PASS Information

Title	Physician Survey to Assess Effectiveness of Strattera Risk Minimisation Activities in Prescribers Treating Adult Patients with ADHD
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Marketing authorisation holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	Evaluate adult patient healthcare provider knowledge and awareness of cardiovascular risks associated with Strattera and their compliance to the recommendations in the SmPC. Assess their awareness of the availability of risk minimisation tools.
Country(-ies) of study	Denmark, the Netherlands, Spain, Sweden, and the United Kingdom
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Marketing Authorisation Holder

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2. List of abbreviations

Term	Definition
ADHD	attention deficit/hyperactivity disorder
ADM	Arbeitskreis Deutscher Markt- und Sozialforschungsinstitute e.V.- work council of German market research agencies
AE	adverse event
BVM	Berufsverband Deutscher Markt- und Sozialforscher - Association of German market researchers
CV	cardiovascular
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EphMRA	European Pharmaceutical Market Research Association
ERB	ethical review board
ESOMAR	European Society for Opinion and Marketing Research
EU	European Union
HCPs	healthcare providers
MAH	Marketing Authorisation Holder
PAS	postauthorisation study
PASS	postauthorisation safety study
PSUR	Strattera Periodic Safety Update Report
SmPC	Summary of Product Characteristics
UK	United Kingdom

3. Responsible parties

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4. Abstract

Title: Physician Survey to Assess Effectiveness of Strattera Risk Minimisation Activities in Prescribers Treating Adult Patients with ADHD

Rationale and background:

In response to European Union (EU) Pharmacovigilance Working Party recommendations of September 2011, Eli Lilly and Company (Lilly) implemented additional risk minimisation activities beyond amendments to the Summary of Product Characteristics (SmPC) for Strattera. These activities were implemented following an extensive analysis of cardiovascular data from the Lilly clinical trial database that indicated clinically significant effects on blood pressure and heart rate. The purpose of the additional risk minimisation activities is to ensure, as far as possible, appropriate Strattera prescribing and patient monitoring of cardiovascular parameters. In particular, the physician communications, including associated checklists and the measurement recording chart, are intended to inform physicians of the cardiovascular or cerebrovascular disorder contraindication and the recommendation to monitor blood pressure and heart rate in all patients at baseline and during treatment with Strattera. An initial assessment of paediatric patient prescribers was completed and results were reported in 2012. The second assessment of paediatric patient prescribers was completed in Q4 2013 and reported in Q1 2014. The results of these 2 surveys were consistent and demonstrated that physicians were knowledgeable of the risk minimisation measures and were practicing in compliance with the SmPC.

In May 2013, the Marketing Authorisation Holder (MAH) received a positive outcome to extend the use of Strattera to the treatment of adult attention deficit/hyperactivity disorder (ADHD) patients and the adult indication was included in the SmPC for EU countries. The MAH committed to assessing this new population of prescribers in the same manner as paediatric prescribers.

Research question and objectives:

Research questions

- Are healthcare providers (HCPs) that prescribe Strattera or manage/monitor adult patients using Strattera aware of the cardiovascular risk minimisation measures and are they adherent with the SmPC recommendations to monitor or manage cardiovascular risk?
- Are HCPs that prescribe Strattera or manage/monitor adult patients using Strattera aware that Strattera risk minimisation tools are available?

Study objectives:

The main objective of this a survey is to assess the knowledge and awareness of Strattera risk minimisation measures among psychiatrists who prescribe Strattera or monitor adult patients

treated with Strattera. The secondary objective includes an assessment of awareness of the available risk minimisation tools.

Study design:

This is a cross-sectional survey to be administered in Denmark, Sweden, the Netherlands, Spain, and the United Kingdom (UK) among psychiatrists who prescribe Strattera and/or monitor adult patients treated with Strattera.

Population:

Psychiatrists will be identified via open recruiting using a panel of HCPs within the GfK SE network who have agreed to participate in research surveys. Psychiatrists will be invited to participate by phone and email and, if they agree, an email will be sent with the link to the online survey.

Variables:

Awareness, knowledge, and adherence will be evaluated and expressed as proportions. Summary tables will include descriptive statistics and no formal hypothesis testing will be conducted.

Data sources:

The data for this assessment will be obtained using an online survey of healthcare professionals from Denmark, Sweden, the Netherlands, Spain, and the UK.

Study size:

This survey will include 250 psychiatrists that prescribe Strattera, or manage/monitor adult ADHD patients using Strattera.

Data analysis:

Data analyses will be descriptive and will entail tabular displays of mean values and the frequency distribution of item responses. Results will be expressed as proportions and means. Summary tables will include descriptive statistics for continuous variables (means) and categorical variables (frequencies, percentages). Results will be analysed on an item-by-item or variable-by-variable basis. These descriptive statistics will allow for the assessment of how rates vary for each of the items evaluated. No formal hypothesis testing will be conducted.

The risk minimisation activities will be considered successful if a majority of psychiatrists participating in the survey are aware of and prescribe Strattera in accordance with the cardiovascular/cerebrovascular contraindications, warnings and precautions, and the recommendation to monitor blood pressure and heart rate in all patients at baseline and during treatment with Strattera.

5. Amendments and updates

Not applicable.

6. Milestones

Milestone	Planned date
Start of data collection	30 Jun 2014
End of data collection	30 Sep 2014
Study progress report 1	Not applicable
Interim report 1	Not applicable
Registration in the EU PAS register	08 May 2014
Final report of study results	January 2015

7. Rationale and background

In response to EU Pharmacovigilance Working Party recommendations of September 2011, Eli Lilly and Company (Lilly) implemented additional risk minimisation activities beyond amendments to the SmPC for Strattera. These activities were implemented as a result of an extensive analysis of cardiovascular data from the Lilly clinical trial database that indicated more clinically significant effects on blood pressure and heart rate than