines. The listed comorbid medical conditions included mainly mental health-related or general medical conditions and health care service encounters.

In both UK and Sweden, neither cardiovascular conditions nor medication for cardiovascular disease were listed among the 30 most common conditions/medications.

12.2. Key Results: Strattera Oral Solution

12.2.1. Age

Overall, the number of prevalent Strattera oral solution users in both Germany and Sweden increased from 2015 to 2016. This increase is expected due to recent approval of Strattera oral solution use in these countries in 2015.

In both Sweden and Germany, the majority of prevalent Strattera oral solution users were less than 18 years of age, both in 2015 and in 2016. The highest proportion of Strattera oral solution users both in Sweden and in Germany were between 6 to 9 years of age in both 2015 and 2016. Strattera oral solution use among patients 18 years of age or older was also very limited in both countries in both 2015 and in 2016 (that is, less than 8% of all Strattera oral solution users).

Strattera oral solution use among children aged 0 to 5 years was less than 5% of Strattera oral solution users in both countries in 2016. While the percentage of prevalent oral solution users 0 to 5 years of age in Germany and Sweden is higher than the percentage of capsule users 0 to 5 years of age, the numbers of Strattera oral solution users in this age group in both countries in 2015 and in 2016 were approximately equal to the numbers of capsule users. The proportion of Strattera users (oral solution and capsule combined) 0 to 5 years of age in Germany and Sweden was less than 0.5% of all Strattera users in both countries in 2015 and 2016 and these results are consistent with the previous study (B025).

Similarly, among new Strattera oral solution users both in Germany and in Sweden, the majority were less than 18 years of age (96.59% in Germany and 97.53% in Sweden) and the highest proportion of new Strattera oral solution users in both Sweden and Germany were between 6 to 9 years of age.

12.2.2. Gender

In both Sweden and Germany, majority of prevalent Strattera oral solution users were male both in 2015 and in 2016 and the number of male users was consistently approximately 2 times higher than the number of female users. As noted previously, these results are also consistent with findings from epidemiological studies that show a higher prevalence of ADHD among males compared to females. Similarly, among new users of Strattera oral solution in both countries, the majority were male and the number of male users was consistently approximately 2 times higher than the number of female users.

12.2.3. Mean Daily Dose

The overall MDD for Strattera oral solution was 24.8 mg in Germany and 35.5 mg in Sweden which were less than the MDD for oral capsules in both Germany (30.3 mg) and Sweden (47.9 mg). The MDD for Strattera oral solution increased with increasing age in both countries. Among patients less than 18 years of age, MDD was 24.3 mg in Germany and 35.6 mg in Sweden, which were also less than the MDD for oral capsules among patients less than 18 years of age in both Germany (27 mg) and Sweden (43.8 mg). Among patients 18 to 64 years of age, the MDD was 48.4 mg in Germany and not available in Sweden due to low patient counts. The

observed MDD in Sweden seems appropriate for age while the observed MDD in Germany seems to be below the recommended target dose, but is close to the initial starting dose or appropriate for younger or patients with lower body weight.

12.2.4. Mean Days Supplied over 24 Months, the MPR, and Persistence

The overall mean days supplied for Strattera oral solution was 146.1 days in Germany and 440.4 days in Sweden. The mean days supplied among patients less than 18 years of age was 149.3 days in Germany and 445.9 days in Sweden. In Germany, the mean days supplied in all age groups (including the 0 to 5 years age group) for Strattera oral solution was less than the mean days supplied for Strattera capsules, while in Sweden the mean days supplied for oral solution in the 6 to 9 years, 10 to 12 years and 13 to 17 years age groups were comparable to mean days supplied for capsules. Mean days supplied among patients 0 to 5 years of age for capsules in Sweden was not available for comparison due to low patient counts; however, mean days supplied for oral solution among patients 0 to 5 years of age in Sweden was approximately 421 days.

The overall MPR for Strattera oral solution was 0.3 (30% of days) in Germany and 0.8 (80% of days) in Sweden.

12.2.5. Treatment Episodes and Length of Treatment

In both Germany and Sweden, the majority of patients treated with Strattera oral solution received only 1 episode of treatment. The mean duration of treatment was approximately 146 days in Germany and 440 days in Sweden. In Germany, the mean duration of treatment with Strattera oral solution decreased with increasing age from approximately 240 days among patients 0 to 5 years of age PPD to 16 days among patients 18 to 34 years of age PPD. In Sweden the mean duration of treatment with Strattera oral solution ranged from approximately 377 days among patients 13 to 17 years of age to 493 days among patients 6 to 9 years of age.

12.2.6. ADHD Diagnosis

In Sweden, the majority (83.33%) of Strattera oral solution users had a recorded ADHD diagnosis while in Germany these data were not available. Although the proportion of Strattera oral solution users with an ADHD diagnosis in Sweden is high, it is possible that this is an underestimate because some diagnoses may have occurred outside of the 18-month observation window.

12.2.7. Recorded Medication Use and Medical Conditions

In Sweden, not considering an ADHD diagnosis (F900), and codes for health care service encounters (Z0xx, Z711), the top 5 comorbidities among patients using Strattera in Sweden included autistic disorder (F840), acute upper respiratory infection unspecified (J069), constipation (K590), other and unspecified asthma (J459), and viral infection unspecified (B349).

The 5 most frequent drug/treatment ATC codes recorded for an 18-month follow-up period among Strattera oral solution users in Sweden included centrally acting sympathomimetics, beta-

lactamase sensitive penicillins, melatonin receptor agonists, mucolytics, and osmotically acting laxatives.

Neither cardiovascular conditions nor medication for cardiovascular disease were listed among the 30 most common conditions/medications.

12.3. 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 the DA patient database, both of which contained data on written prescriptions, not dispensed prescriptions. 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. This is a reflection of the limited coverage in the UK data sources. Therefore, the findings may not be representative of the entire country.
- The sample sizes for Strattera oral solution use in Germany and Sweden were very limited resulting in unstable estimates for age- and gender-stratified analyses.
- ADHD diagnoses from claims and encounter databases is limited (Habel et al. 2011). This was apparent within this report by the discrepant results from the UK and Sweden. Furthermore, understanding the common comorbidities more generally is limited because administrative and procedural codes were included.

12.4. Interpretation

This study assessed prevalent use of Strattera capsules from 2012 through 2016 and drug utilisation patterns from a 24-month period among new users of Strattera capsules initiating their prescription between 01 January 2015 and 30 June 2015 in Germany, the Netherlands, the UK, and Sweden. The study also assessed prevalent use of Strattera oral solution from April 2015 through December 2016 and drug utilization patterns for an 18-month period among new users of Strattera oral solution initiating their prescription between 01 April 2015 and 31 December 2015 in Germany and Sweden.

Patterns of treatment assessed with MPR, mean days treated, discontinuation, and persistence show that, on average, persistence among both Strattera capsules and oral solution users past 1 year was <50% overall. Strattera oral solution and capsule use among patients 0 to 5 years of age was consistently low. The number of Strattera oral solution users in the 0 to 5 years age group in Germany and Sweden were approximately equal to the number of capsule users in this age group. Consistent with the previous drug utilization studies, the proportion of Strattera users (oral solution and capsule combined) 0 to 5 years of age in Germany and Sweden was less than 0.5% of all Strattera users in both countries in 2015 and 2016. The MDD and mean days supplied by age group for oral solution were less or comparable to mean days supplied for

capsules. The availability of the oral solution did not change the overall frequency of Strattera use or dosing regimens for children. 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 pre-existing 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 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 were aware of, and adhered 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 labelling, are effective in managing these cardiovascular risks.

Overall, duration of treatment was relatively short (1 year on average), majority of patients had only 1 episode of treatment, and the MPR showed that treatment is generally not continuous over time. Overall, the measured key usage parameters were lower than those in the US (Winterstein et al. 2008; Christensen et al. 2010; Schelleman et al. 2011). Additionally, data from short-term and long-term Strattera clinical trials showed that increases in blood pressure and heart rate observed during treatment with Strattera do not persist after the drug was discontinued. These factors may explain why observational studies conducted in the United States (US) have reported no significant difference in cardiovascular outcomes in children (Cooper et al. 2011; Schelleman et al. 2011) or adults (Cooper et al. 2011; Habel et al. 2011) with the use of ADHD medications, which includes Strattera compared to non-users. One study comparing the rate of severe cardiovascular events and death in children aged 3 to 17 years 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 and Food and Drug Administration (FDA) funded, used data from 4 health plans and 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 years (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). A retrospective, population-based cohort study of adults aged 25 through 64 years compared current or new use of an ADHD medication to non- or remote use and found no increased risk of serious cardiovascular events (Habel et al. 2011).

12.5. Generalisability

The countries included in this study represent a large proportion of Strattera use in the EU. As a result, these study findings should be representative of patients and treatment patterns in the EU.

13. Other Information

None.

14. Conclusion

In conclusion, the most frequent diagnoses and medications listed among Strattera capsule and oral solution treated patients were not associated with cardiovascular conditions. This drug utilisation study found the mean treatment episodes for patients treated with either Strattera capsules (UK, Germany, the Netherlands, and Sweden) or oral solution (Germany 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 show that, on average, persistence past 1 year is low (<50%) and the persistence patterns are similar to those reported in the US. 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. Taken together, the utilisation patterns in the EU do not suggest any different potential risks of long-term severe cardiovascular outcomes related to treatment with Strattera than would be expected in the EU from those reported in large cohort studies conducted in the US. This conclusion is the same as noted in the previous studies B022 and B025.

In regards to Strattera use among patients 0 to 5 years of age, the numbers of Strattera oral solution users in Germany and Sweden were approximately equal to the number of capsule users in this age group. Consistent with the previous drug utilization studies, the proportion of Strattera users (oral solution and capsule combined) 0 to 5 years of age in Germany and Sweden was less than 0.5% of all Strattera users in both countries in 2015 and 2016. The MDD and mean days supplied for oral solution were less or comparable to mean days supplied for capsules. The availability of Strattera oral solution was limited (approximately 1600 and 1000 units of oral solution sold in Germany and Sweden, respectively) and it did not change the overall frequency of Strattera use or dosing regimens for children.

15. References

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Annex 1. Tables and Figures

Table 1. Germany: Annual Projected Age Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
0-5 years	32	0.14	25	0.12	23	0.11	17	0.09	23	0.12
6-9 years	2723	12.31	2439	11.90	2345	11.26	2108	10.97	1951	10.40
10-12 years	6033	27.28	5321	25.97	4667	22.42	4129	21.49	3802	20.27
13-17 years	6500	29.39	6841	33.39	6523	31.33	5698	29.66	5357	28.56
18-34 years	1308	5.92	2021	9.86	3406	16.36	4046	21.06	4339	23.13
35-64 years	206	0.93	458	2.24	1440	6.92	1892	9.85	2369	12.63
65+ years	19	0.09	30	0.14	19	0.09	38	0.20	51	0.27
<18 years	15287	69.13	14626	71.38	13559	65.12	11952	62.22	11133	59.36
18-64 years	1514	6.85	2479	12.10	4846	23.27	5938	30.91	6707	35.76
Unknown	5293	23.94	3357	16.38	2398	11.52	1281	6.67	863	4.60
Total	22113	100.00	20491	100.00	20822	100.00	19208	100.00	18754	100.00

Table 2. Germany: Annual Projected Gender Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Female	4076	18.43	3826	18.67	4218	20.26	4171	21.72	3842	20.49
Male	9492	42.92	9275	45.27	9865	47.38	9133	47.55	8834	47.11
Unknown	8546	38.65	7390	36.07	6739	32.37	5904	30.74	6078	32.41
Total	22113	100.00	20491	100.00	20822	100.00	19208	100.00	18754	100.00

Table 3. Germany: Annual Projected Age and Gender Distribution for New Users

	All		Female		Male		Unknown	
	N	%	N	%	N	%	N	%
0-5 years	PP	PPD	PP	PPD	PP	PPD	0	0.00
6-9 years	488	15.61	61	8.66	212	14.47	214	22.60
10-12 years	687	22.00	108	15.22	320	21.85	259	27.29
13-17 years	674	21.59	140	19.70	297	20.26	238	25.06
18-34 years	674	21.59	184	25.97	371	25.33	119	12.53
35-64 years	462	14.80	172	24.18	199	13.60	91	9.62
65+ years	PP	PPD	PP	PPD	PP	PPD	0	0.00
<18 years	1853	59.33	310	43.58	833	56.87	710	74.94
18-64 years	1137	36.39	356	50.15	570	38.93	210	22.15
Unknown	125	4.01	40	5.67	57	3.91	28	2.91
Total	3124	100.00	710	100.00	1465	100.00	948	100.00

Table 4. Netherlands: Annual Projected Age Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
0-5 years	17	0.31	PP	PPD	PP	PPD	PP	PPD	PP	PPD
6-9 years	560	10.12	430	8.50	398	7.98	353	7.50	337	7.49
10-12 years	1285	23.23	979	19.34	889	17.83	832	17.69	676	15.03
13-17 years	1987	35.92	1944	38.41	1854	37.18	1602	34.06	1642	36.51
18-34 years	1016	18.37	1075	21.24	1148	23.02	1198	25.47	1112	24.72
35-64 years	597	10.79	595	11.76	679	13.62	693	14.73	701	15.58
65+ years	35	0.63	PPD	PPD	PP	PPD	PPD	PPD	PPD	PPD
<18 years	3849	69.59	3361	66.41	3144	63.04	2793	59.38	2657	59.07
18-64 years	1613	29.16	1670	33.00	1827	36.64	1891	40.20	1813	40.31
Unknown	34	0.61	13	0.26	7	0.14	10	0.21	4	0.09
Total	5531	100.00	5061	100.00	4987	100.00	4704	100.00	4498	100.00

Table 5. Netherlands: Annual Projected Gender Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Female	1247	22.55	1231	24.32	1280	25.67	1270	27.00	1160	25.79
Male	4284	77.45	3830	75.68	3707	74.33	3434	73.00	3338	74.21
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	5531	100.00	5061	100.00	4987	100.00	4704	100.00	4498	100.00

Table 6. Netherlands: Annual Projected Age and Gender Distribution for New Users

	All		Female		Male	
	N	%	N	%	N	%
0-5 years	PP	PPD	PP	PPD	PP	PPD
6-9 years	136	13.61	24	8.00	112	16.02
10-12 years	206	20.62	45	15.00	161	23.03
13-17 years	210	21.02	56	18.67	154	22.03
18-34 years	274	27.43	85	28.33	189	27.04
35-64 years	160	16.02	84	28.00	76	10.87
65+ years	PP	PPD	PP	PPD	PP	PPD
<18 years	554	55.46	125	41.67	429	61.37
18-64 years	434	43.44	169	56.33	265	37.91
Unknown	7	0.70	4	1.33	3	0.43
Total	999	100.00	300	100.00	699	100.00

Table 7. UK: Annual Age Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
0-5 years	0	0.00	—*	—	—*	—	0	0.00	—*	—
6-9 years	79	10.30	100	12.50	85	10.60	72	9.20	62	9.10
10-12 years	193	25.20	167	20.90	144	17.90	132	16.90	127	18.60
13-17 years	335	43.70	318	39.80	318	39.60	271	34.70	232	34.00
18-34 years	137	17.90	179	22.40	209	26.00	247	31.60	207	30.40
35-64 years	23	3.00	34	4.30	48	6.00	60	7.70	54	7.90
65+ years	0	0.00	0	0.00	—†	—	—†	—	—†	—
<18 years	607	79.10	585	73.30	547	68.00	475	60.70	421	61.70
18-64 years	160	20.90	213	26.70	257	32.00	307	39.30	261	38.30
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	767	100.00	798	100.00	804	100.00	782	100.00	682	100.00

*The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

†The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

Table 8. UK: Annual Gender Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Female	141	18.40	153	19.20	159	19.80	161	20.60	146	21.40
Male	626	81.60	645	80.80	645	80.20	621	79.40	536	78.60
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	767	100.00	798	100.00	804	100.00	782	100.00	682	100.00

Table 9. UK: Annual Age and Gender Distribution for New Users

	All		Female		Male	
	N	%	N†	%	N†	%
0-5 years	0	0.00	0	0.00	0	0.00
6-9 years	16	13.30	<6	—	PPD	PPD
10-12 years	17	14.20	<6	—	PPD	PPD
13-17 years	36	30.00	PPD	PPD	PPD	PPD
18-34 years	38	31.70	<6	—	***‡	—
35-64 years	13	10.80	***‡	—	<6	—
65+ years	—*	—	—*	—	—*	—
<18 years	69	57.50	PPD	PPD	PPD	PPD
18-64 years	51	42.50	PPD	PPD	PPD	PPD
Unknown	0	0.00	0	0.00	0	0.00
Total	120	100.00	23	100.00	97	100.00

* The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

† Counts presented only for groups of sufficient size (N≥6) or to prevent recalculation of low numbers

‡ Although this value is not <6, it was obscured to prevent recalculation of other low numbers

Table 10. Sweden: Annual Age Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
0-5 years	18	0.20	17	0.17	23	0.20	14	0.12	PPD	PPD
6-9 years	938	10.46	973	9.50	1002	8.88	927	8.05	880	7.85
10-12 years	1605	17.90	1837	17.94	1922	17.03	1932	16.77	1743	15.54
13-17 years	2718	30.32	2927	28.59	3071	27.21	3151	27.35	3176	28.32
18-34 years	2347	26.18	2831	27.65	3289	29.14	3430	29.77	3370	30.05
35-64 years	1316	14.68	1629	15.91	1946	17.24	2034	17.65	1999	17.83
65+ years	22	0.25	25	0.24	32	0.28	34	0.30	PPD	PPD
<18 years	5279	58.89	5754	56.20	6018	53.33	6024	52.28	5811	51.82
18-64 years	3663	40.86	4460	43.56	5235	46.39	5464	47.42	5369	47.88
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	8964	100.00	10239	100.00	11285	100.00	11522	100.00	11213	100.00

Table 11. Sweden: Annual Gender Distribution for all Prevalent Patients

	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Female	3051	34.04	3664	35.78	4080	36.15	4248	36.87	4224	37.67
Male	5913	65.96	6575	64.22	7205	63.85	7274	63.13	6989	62.33
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total*	8964	100.00	10239	100.00	11285	100.00	11522	100.00	11213	100.00

Table 12. Sweden: Annual Age and Gender Distribution for New Users

	All		Female		Male	
	N	%	N	%	N	%
0-5 years	—*	—	—*	—	—*	—
6-9 years	246	9.87	66	6.44	180	12.27
10-12 years	384	15.41	111	10.83	273	18.61
13-17 years	529	21.23	205	20.00	324	22.09
18-34 years	830	33.31	416	40.59	414	28.22
35-64 years	503	20.18	227	22.15	276	18.81
65+ years	—†	—	—†	—	—†	—
<18 years	1159	46.51	382	37.27	777	52.97
18-64 years	1333	53.49	643	62.73	690	47.03
Unknown	0	—	0	—	0	—
Total	2492	100.00	1025	100.00	1467	100.00

* The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

† The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

Table 13. Germany: Mean Daily Dose, Days Supply, and Medication Possession Ratio in New Users

		Mean Daily Dose (MDD), mg		Days supply		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
0-5 years	[redacted]	9.4	0.1	564.0	138.6	0.8	0.2
6-9 years	230	19.7	8.6	318.2	224.9	0.4	0.3
10-12 years	324	24.7	12.5	306.4	218.3	0.4	0.3
13-17 years	318	34.6	16.2	333.2	216.0	0.5	0.3
18-34 years	318	35.9	19.2	286.7	214.9	0.4	0.3
35-64 years	218	35.2	20.3	325.0	240.2	0.4	0.3
65+ years	[redacted]	31.1	21.4	124.8	138.3	0.2	0.2
<18 years	874	27.0	14.5	319.9	219.4	0.4	0.3
18-64 years	536	35.6	19.6	302.3	226.1	0.4	0.3
Unknown	59	30.7	16.1	345.3	227.6	0.5	0.3
Total	1473	30.3	17.1	314.0	222.3	0.4	0.3

Table 14. Germany: Number of Episodes and Length of Treatment in New Users

	One episode		Two episodes		Three episodes		Four episodes		Cumulative length of therapy (days), Patient-level		
	No. patients	%	No. patients	%	No. patients	%	No. patients	%	No. patients	Mean	Standard deviation
0-5 years	PPD	PPD	PPD	PPD	0	0.00	0	0.00	PPD	564.0	138.6
6-9 years	195	16.57	PPD	PPD	PP	PPD	0	0.00	230	318.2	224.9
10-12 years	259	22.01	51	20.40	14	31.11	0	0.00	324	306.4	218.3
13-17 years	247	20.99	59	23.60	PPD	PPD	PPI	PPD	318	333.2	216.0
18-34 years	251	21.33	57	22.80	PPD	PPD	0	0.00	318	286.7	214.9
35-64 years	171	14.53	44	17.60	PP	PPD	0	0.00	218	325.0	240.2
65+ years	PPI	PPD	0	0.00	0	0.00	0	0.00	PPI	124.8	138.3
<18 years	702	59.64	139	55.60	32	71.11	PPI	PPD	874	319.9	219.4
18-64 years	422	35.85	101	40.40	13	28.89	0	0.00	536	302.3	226.1
Unknown	49	4.16	10	4.00	0	0.00	0	0.00	59	345.3	227.6
Total	1177	100.00	250	100.00	45	100.00	PPI	PPD	1473	314.0	222.3

Table 15. Netherlands: Mean Daily Dose and Medication Possession Ratio in New Users

		Mean Daily Dose (MDD)*, mg		Days supply		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
0-5 years	0	—	—	45.0	—	0.1	—
6-9 years	PPD	22.2	9.1	305.0	281.2	0.4	0.4
10-12 years	89	30.8	15.1	336.9	282.7	0.5	0.4
13-17 years	95	42.2	23.0	303.4	276.8	0.4	0.4
18-34 years	119	50.7	26.6	230.8	255.9	0.3	0.4
35-64 years	72	57.9	26.3	289.9	281.3	0.4	0.4
65+ years	PPI	42.8	38.4	55.0	46.7	0.1	0.1
<18 years	244	33.1	19.3	314.9	279.3	0.4	0.4
18-64 years	191	53.4	26.6	252.9	266.5	0.4	0.4
Unknown	4	9.7	8.7	25.3	15.0	0.0	0.0
Total	441	41.8	25.0	284.0	274.8	0.4	0.4

* Patients with 7 days between their first and last prescription are excluded from MDD calculations to avoid stochastic results.

Table 16. Netherlands: Number of Episodes and Length of Treatment in New Users

	One episode		Two episodes		Three episodes		Cumulative length of therapy (days), Patient-level		
	No. patients	%	No. patients	%	No. patients	%	No. patients	Mean	Standard deviation
0-5 years	PP	PPD	0	0.00	0	0.00	PP	45.0	—
6-9 years	60	13.95	PP	PPD	0	0.00	62	305.0	281.2
10-12 years	86	20.00	PP	PPD	PP	PPD	91	336.9	282.7
13-17 years	91	21.16	PP	PPD	PP	PPD	97	303.4	276.8
18-34 years	116	26.98	PP	PPD	PP	PPD	126	230.8	255.9
35-64 years	73	16.98	PP	PPD	0	0.00	75	289.9	281.3
65+ years	PP	PPD	0	0.00	0	0.00	PP	55.0	46.7
<18 years	238	55.35	PPD	PPD	PP	PPD	251	314.9	279.3
18-64 years	189	43.95	PPD	PPD	PP	PPD	201	252.9	266.5
Unknown	1	0.23	3	12.50	0	0.00	4	25.3	15.0
Total	430	100.00	24	100.00	4	100.00	458	284.0	274.8

Table 17. United Kingdom: Mean Daily Dose, Days Supply and Medication Possession Ratio in New Users

		Mean Daily Dose (MDD)*, mg		Days supply		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients	Mean†	Standard deviation†	Mean†	Standard deviation†	Mean†	Standard deviation†
0-5 years	0	—	—	—	—	—	—
6-9 years	16	34.8	8.7	423.2	212.0	0.6	0.3
10-12 years	17	37.9	14.8	387.9	272.1	0.5	0.4
13-17 years	36	47.2	17.1	307.3	227.1	0.4	0.3
18-34 years	38	57.8	23.5	385.9	434.8	0.5	0.6
35-64 years	13	76.1	23.6	351.6	250.5	0.5	0.3
65+ years	—*	—	—	—	—	—	—
<18 years	69	42.0	15.8	354.0	237.6	0.5	0.3
18-64 years	51	62.5	24.7	377.2	393.9	0.5	0.5
Unknown	0	—	—	—	—	—	—
Total	120	50.7	22.4	363.9	312.4	0.5	0.4

*The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

† Mean, standard deviation and median values were calculated after row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients in the 35-64 years category and in the 65+ years category.

Table 18. United Kingdom: Number of Episodes and Length of Treatment in New Users

	One episode		Two episodes*		Three episodes*		Four episodes*		Cumulative length of therapy (days), Patient-level		
	No. patients	%	No. patients	%	No. patients	%	No. patients	%	No. patients	Mean‡	Standard deviation‡
0-5 years	PPD	PPD	0	0.00	0	0.00	0	0.00	0	—	—
6-9 years	16	14.70	<6	—	<6	—	<6	—	16	415.3	203.7
10-12 years	15	13.80	<6	—	<6	—	<6	—	17	378.6	265.5
13-17 years	34	31.20	<6	—	<6	—	<6	—	36	302.4	220.8
18-34 years	34	31.20	<6	—	<6	—	<6	—	38	377.4	424.3
35-64 years	PPD	PPD	<6	—	<6	—	<6	—	13	347.8	246.0
65+ years	—†	—	—†	—	—†	—	—†	—	—†	—	—
<18 years	65	59.60	<6	—	<6	—	<6	—	69	347.4	230.7
18-64 years	44	40.40	<6	—	<6	—	<6	—	51	369.9	384.6
Unknown	0	0.00	0	0.00	0	0.00	0	0.00	0	—	—
Total	109	100.00	8	100.00	<6	—	<6	—	120	356.9	304.5

*Results were over-masked to avoid recalculation of small numbers in other tables

†The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

‡ Mean, standard deviation and median values were calculated after row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients in the 35-64 years category and in the 65+ years category.

Table 19. Sweden: Mean Daily Dose and Medication Possession Ratio in New Users

	Mean Daily Dose (MDD)*, mg			Days supply		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients	Mean**	Standard deviation**	Mean	Standard deviation	Mean‡,**	Standard deviation‡,**
0-5 years	—†	—	—	—	—	—	—
6-9 years	246	31.8	17.6	434.3	307.3	60.3	42.7
10-12 years	384	39.5	17.7	448.1	307.5	62.2	42.7
13-17 years	529	52.6	24.8	378.1	290.3	52.5	40.3
18-34 years	829	49.6	26.5	291.9	274.8	40.5	38.2
35-64 years	503	54.9	30.7	344.0	294.2	47.8	40.9
65+ years	—‡	—	—	419.6	253	58.3	35.1
<18 years	1159	43.8	22.8	414.0	301.3	57.5	41.9
18-64 years	1332	51.6	28.2	311.3	283.2	43.2	39.3
Unknown	0	—	—	—	—	—	—
Total	2491	47.9	26.2	359.6	296.0	49.9	41.1

* Patients with 7 days between their first and last prescription are excluded from results in this table to avoid stochastic results.

† The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

‡ The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

** Mean, standard deviation and median values were calculated before row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients only in the 35-64 years category and not in the 65+ years category.

Table 20. Sweden: Number of Episodes and Length of Treatment in New Users

	One episode		Two episodes		Three episodes		Cumulative length of therapy (days), Patient-level		
	No. patients	%	No. patients	%	No. patients†	%	No. patients	Mean**	Standard deviation**
0-5 years	—*	—	0	0.00	0	0.00	—*	—	—
6-9 years	224	10.16	21	7.58	<10	—	246	434.3	307.3
10-12 years	348	15.79	36	13.00	0	0.00	384	448.1	307.5
13-17 years	452	20.51	74	26.71	<10	—	529	378.1	290.3
18-34 years	737	33.44	87	31.41	<10	—	830	291.9	274.8
35-64 years	443	20.10	59	21.30	<10	—	503	344.0	294.2
65+ years	—‡	—	—‡	—	0	0.00	—‡	—	—
<18 years	1024	46.46	131	47.29	<10	—	1159	414.0	301.3
18-64 years	1180	53.54	146	52.71	<10	—	1333	311.3	283.2
Unknown	0	0.00	0	0.00	0	0.00	0	—	—
Total	2204	100.00	277	100.00	11	100.00	2492	359.6	296.0

* The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

† Counts presented only for groups of sufficient size (N≥10)

‡ The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

** Mean, standard deviation and median values were calculated before row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients only in the 35-64 years category and not in the 65+ years category.

Table 21. Germany: Proportion of New Users Persistent by Month, over a 24-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100.00%	100.00%	100.00%	99.93%	98.10%	91.11%	82.01%	73.52%	66.19%	61.10%	56.55%	52.34%
Discontinuation	0.00%	0.00%	0.00%	0.07%	1.83%	8.76%	17.52%	25.59%	31.84%	36.18%	39.92%	43.11%
Reinitiation	0.00%	0.00%	0.00%	0.00%	0.07%	0.14%	0.48%	0.88%	1.97%	2.72%	3.53%	4.55%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	49.97%	47.25%	44.06%	42.43%	40.33%	38.42%	36.73%	35.30%	34.49%	33.47%	32.32%	31.50%
Discontinuation	44.74%	47.32%	50.17%	51.12%	53.09%	54.65%	55.67%	56.89%	57.50%	58.18%	58.93%	58.93%
Reinitiation	5.30%	5.43%	5.77%	6.45%	6.59%	6.92%	7.60%	7.81%	8.01%	8.35%	8.76%	9.57%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 22. Germany: Patients Restarting Therapy over a 24-month Period (New Users)

	All new users	All restarters		Restarters with 2 episodes only		Restarters with 3 episodes only		Restarters with 4 episodes only	
	No. patients	No. patients	%	No. patients	%	No. patients	%	No. patients	%
0-5 years	PP	PP	PPD	PP	PPD	0	0.00	0	0.00
6-9 years	230	PPD	PPD	PPD	PPD	PP	PPD	0	0.00
10-12 years	324	65	21.96	51	20.40	14	31.11	0	0.00
13-17 years	318	71	23.99	59	23.60	PPD	PPD	PP	PPD
18-34 years	318	67	22.64	57	22.80	PPD	PPD	0	0.00
35-64 years	218	47	15.88	44	17.60	PP	PPD	0	0.00
65+ years	PP	0	0.00	0	0.00	0	0.00	0	0.00
<18 years	874	172	58.11	139	55.60	32	71.11	PP	PPD
18-64 years	536	114	38.51	101	40.40	13	28.89	0	0.00
Unknown	59	10	3.38	10	4.00	0	0.00	0	0.00
Total	1473	296	100.00	250	100.00	45	100.00	PP	PPD

Table 23. Germany: Mean Gap (in Days) between Treatment Episodes in New Users during the 24-month Follow-up Period, by Age Group

	All the episode gaps			Gap between episode 1 and 2			Gap between episode 2 and 3			Gap between episode 3 and 4		
	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥3 episodes	Mean	Standard deviation	No. patients with ≥4 episodes	Mean	Standard deviation
0-5 years	PP	8.0	—	PP	8.0	—	0	—	—	0	—	—
6-9 years	35	119.6	118.6	35	128.1	122.3	PP	76.9	93.8	0	—	—
10-12 years	65	97.1	108.1	65	103.1	111.1	14	69.1	91.1	0	—	—
13-17 years	71	81.3	100.9	71	79.5	105.0	PPD	98.3	76.7	1	12.0	—
18-34 years	67	118.7	126.3	67	124.0	131.0	PPD	83.2	85.0	0	—	—
35-64 years	47	123.2	131.9	47	122.1	131.3	PP	139.7	171.7	0	—	—
65+ years	0	—	—	0	—	—	0	—	—	0	—	—
<18 years	172	94.8	107.8	172	97.9	111.8	33	81.3	85.0	1	12.0	—
18-64 years	114	120.5	128.0	114	123.3	130.5	13	96.2	104.6	0	—	—
Unknown	PPD	160.7	133.8	PPD	160.7	133.8	0	—	—	0	—	—
Total	296	106.2	117.1	296	109.8	120.6	46	85.5	90.0	1	12.0	—

Table 24. Netherlands Proportion of New Users Persistent by Month, over a 24-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100.00%	100.00%	100.00%	98.69%	89.30%	74.45%	64.63%	55.90%	49.56%	46.07%	43.01%	40.17%
Discontinuation	0.00%	0.00%	0.00%	1.31%	10.70%	25.11%	34.93%	43.23%	49.34%	52.62%	55.68%	58.08%
Reinitiation	0.00%	0.00%	0.00%	0.00%	0.00%	0.44%	0.44%	0.87%	1.09%	1.31%	1.31%	1.75%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	38.65%	36.03%	34.50%	32.75%	30.57%	29.48%	28.17%	26.86%	25.76%	25.55%	24.89%	24.02%
Discontinuation	59.39%	62.23%	63.54%	64.85%	66.81%	67.90%	69.00%	69.87%	70.96%	70.74%	72.05%	72.93%
Reinitiation	1.97%	1.75%	1.97%	2.40%	2.62%	2.62%	2.84%	3.28%	3.28%	3.71%	3.06%	3.06%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 25. Netherlands: Patients Restarting Therapy over a 24-month Period (New Users)

	All new users	All restarters		Restarters with 2 episodes only		Restarters with 3 episodes only	
	No. patients	No. patients	%	No. patients	%	No. patients	%
0-5 years	PP	0	0.00%	0	0.00%	0	0.00%
6-9 years	PPD	PP	PPD	PP	PPD	0	0.00%
10-12 years	91	PP	PPD	PP	PPD	PP	PPD
13-17 years	97	PP	PPD	PP	PPD	PP	PPD
18-34 years	126	PPD	PPD	PP	PPD	PP	PPD
35-64 years	75	PP	PPD	PP	PPD	0	0.00%
65+ years	PP	0	0.00%	0	0.00%	0	0.00%
<18 years	251	13	46.43%	PPD	PPD	PP	PPD
18-64 years	201	PPD	PPD	PPD	PPD	PP	PPD
Unknown	4	3	10.71%	3	12.50%	0	0.00%
Total	458	28	100.00%	24	100.00%	4	100.00%

Table 26. Netherlands: Mean Gap (in Days) between Treatment Episodes in New Users during the 24-month Follow-up Period, by Age Group

	All the episode gaps			Gap between episode 1 and 2			Gap between episode 2 and 3		
	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥3 episodes	Mean	Standard deviation
0-5 years	0	—	—	0	—	—	0	—	—
6-9 years	PP	82.5	48.8	PP	82.5	48.8	0	—	—
10-12 years	PP	122.7	126.4	PP	141.4	131.7	PP	29.0	—
13-17 years	PP	62.9	71.7	PP	68.5	76.9	PP	29.0	—
18-34 years	PPD	121.1	179.0	PPD	139.2	192.2	PP	30.5	12.0
35-64 years	PP	399.0	207.9	PP	399.0	207.9	0	—	—
65+ years	0	—	—	0	—	—	0	—	—
<18 years	13	89.4	94.4	13	98.7	98.5	PP	29.0	—
18-64 years	PPD	160.8	201.5	PPD	182.5	210.7	PP	30.5	12.0
Unknown	3	210.0	206.3	3	210.0	206.3	0	—	—
Total	28	131.9	160.1	28	146.5	166.3	4	29.8	7.0

Table 27. United Kingdom: Proportion of New Users Persistent by Month, over a 24-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100.00%	100.00%	100.00%	100.00%	95.00%	91.67%	79.17%	70.00%	65.00%	61.67%	56.67%	49.17%
Discontinuation	0.00%	0.00%	0.00%	0.00%	5.00%	8.33%	15.83%	25.00%	30.00%	33.33%	38.33%	45.83%
Reinitiation	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	47.50%	44.17%	43.33%	40.83%	39.17%	35.00%	32.50%	28.33%	29.17%	28.33%	26.67%	25.83%
Discontinuation	47.50%	50.83%	51.67%	54.17%	55.83%	60.00%	62.50%	66.67%	65.83%	65.83%	65.83%	66.67%
Reinitiation	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%	5.83%	7.50%	7.50%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 28. United Kingdom: Patients Restarting Therapy over a 24-month Period (New Users)

	All new users	All restarters*		Restarters with 2 episodes only*		Restarters with 3 episodes only*		Restarters with 4 episodes only*	
	No. patients	No. patients	%	No. patients	%	No. patients	%	No. patients	%
0-5 years	0	0	0.00	0	0.00	0	0.00	0	0.00
6-9 years	16	<6	—	<6	—	<6	—	<6	—
10-12 years	17	<6	—	<6	—	<6	—	<6	—
13-17 years	36	<6	—	<6	—	<6	—	<6	—
18-34 years	38	<6	—	<6	—	<6	—	<6	—
35-64 years	13	<6	—	<6	—	<6	—	<6	—
65+ years	—†	—†	—	—†	—	—†	—	—†	—
<18 years	69	<6	—	<6	—	<6	—	<6	—
18-64 years	51	PP	PPD	<6	—	<6	—	<6	—
Unknown	0	0	—	0	—	0	—	0	—
Total	120	11	100.00	8	100.00	<6	—	<6	—

*Results were over-masked to avoid recalculation of low numbers

†The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers.

Table 29. United Kingdom: Mean Gap (in Days) between Treatment Episodes in New Users during the 24-month Follow-up Period, by Age Group

	All the episode gaps*			Gap between episode 1 and 2*			Gap between episode 2 and 3*			Gap between episode 3 and 4*		
	No. pts. with ≥2 episodes	Mean‡	SD‡	No. pts. with ≥2 episodes	Mean‡	SD‡	No. pts. with ≥3 episodes	Mean‡	SD‡	No. pts. with ≥4 episodes	Mean‡	SD‡
0-5 years	0	—	—	0	—	—	0	—	—	0	—	—
6-9 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
10-12 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
13-17 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
18-34 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
35-64 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
65+ years	—†	—	—	—†	—	—	—†	—	—	—†	—	—
<18 years	<6	—	—	<6	—	—	<6	—	—	<6	—	—
18-64 years	[redacted]	198.0	109.5	[redacted]	208.9	129.2	<6	—	—	<6	—	—
Unknown	0	—	—	0	—	—	0	—	—	0	—	—
Total	11	178.1	95.3	11	179.0	110.5	<6	—	—	<6	—	—

Abbreviations: pts. = patients; SD = Standard deviation.

*Results were over-masked to avoid recalculation of low numbers

†The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

‡ Mean, standard deviation and median values were calculated after row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients in the 35-64 years category and in the 65+ years category.

Table 30. Sweden: Proportion of New Users Persistent by Month, over a 24-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9	10	11	12
Persistence	100.00%	100.00%	100.00%	96.91%	79.61%	67.22%	58.71%	52.13%	47.75%	43.50%	40.29%	37.28%
Discontinuation	0.00%	0.00%	0.00%	2.69%	19.66%	30.50%	37.48%	42.46%	45.91%	49.40%	52.01%	54.33%
Reinitiation	0.00%	0.00%	0.00%	0.40%	0.72%	2.29%	3.81%	5.42%	6.34%	7.10%	7.70%	8.39%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Persistence	35.39%	33.11%	31.46%	29.94%	28.49%	27.13%	26.24%	24.92%	23.52%	22.35%	21.15%	20.30%
Discontinuation	55.66%	57.26%	58.43%	59.67%	60.91%	62.12%	62.84%	63.92%	65.17%	66.21%	67.30%	68.14%
Reinitiation	8.95%	9.63%	10.11%	10.39%	10.59%	10.75%	10.91%	11.16%	11.32%	11.44%	11.56%	11.56%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 31. Sweden: Patients Restarting Therapy over a 24-month Period (New Users)

	All new users	All restarters		Restarters with 2 episodes only		Restarters with 3 episodes only	
	No. patients	No. patients	%	No. patients	%	No. patients†	%
0-5 years	—*	0	0.00	0	0.00	0	0.00
6-9 years	246	22	7.64	21	7.58	<10	—
10-12 years	384	36	12.50	36	13.00	0	0.00
13-17 years	529	77	26.74	74	26.71	<10	—
18-34 years	830	93	32.29	87	31.41	<10	—
35-64 years	503	60	20.83	59	21.30	<10	—
65+ years	—‡	—‡	—	—‡	—	0	0.00
<18 years	1159	135	46.88	131	47.29	<10	—
18-64 years	1333	153	53.13	146	52.71	<10	—
Unknown	0	0	0.00	0	0.00	0	0.00
Total	2492	288	100.00	277	100.00	11	100.00

* The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

† Counts presented only for groups of sufficient size (N≥10)

‡ The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers.

Table 32. Sweden: Mean Gap (in Days) between Treatment Episodes in New Users during the 24-month Follow-up Period, by Age Group

	All the episode gaps			Gap between episode 1 and 2			Gap between episode 2 and 3		
	No. patients with ≥2 episodes*	Mean‡	Standard deviation‡	No. patients with ≥2 episodes*	Mean‡	Standard deviation‡	No. patients with ≥3 episodes*	Mean‡	Standard deviation‡
0-5 years	0	—	—	0	—	—	0	—	—
6-9 years	22	262.0	109.5	22	265.4	112.7	<10	—	—
10-12 years	36	227.2	92.1	36	227.7	93.3	0	—	—
13-17 years	77	240.1	129.1	77	242.5	132.5	<10	—	—
18-34 years	93	219.3	93.2	93	221.6	95.8	<10	—	—
35-64 years	60	225.7	92.8	60	225.3	94.0	<10	—	—
65+ years	—†	—	—	—†	—	—	0	—	—
<18 years	135	240.4	117.2	135	242.3	119.8	<10	—	—
18-64 years	153	221.7	92.8	153	223.0	94.8	<10	—	—
Unknown	0	—	—	0	—	—	0	—	—
Total	288	231.3	106.1	288	233.0	108.5	11	193.2	39.6

* Counts presented only for groups of sufficient size (N≥10)

† The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

‡ Mean, standard deviation and median values were calculated before row categories were combined for masking. For example, these values for the 35-64 years row were calculated among patients only in the 35-64 years category and not in the 65+ years category.

Table 33. United Kingdom: Proportion of Patients in Prevalent User Cohort with ≥1 ICD-10 Code for ADHD and at Least 24-months of Follow-up

	UK Disease Analyzer and Clinical Practice Research Datalink Databases		
	Number of atomoxetine users	**Number of patients with ADHD**	**Row %**
0-5 years	—*	—*	—
6-9 years	176	46	26.14%
10-12 years	272	50	18.38%
13-17 years	417	68	16.31%
18-34 years	224	67	29.91%
35-64 years	61	PPD	18.03%
65+ years	—†	—†	—
<18 years	865	164	18.96%
18-64 years	285	78	27.37%
Unknown Age	0	0	—
Total	1150	242	21.04%

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

*The 0-5 years age group was combined with the 6-9 years age group to avoid recalculation of low numbers

†The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers

Table 34. United Kingdom: 30 Most Frequent Diagnosis Codes among Prevalent Users Cohort with at Least 24-months of Follow-up (CPRD and DA)

ICD-10 code (Level 4)	Description	No. patients	%
Z518	OTH SPEC MEDICAL CARE	400	45.66
F900	DISTURBANCE ACTVTY/ATTEN	220	25.11
R693	NOT STATED DIAG DOC	126	14.38
Z408	OTH PROPHYLACTIC SURGERY	121	13.81
J069	AC UPP RESP INFECT UNSP	113	12.90
Z519	MEDICAL CARE UNSP	97	11.07
L700	ACNE VULGARIS	80	9.13
J459	ASTHMA UNSPECIFIED	73	8.33
M796	PAIN IN LIMB	71	8.11
Z000	GENERAL MEDICAL EXAM	71	8.11
Z718	OTH SPEC COUNSELLING	69	7.88
Z017	LABORATORY EXAMINATION	67	7.65
Z138	SPEC SCR OTH SPEC DIS	61	6.96
J039	ACUTE TONSILLITIS UNSP	59	6.74
B070	VIRAL WARTS	52	5.94
J220	UNSP AC LOW RESP INFECT	49	5.59
F909	HYPERKINETIC DIS UNSP	47	5.37
F840	CHILDHOOD AUTISM	43	4.91
Z760	ISSUE REP PRESCRIPT	43	4.91
Z018	OTH SPEC SPECIAL EXAMS	41	4.68
Z539	PROCED NOT DONE UNS REAS	41	4.68
H603	OTH INF OTITIS EXTERNA	40	4.57
R104	OTH AND UNSP ABDO PAIN	39	4.45
L989	DIS SKN/SUBCUT TISS UNSP	37	4.22
R688	OTH SPEC GENL SYM/SIGNS	37	4.22
Z719	COUNSELLING UNSPECIFIED	37	4.22
F990	MNTL DIS NOT O/WISE SPEC	36	4.11
M255	PAIN IN JOINT	36	4.11
T149	INJURY UNSPECIFIED	36	4.11
Z029	EXAM ADMIN PURPOSES UNSP	35	4.00
TOTAL†		**876**	

Abbreviatons: CPRD = Clinical Practice Research Datalink; DA = ; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems

† Number of patients with at least one diagnosis for one or more of the top 30 comorbidities.

Table 35. United Kingdom: Top 30 Concomitant Medications in the Prevalent Users Cohort with at Least 24-month Follow-up Period in the DA

ATC code	Description	No. patients	%
N07X0	ALL OTHER CNS DRUGS	139	94.56
N06B0	PSYCHOSTIMULANTS	57	38.78
N05B1	NON-BARBITURATE PLAIN	32	21.77
J01C1	BROAD SPECT PENICILL ORAL	28	19.05
N02B0	NON-NARCOTIC ANALGESICS	28	19.05
N05A1	ATYPICAL ANTIPSYCHOTICS	28	19.05
J01H1	MED/NARROW SPECT PEN PLAI	24	16.33
R03A4	SHORT-ACT B2-AGON INHAL	23	15.65
N06A4	SSRI ANTIDEPRESSANTS	21	14.29
M01A1	ANTIRHEUMATICS NON-S PLN	20	13.61
R06A0	ANTIHISTAMINES SYSTEMIC	19	12.93
D02A0	EMOLLIENTS & PROTECTIVES	14	9.52
R01A1	NASAL CORTIC W/O ANTI-INF	14	9.52
A02B2	PROTON PUMP INHIBITORS	12	8.16
D07A0	TOP CORTICOSTEROIDS PLAIN	12	8.16
R03D1	CORTICOIDS INHALANTS	11	7.48
D10A0	TOPICAL ANTI-ACNE PREPS	10	6.80
N01B3	ANAESTH LOCAL TOPICAL	10	6.80
N05C0	TRANQUILLISERS	10	6.80
D01A3	TOP SCALP ANTIFUNGALS	9	6.12
D07B2	TOP STEROIDS+ANTI-FUNG	9	6.12
N03A0	ANTI-EPILEPTICS	9	6.12
D01A1	TOPICAL DERMAT ANTIFUNGAL	8	5.44
J01A0	TETRACYCLINES & COMBS	8	5.44
Y19A0	SPACERS	8	5.44
A03A0	ANTISPASM+ANTICHOL PLAIN	7	4.76
D11A0	OTHER DERMATOLOGICAL PREP	7	4.76
H02A2	ORAL CORTICOSTEROID PLAIN	7	4.76
J01E0	TRIMETHOPRIM COMBS	7	4.76
J01F0	MACROLIDES & SIMILAR TYPE	7	4.76
Total†		147	

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification System; DA =Disease Analyzer .

† Number of patients with at least one prescription for one or more of the top 30 concomitant medications.

Table 36. United Kingdom: Top 30 Concomitant Medications in the Prevalent Users Cohort with at Least 24-month Follow-up Period in the CPRD

BNF Chapter	No. patients	%
CNS STIMULANTS AND DRUGS USED FOR ATTENTION DEFICI	964	98.27
HYPNOTICS	300	30.58
BROAD-SPECTRUM PENICILLINS	233	23.75
SELECTIVE BETA 2 AGONISTS	200	20.39
SECOND-GENERATION ANTIPSYCHOTIC DRUGS	146	14.88
NON-SEDATING ANTIHISTAMINES	131	13.35
PENICILLINASE-RESISTANT PENICILLINS	124	12.64
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS	114	11.62
NON-OPIOID AND COMPOUND ANALGESICS	110	11.21
SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS	102	10.40
CORTICOSTEROIDS (FOR RESPIRATORY CONDITIONS)	100	10.19
PROTON PUMP INHIBITORS	76	7.75
TOPICAL CORTICOSTEROIDS/TOPICAL CORTICOSTEROIDS WI	73	7.44
OSMOTIC LAXATIVES	72	7.34
BENZYLPENICILLIN AND PHENOXYMETHYLPENICILLIN	72	7.34
EMOLLIENT SKIN PREPARATIONS	68	6.93
CORTICOSTEROIDS USED IN NASAL ALLERGY	63	6.42
NON-OPIOID AND COMPOUND ANALGESICS/NON-STEROIDAL A	58	5.91
NON-OPIOID AND COMPOUND ANALGESICS/OPIOID ANALGESI	55	5.61
MACROLIDES	55	5.61
TOPICAL CORTICOSTEROIDS/MILD TOPICAL CORTICOSTEROI	55	5.61
SEDATING ANTIHISTAMINES	49	4.99
ANTIBACTERIAL PREPARATIONS ONLY USED TOPICALLY/ANT	49	4.99
ANTIBACTERIALS (IN EYE PREPARATION)	44	4.49
CONTROL OF EPILEPSY	43	4.38
SULPHONAMIDES AND TRIMETHOPRIM	42	4.28
TETRACYCLINES	40	4.08
SPACER|HOLDING CHAMBER DEVICE TYPE 3	40	4.08
BENZODIAZEPINES/DRUGS USED IN STATUS EPILEPTICUS/F	37	3.77
OTHER ANTIDEPRESSANT DRUGS	37	3.77
Total†	**981**	

Abbreviations: BNF =British National Formulary ; CPRD = Clinical Practice Research Datalink;

† Number of patients with at least one prescription for one or more of the top 30 concomitant medications.

Table 37. Sweden: Proportion of Patients in Prevalent User Cohort with ≥1 ICD-10 Code for ADHD and at Least 24-months Follow-up

	Swedish Prescription Drug Register		
	Number of atomoxetine users	**Number of patients with ADHD**	**Row %**
0-5 years	58	49	84.48
6-9 years	2462	2187	88.83
10-12 years	3552	3169	89.22
13-17 years	5376	4854	90.29
18-34 years	6215	5534	89.04
35-64 years	3643	3065	84.13
65+ years	62	37	59.68
<18 years	11448	10259	89.61
18-64 years	9858	8599	87.23
Unknown Age	0	0	—
Total	21368	18895	88.43

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

Table 38. Sweden: 30 Most Frequent Diagnosis Codes among Prevalent User Cohort with at Least 24-months of Follow-up for All Patients

ICD-10 code (Level 4)*	Description	No. patients	%
F900	ATTENTION-DEFICIT HYPERACTIVITY DISORDER, PREDOMINANTLY INATTENTIVE TYPE	19046	89.13
R104	PAIN LOCALIZED TO OTHER PARTS OF LOWER ABDOMEN	4828	22.59
F419	ANXIETY DISORDER, UNSPECIFIED	3784	17.71
Z004	ENCOUNTER FOR EXAMINATION FOR ADOLESCENT DEVELOPMENT STATE	3684	17.24
F329	MAJOR DEPRESSIVE DISORDER, SINGLE EPISODE, UNSPECIFIED	3180	14.88
F412	GENERALIZED ANXIETY DISORDER	2864	13.40
Z038	ENCOUNTER FOR OBSERVATION FOR OTHER SUSPECTED DISEASES AND CONDITIONS RULED OUT	2697	12.62
Z032	ENCOUNTER FOR MEDICAL OBSERVATION FOR SUSPECTED DISEASES AND CONDITIONS RULED OUT	2536	11.87
F845	ASPERGER'S SYNDROME	2270	10.62
Z090	ENCOUNTER FOR FOLLOW-UP EXAMINATION AFTER COMPLETED TREATMENT FOR CONDITIONS OTHER THAN MALIGNANT NEOPLASM	2151	10.07
R699	ILLNESS, UNSPECIFIED	2050	9.59
F321	MAJOR DEPRESSIVE DISORDER, SINGLE EPISODE, MODERATE	1950	9.13
M796	PAIN IN LIMB, HAND, FOOT, FINGERS AND TOES	1864	8.72
F840	AUTISTIC DISORDER	1588	7.43
Z094	ENCOUNTER FOR FOLLOW-UP EXAMINATION AFTER COMPLETED TREATMENT FOR CONDITIONS OTHER THAN MALIGNANT NEOPLASM	1538	7.20
R074	PRECORDIAL PAIN	1520	7.11
J459	OTHER AND UNSPECIFIED ASTHMA	1432	6.70
R519	HEADACHE	1407	6.58
K590	CONSTIPATION	1406	6.58
Z711	PERSON WITH FEARED HEALTH COMPLAINT IN WHOM NO DIAGNOSIS IS MADE	1392	6.51
T509	POISONING BY, ADVERSE EFFECT OF AND UNDERDOSING OF OTHER AND UNSPECIFIED DRUGS, MEDICAMENTS AND BIOLOGICAL SUBSTANCES	1382	6.47
F430	ACUTE STRESS REACTION	1337	6.26
F192	OTHER PSYCHOACTIVE SUBSTANCE DEPENDENCE	1328	6.21
F100	ALCOHOL RELATED DISORDERS	1304	6.10
Z010	ENCOUNTER FOR EXAMINATION OF EYES AND VISION	1297	6.07
Z011	ENCOUNTER FOR EXAMINATION OF EARS AND HEARING	1293	6.05
F909	ATTENTION-DEFICIT HYPERACTIVITY DISORDER, UNSPECIFIED TYPE	1252	5.86
Z039	ENCOUNTER FOR OBSERVATION FOR OTHER SUSPECTED DISEASES AND CONDITIONS RULED OUT	1195	5.59
F331	MAJOR DEPRESSIVE DISORDER, RECURRENT, MODERATE	1191	5.57
Z719	COUNSELING, UNSPECIFIED	1186	5.55
Total		**21368**	

* International Classification of Diseases, 10th edition, Sweden (ICD-10-SE) codes used.

Table 39. Sweden: Top 30 Concomitant Medications among Prevalent User Cohort with at Least 24-months of Follow-up

ATC code	Description	No. patients	%
N06BA	CENTRALLY ACTING SYMPATHOMIMETICS	18534	86.74
J01CE	BETA-LACTAMASE SENSITIVE PENICILLINS	12710	59.48
N05CH	MELATONIN RECEPTOR AGONISTS	10634	49.77
N06AB	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	9685	45.32
N05BB	DIPHENYLMETHANE DERIVATIVES	8201	38.38
R06AD	PHENOTHIAZINE DERIVATIVES	7962	37.26
N06AX	OTHER ANTIDEPRESSANTS	6514	30.48
R05CB	MUCOLYTICS	6443	30.15
N02BE	ANILIDES	6412	30.01
J01CF	BETA-LACTAMASE RESISTANT PENICILLINS	6226	29.14
M01AE	PROPIONIC ACID DERIVATIVES	6114	28.61
R03AC	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	5708	26.71
R01AD	CORTICOSTEROIDS	5663	26.50
A02BC	PROTON PUMP INHIBITORS	5521	25.84
N05CF	BENZODIAZEPINE RELATED DRUGS	5460	25.55
N05CM	OTHER HYPNOTICS AND SEDATIVES	5395	25.25
M01AB	ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	5331	24.95
J01CA	PENICILLINS WITH EXTENDED SPECTRUM	5182	24.25
R06AX	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	5088	23.81
R05FA	OPIUM DERIVATIVES AND EXPECTORANTS	4884	22.86
J01AA	TETRACYCLINES	4371	20.46
N05BA	BENZODIAZEPINE DERIVATIVES	4308	20.16
A06AD	OSMOTICALLY ACTING LAXATIVES	4239	19.84
N03AX	OTHER ANTIEPILEPTICS	4210	19.70
N02AJ	OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	3952	18.49
S03CA	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	3926	18.37
N05AH	DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	3920	18.35
A01AA	CARIES PROPHYLACTIC AGENTS	3833	17.94
H02AB	GLUCOCORTICOIDS	3670	17.18
N05AX	OTHER ANTIPSYCHOTICS	3669	17.17
Total		**21368**	

Abbreviations: ATC = Anatomical Therapeutic Chemical Classification System.

Tables oral solution

Table 40. Germany: Annual Projected Age Distribution for all Prevalent Oral Solution users

	Projected			
	2015		2016	
	N	%	N	%
0-5 years	PPD	PPD	25	4.40
6-9 years	130	53.77	232	40.80
10-12 years	66	27.36	193	34.00
13-17 years	27	11.32	68	12.00
18-34 years	PPD	PPD	27	4.80
35-64 years	0	0.00	14	2.40
65+ years	0	0.00	0	0.00
<18 years	232	96.23	518	91.20
18-64 years	PPD	PPD	41	7.20
Unknown	2	0.94	9	1.60
Total	241	100.00	568	100.00

Table 41. Germany: Annual Projected Gender Distribution for all Prevalent Oral Solution Users

	Projected			
	2015		2016	
	N	%	N	%
Female	59	24.53	95	16.80
Male	102	42.45	252	44.40
Unknown	80	33.02	220	38.80
Total	241	100.00	568	100.00

Table 42. Germany: Annual Projected Age and Gender Distribution for New Oral Solution Users

	Projected							
	All		Female		Male		Unknown	
	N	%	N	%	N	%	N	%
0-5 years	PPD	PPD	PPD	PPD	PPD	PPD	0	0.00
6-9 years	114	56.82	25	52.38	55	60.00	34	55.56
10-12 years	50	25.00	14	28.57	16	17.50	20	33.33
13-17 years	23	11.36	PPD	PPD	PPD	PPD	7	11.11
18-34 years	PPD	PPD	PPD	PPD	PPD	PPD	0	0.00
35-64 years	0	0.00	0	0.00	0	0.00	0	0.00
65+ years	0	0.00	0	0.00	0	0.00	0	0.00
<18 years	193	96.59	45	95.24	86	95.00	61	100.00
18-64 years	PPD	PPD	PPD	PPD	PPD	PPD	0	0.00
Unknown	2	1.14	0	0.00	2	2.50	0	0.00
Total	200	100.00	48	100.00	91	100.00	61	100.00

Table 43. Sweden: Annual Age Distribution for all Prevalent Oral Solution Users

	2015		2016	
	N*	%	N*	%
0-5 years	14	8.48	13	4.35
6-9 years	77	46.67	139	46.49
10-12 years	48	29.09	87	29.10
13-17 years	21	12.73	45	15.05
18-34 years	<10	—	PPD	PPD
35-64 years	<10	—	<10	—
65+ years	<10†	—	<10†	—
<18 years	160	96.97	284	94.98
18-64 years	<10	—	15	5.02
Unknown	0	0.00	0	0.00
Total	165	100.00	299	100.00

* Counts presented only for groups of sufficient size (N≥10)

† The 65+ years age group was combined with the 35-64 years and 18-64 years age groups to avoid recalculation of low numbers .

Table 44. Sweden: Annual Gender Distribution for all Prevalent Oral Solution Users

	2015		2016	
	N	%	N	%
Female	50	30.30	80	26.76
Male	115	69.70	219	73.24
Unknown	0	0.00	0	0.00
Total	165	100.00	299	100.00

Table 45. Sweden: Annual Projected Age and Gender Distribution for New Oral Solution Users

	All		Female		Male	
	N*	%	N*	%	N*	%
0-5 years	14	8.64	<10	—	PPD	PPD
6-9 years	76	46.91	23	48.94	53	46.09
10-12 years	48	29.63	14	29.79	34	29.57
13-17 years	20	12.35	<10	—	14	12.17
18-34 years	<10	—	<10	—	<10	—
35-64 years	<10	—	<10	—	<10	—
65+ years	<10	—	<10	—	<10	—
<18 years	158	97.53	47	100.00	111	96.52
18-64 years	<10	—	<10	—	<10	—
Unknown	<10	—	<10	—	<10	—
Total	162	100.00	47	100.00	115	100.00

* Counts presented only for groups of sufficient size (N≥10)

Table 46. Germany: Mean Daily Dose, Days Supply, and Medication Possession Ratio in New Oral Solution Users

	Mean Daily Dose (MDD), mg			Days supply equivalent		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
0-5 years	PP	8.7	5.6	240.4	74.3	0.4	0.1
6-9 years	50	19.7	5.8	142.2	166.8	0.3	0.3
10-12 years	22	29.7	8.1	177.6	180.7	0.3	0.3
13-17 years	PPD	39.7	13.0	95.6	143.5	0.2	0.3
18-34 years	PP	48.4	31.9	16.2	1.0	0.0	0.0
35-64 years	0	—	—	—	—	—	—
65+ years	0	—	—	—	—	—	—
<18 years	85	24.3	10.6	149.3	166.1	0.3	0.3
18-64 years	PP	48.4	31.9	16.2	1.0	0.0	0.0
Unknown	1	20.0	—	132.0	—	0.2	—
Total	88	24.8	11.5	146.1	164.5	0.3	0.3

Table 47. Germany: Number of Episodes and Length of Treatment in New Oral Solution Users

	One episode		Two episodes		Three episodes		Cumulative length of therapy (days), Patient-level		
	No. patients	%	No. patients	%	No. patients	%	No. patients	Mean	Standard deviation
0-5 years	PP	PPD	0	0.00	0	0.00	PP	240.4	74.3
6-9 years	45	56.25	PP	PPD	0	0.00	50	142.2	166.8
10-12 years	21	26.25	PP	PPD	0	0.00	22	177.6	180.7
13-17 years	PP	PPD	PP	PPD	PPI	PPD	PPD	95.6	143.5
18-34 years	PP	PPD	0	0.00	0	0.00	PP	16.2	1.0
35-64 years	0	0.00	0	0.00	0	0.00	0	—	—
65+ years	0	0.00	0	0.00	0	0.00	0	—	—
<18 years	77	96.25	PP	PPD	PPI	PPD	85	149.3	166.1
18-64 years	PP	PPD	0	0.00	0	0.00	PP	16.2	1.0
Unknown	1	1.25	0	0.00	0	0.00	1	132.0	—
Total	80	100.00	7	100.00	PPI	PPD	88	146.1	164.5

Table 48. Sweden: Mean Daily Dose, Days Supply, and Medication Possession Ratio in New Oral Solution Users

	Mean Daily Dose (MDD), mg			Days supply equivalent		Medication Possession Ratio (MPR) for Days Supplied	
	No. patients*	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
0-5 years	14	19.0	11.1	420.7	255.3	0.8	0.5
6-9 years	76	33.4	18.7	493.0	299.6	0.9	0.5
10-12 years	48	37.4	17.2	407.7	289.8	0.7	0.5
13-17 years	20	51.5	25.6	376.6	271.3	0.7	0.5
18-34 years	<10	—	—	—	—	—	—
35-64 years	<10	—	—	—	—	—	—
65+ years	<10	—	—	—	—	—	—
<18 years	158	35.6	20.1	445.9	290.7	0.8	0.5
18-64 years	<10	—	—	—	—	—	—
Unknown	0	—	—	—	—	—	—
Total	162	35.5	19.9	440.4	290.6	0.8	0.5

* Counts presented only for groups of sufficient size (N≥10).

Table 49. Sweden: Number of Episodes and Length of Treatment in New Oral Solution Users

	One episode		Two episodes		Cumulative length of therapy (days), Patient-level		
	No. patients*	%	No. patients*	%	No. patients*	Mean	Standard deviation
0-5 years	13	8.97	<10	—	14	420.7	255.3
6-9 years	69	47.59	<10	—	76	493	299.6
10-12 years	44	30.34	<10	—	48	407.7	289.8
13-17 years	16	11.03	<10	—	20	376.6	271.3
18-34 years	<10	—	<10	—	<10	—	—
35-64 years	<10	—	0	0.00	<10	—	—
65+ years	<10	—	0	0.00	<10	—	—
<18 years	142	97.93	16	94.12	158	445.9	290.7
18-64 years	<10	—	<10	—	<10	—	—
Unknown	0	0.00	0	0.00	0	—	—
Total	145	100.00	17	100.00	162	440.4	290.6

Table 50. Germany: Proportion of New Oral Solution Users Persistent by Month, over a 18-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9
Persistence	100.00%	100.00%	100.00%	100.00%	92.05%	75.00%	55.68%	50.00%	46.59%
Discontinuation	0.00%	0.00%	0.00%	0.00%	7.95%	25.00%	44.32%	48.86%	50.00%
Reinitiation	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.14%	3.41%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Persistence	39.77%	30.68%	26.14%	22.73%	21.59%	20.45%	19.32%	17.05%	17.05%
Discontinuation	56.82%	65.91%	70.45%	72.73%	75.00%	77.27%	78.41%	80.68%	78.41%
Reinitiation	3.41%	3.41%	3.41%	4.55%	3.41%	2.27%	2.27%	2.27%	4.55%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 51. Germany: Patients Restarting Oral Solution Therapy over a 18-month Period (New Users)

	All new users	All restarters		Restarters with 2 episodes only		Restarters with 3 episodes only	
	No. patients	No. patients	%	No. patients	%	No. patients	%
0-5 years	PPD	0	0.00	0	0.00	0	0.00
6-9 years	50	PPD	PPD	PPD	PPD	0	0.00
10-12 years	22	PPD	PPD	PPD	PPD	0	0.00
13-17 years	PPD	PPD	PPD	PPD	PPD	PPD	PPD
18-34 years	PPD	0	0.00	0	0.00	0	0.00
35-64 years	0	0	0.00	0	0.00	0	0.00
65+ years	0	0	0.00	0	0.00	0	0.00
<18 years	85	PPD	PPD	PPD	PPD	PPD	PPD
18-64 years	PPD	0	0.00	0	0.00	0	0.00
Unknown	PPD	0	0.00	0	0.00	0	0.00
Total	88	8	100.00	7	100.00	PPD	PPD

Table 52. Germany: Mean Gap (in Days) between Treatment Episodes in New Oral Solution Users during the 18-month Follow-up Period, by Age Group

	All the episode gaps			Gap between episode 1 and 2			Gap between episode 2 and 3		
	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥2 episodes	Mean	Standard deviation	No. patients with ≥3 episodes	Mean	Standard deviation
0-5 years	0	—	—	0	—	—	0	—	—
6-9 years	PPI	119.9	156.5	PPI	119.9	156.5	0	—	—
10-12 years	PPI	191.4	—	PPI	191.4	—	0	—	—
13-17 years	PPI	134.2	109.1	PPI	150.6	149.0	PP	101.3	—
18-34 years	0	—	—	0	—	—	0	—	—
35-64 years	0	—	—	0	—	—	0	—	—
65+ years	0	—	—	0	—	—	0	—	—
<18 years	PPI	132.6	125.5	PPI	136.5	133.6	PP	101.3	—
18-64 years	0	—	—	0	—	—	0	—	—
Unknown	0	—	—	0	—	—	0	—	—
Total	8	132.6	125.5	8	136.5	133.6	PP	101.3	—

Table 53. Sweden: Proportion of New Oral Solution Users Persistent by Month, over a 18-month Follow-up Period

Month	1	2	3	4	5	6	7	8	9
Persistence	100.00%	100.00%	100.00%	93.83%	87.65%	72.84%	66.67%	61.73%	58.02%
Discontinuation	0.00%	0.00%	0.00%	6.17%	6.17%	20.99%	27.16%	32.10%	35.80%
Reinitiation	0.00%	0.00%	0.00%	0.00%	6.17%	6.17%	6.17%	6.17%	6.17%
Total	0.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
Month	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Persistence	54.32%	50.62%	46.30%	45.06%	40.74%	40.12%	38.89%	37.04%	37.04%
Discontinuation	38.89%	41.36%	44.44%	45.68%	49.38%	49.38%	50.62%	52.47%	52.47%
Reinitiation	6.79%	8.02%	9.26%	9.26%	9.88%	10.49%	10.49%	10.49%	10.49%
Total	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

Table 54. Sweden: Patients Restarting Oral Solution Therapy over a 18-month Period (New Users)

	All new users	All restarters		Restarters with 2 episodes only	
	No. patients*	No. patients*	No. patients*	No. patients*	%
0-5 years	14	<10	—	<10	—
6-9 years	76	<10	—	<10	—
10-12 years	48	<10	—	<10	—
13-17 years	20	<10	—	<10	—
18-34 years	<10	<10	—	<10	—
35-64 years	<10	0	0.00	0	0.00
65+ years	<10	0	0.00	0	0.00
<18 years	158	16	94.12	16	94.12
18-64 years	<10	<10	—	<10	—
Unknown	0	0	0.00	0	0.00
Total	162	17	100.00	17	100.00

* Counts presented only for groups of sufficient size (N≥10)

Table 55. Sweden: Mean Gap (in Days) between Treatment Episodes in New Oral Solution Users during the 18-month Follow-up Period, by Age Group

	All the episode gaps			Gap between episode 1 and 2			Gap between episode 2 and 3		
	No. patients with ≥2 episodes*	Mean	Standard deviation	No. patients with ≥2 episodes*	Mean	Standard deviation	No. patients with ≥3 episodes	Mean	Standard deviation
0-5 years	<10	—	—	<10	—	—	0	—	—
6-9 years	<10	—	—	<10	—	—	0	—	—
10-12 years	<10	—	—	<10	—	—	0	—	—
13-17 years	<10	—	—	<10	—	—	0	—	—
18-34 years	<10	—	—	<10	—	—	0	—	—
35-64 years	0	—	—	0	—	—	0	—	—
65+ years	0	—	—	0	—	—	0	—	—
<18 years	16	200.6	78.1	16	200.6	78.1	0	—	—
18-64 years	<10	—	—	<10	—	—	0	—	—
Unknown	0	—	—	0	—	—	0	—	—
Total	17	195.2	75.2	17	195.2	75.2	0	—	—

* Counts presented only for groups of sufficient size (N≥10)

Table 56. Sweden: Proportion of Patients in Prevalent Oral Solution User Cohort with ≥1 ICD-10 Code for ADHD* and at Least 18-months Follow-up

	Swedish Prescription Drug Register		
	Number of atomoxetine users†	Number of patients with ADHD†	Row %
0-5 years	14	13	92.86
6-9 years	76	63	82.89
10-12 years	48	42	87.50
13-17 years	20	15	75.00
18-34 years	<10	<10	—
35-64 years	<10	<10	—
65+ years	<10	<10	—
<18 years	158	133	84.18
18-64 years	<10	<10	—
Unknown Age	0	0	—
Total	162	135	83.33

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; ICD-10 = 10th revision of the International Statistical Classification of Diseases and Related Health Problems.

* All F90 codes were included

† Counts presented only for groups of sufficient size (N≥10)

Table 57. Sweden: 30 Most Frequent Diagnosis Codes among Prevalent Oral Solution User Cohort with at Least 18-months of Follow-up for All Patients

ICD-10 code (Level 4)*	Description	No. patients	%
F900	ATTENTION-DEFICIT HYPERACTIVITY DISORDER, PREDOMINANTLY INATTENTIVE TYPE	132	81.48
Z004	ENCOUNTER FOR EXAMINATION FOR ADOLESCENT DEVELOPMENT STATE	34	20.99
Z010	ENCOUNTER FOR EXAMINATION OF EYES AND VISION	26	16.05
Z011	ENCOUNTER FOR EXAMINATION OF EARS AND HEARING	25	15.43
F840	AUTISTIC DISORDER	24	14.81
J069	ACUTE UPPER RESPIRATORY INFECTION, UNSPECIFIED	24	14.81
K590	CONSTIPATION	24	14.81
Z038	ENCOUNTER FOR OBSERVATION FOR OTHER SUSPECTED DISEASES AND CONDITIONS RULED OUT	24	14.81
J459	OTHER AND UNSPECIFIED ASTHMA	23	14.20
B349	VIRAL INFECTION, UNSPECIFIED	21	12.96
H520	HYPERMETROPIA	21	12.96
J451	ASTHMA	21	12.96
H522	ASTIGMATISM	20	12.35
R104	PAIN LOCALIZED TO OTHER PARTS OF LOWER ABDOMEN	20	12.35
Z032	ENCOUNTER FOR MEDICAL OBSERVATION FOR SUSPECTED DISEASES AND CONDITIONS RULED OUT	20	12.35
H660	ACUTE SUPPURATIVE OTITIS MEDIA	19	11.73
Z039	ENCOUNTER FOR OBSERVATION FOR OTHER SUSPECTED DISEASES AND CONDITIONS RULED OUT	19	11.73
R699	ILLNESS, UNSPECIFIED	17	10.49
J352	HYPERTROPHY OF ADENOIDS	14	8.64
H659	UNSPECIFIED NONSUPPURATIVE OTITIS MEDIA	13	8.02
A099	INFECTIOUS GASTROENTERITIS AND COLITIS, UNSPECIFIED	12	7.41
R418	OTHER SYMPTOMS AND SIGNS INVOLVING COGNITIVE FUNCTIONS AND AWARENESS	12	7.41
Z711	PERSON WITH FEARED HEALTH COMPLAINT IN WHOM NO DIAGNOSIS IS MADE	12	7.41
F909	ATTENTION-DEFICIT HYPERACTIVITY DISORDER, UNSPECIFIED TYPE	11	6.79
F913	OPPOSITIONAL DEFIANT DISORDER	11	6.79
H612	IMPACTED CERUMEN	11	6.79
Z018	ENCOUNTER FOR OTHER SPECIFIED SPECIAL EXAMINATIONS	11	6.79
Z090	ENCOUNTER FOR FOLLOW-UP EXAMINATION AFTER COMPLETED TREATMENT FOR CONDITIONS OTHER THAN MALIGNANT NEOPLASM	11	6.79
F849	PERVASIVE DEVELOPMENTAL DISORDER, UNSPECIFIED	10	6.17
J050	ACUTE OBSTRUCTIVE LARYNGITIS [CROUP]	10	6.17
Total		162	

* International Classification of Diseases, 10th edition, Sweden (ICD-10-SE) codes used.

Table 58. Sweden: Top 30 Concomitant Medications among Prevalent Oral Solution User Cohort with at Least 18-months of Follow-up

ATC code	Description	Total	
		No. patients	%
N06BA	CENTRALLY ACTING SYMPATHOMIMETICS	144	88.89
J01CE	BETA-LACTAMASE SENSITIVE PENICILLINS	101	62.35
N05CH	MELATONIN RECEPTOR AGONISTS	86	53.09
R05CB	MUCOLYTICS	70	43.21
A06AD	OSMOTICALLY ACTING LAXATIVES	53	32.72
R03AC	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	50	30.86
R03BA	GLUCOCORTICOIDS	44	27.16
R06AX	OTHER ANTIHISTAMINES FOR SYSTEMIC USE	44	27.16
S01AA	ANTIBIOTICS	43	26.54
J01CA	PENICILLINS WITH EXTENDED SPECTRUM	41	25.31
R03CC	SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	39	24.07
J01CF	BETA-LACTAMASE RESISTANT PENICILLINS	38	23.46
Y75BE	NUTRITIONAL BEVERAGE	38	23.46
R06AA	AMINOALKYL ETHERS	37	22.84
D02AX	OTHER EMOLLIENTS AND PROTECTIVES	36	22.22
Y93DC	INHALATION ASSISTANT FOR AEROSOLS	31	19.14
C02AC	IMIDAZOLINE RECEPTOR AGONISTS	29	17.90
S03CA	CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	28	17.28
R06AD	PHENOTHIAZINE DERIVATIVES	25	15.43
J01DB	FIRST-GENERATION CEPHALOSPORINS	23	14.20
D07AA	CORTICOSTEROIDS, WEAK (GROUP I)	21	12.96
D07AB	CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	20	12.35
R05FA	OPIUM DERIVATIVES AND EXPECTORANTS	20	12.35
-	EXTEMPORE E-PRESCRIPTION	19	11.73
N05	PSYCHOLEPTICS	19	11.73
N06AB	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	19	11.73
Y93DB	INHALATION ASSISTANT FOR AEROSOLS	19	11.73
D06AX	OTHER ANTIBIOTICS FOR TOPICAL USE	18	11.11
N05AX	OTHER ANTIPSYCHOTICS	18	11.11
R05DA	OPIUM ALKALOIDS AND DERIVATIVES	18	11.11
Total		162	

Abbreviations: Anatomical Therapeutic Chemical Classification System.

Figures

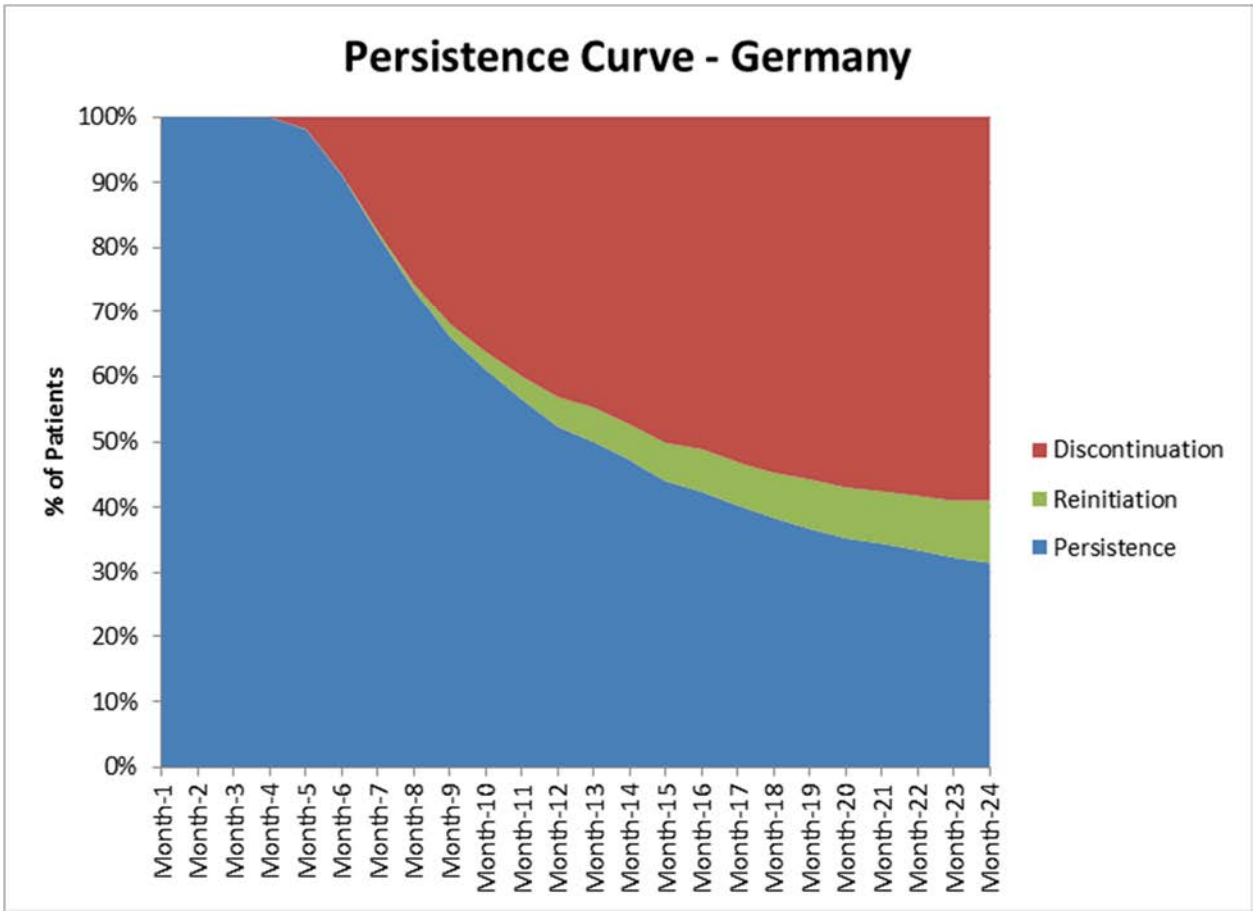

Figure 1. **Germany: Persistence over a 24-month period among capsule users between 01 July 2015 through 30 June 2017.**

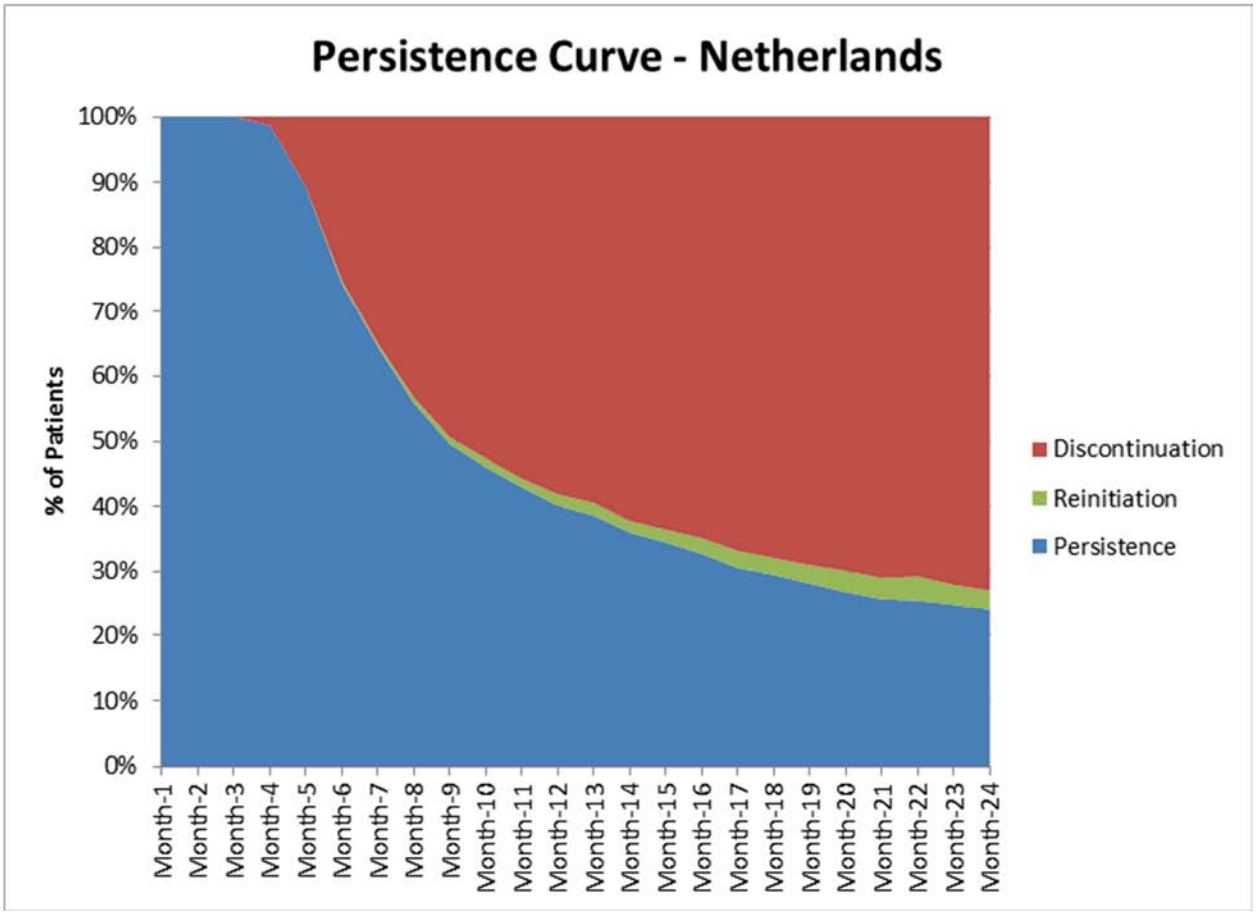

Figure 2. **Netherlands: Persistence over a 24-month period among capsule users between 01 July 2015 through 30 June 2017.**

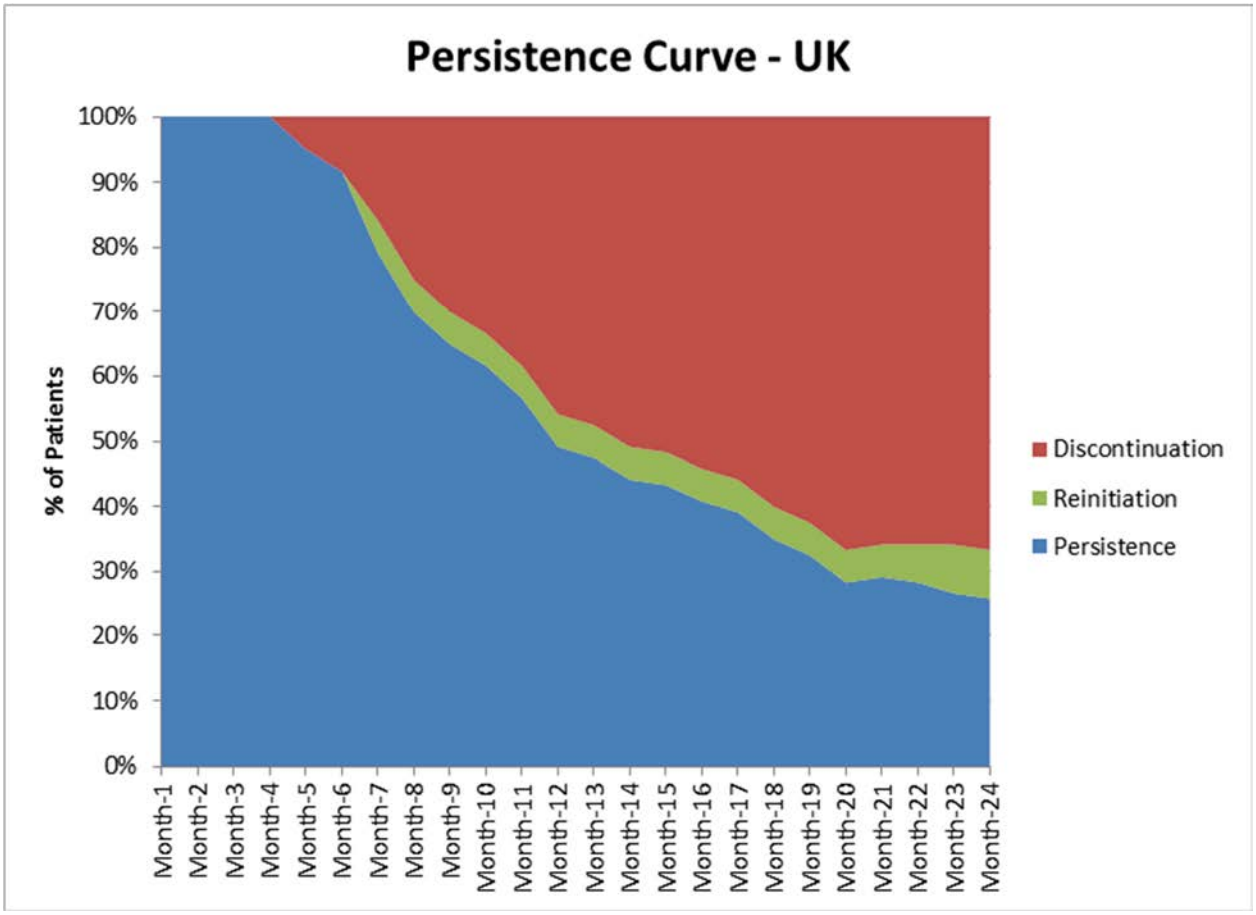

Figure 3. **United Kingdom: Persistence over a 24-month period among capsule users between 01 July 2015 through 30 June 2017.**

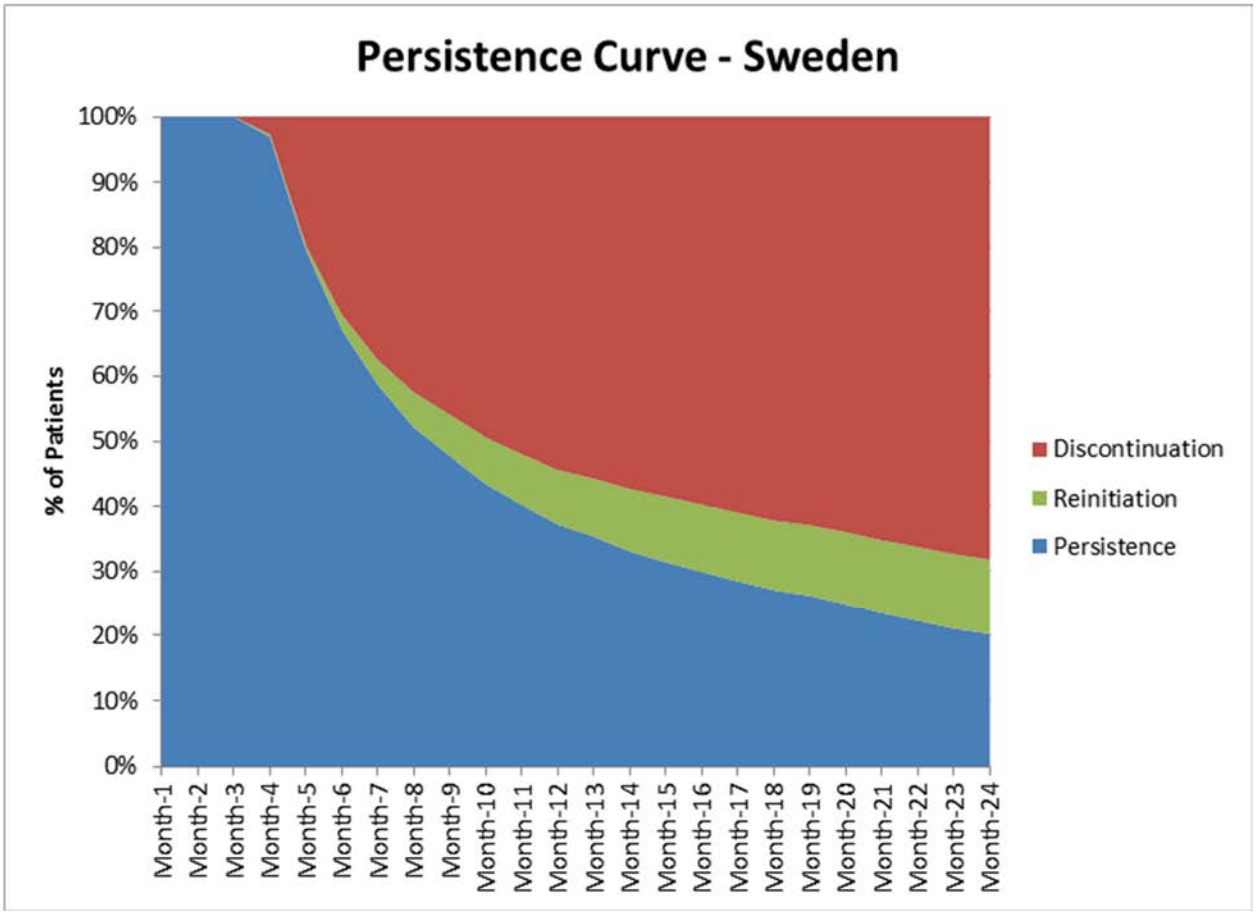

Figure 4. **Sweden: Persistence over a 24-month period among capsule users between 01 July 2015 through 30 June 2017.**

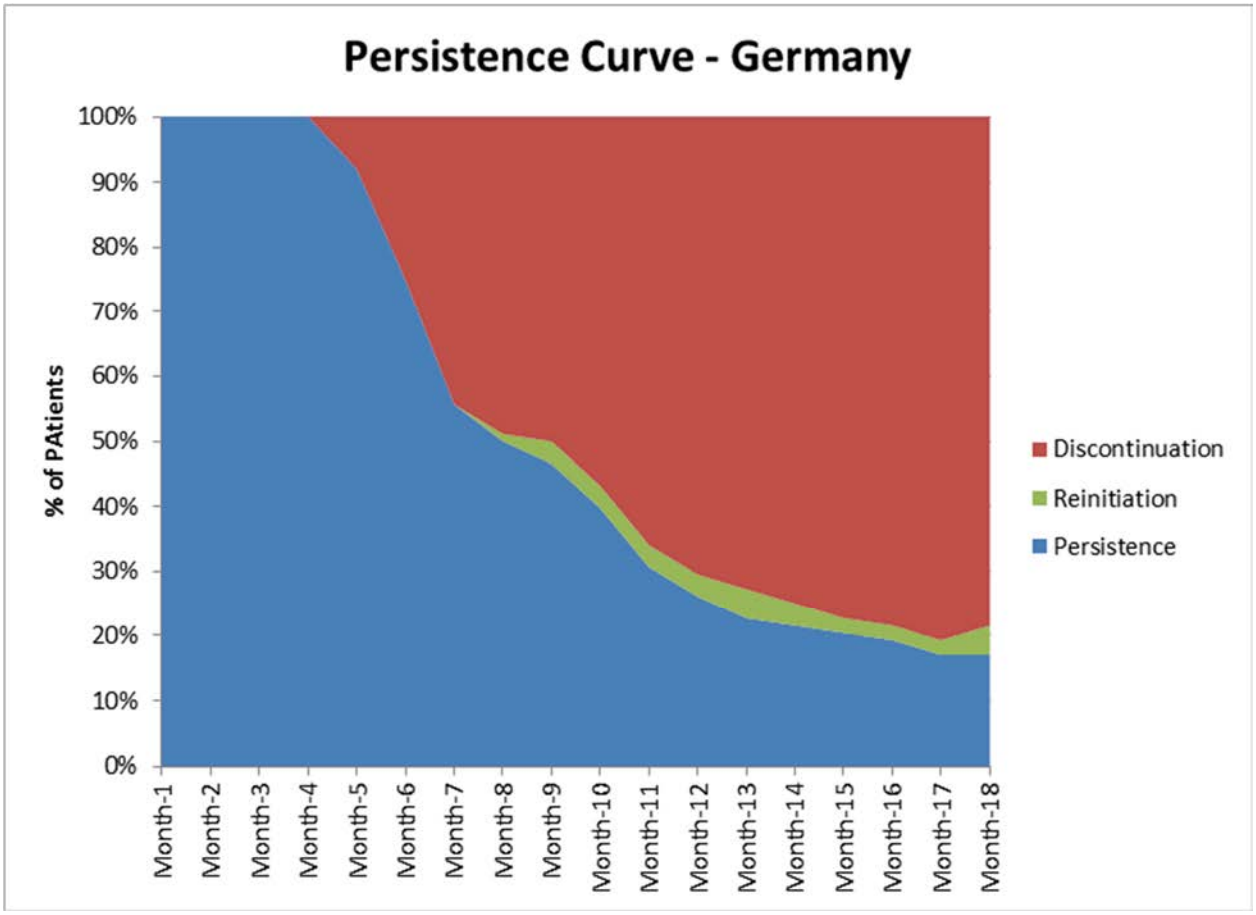

Figure 5. **Germany: Persistence over an 18-month period among oral solution users between 01 January 2016 through 30 June 2017.**

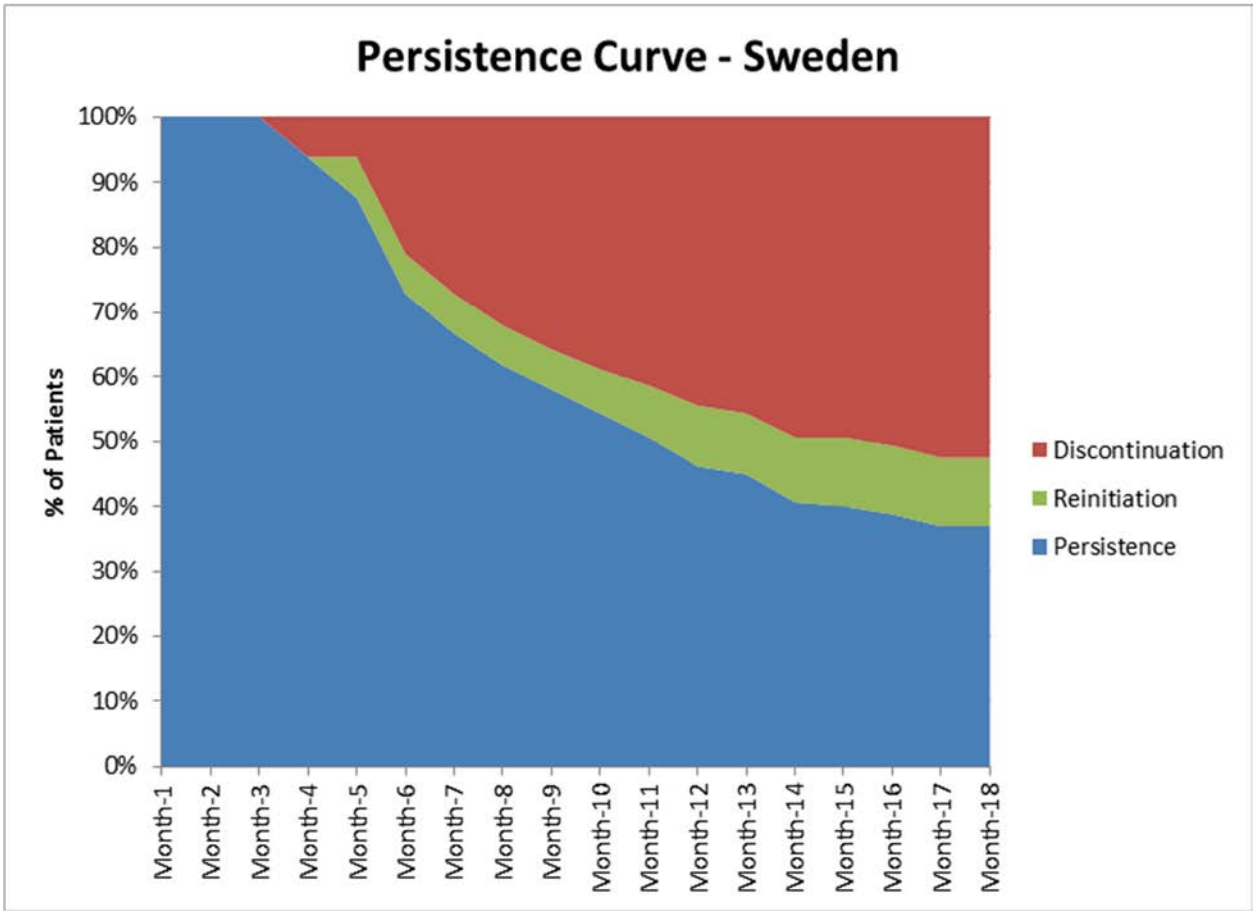

Figure 6. **Sweden: Persistence over an 18-month period among oral solution users between 01 January 2016 through 30 June 2017.**

Annex 2. Additional information

Not applicable.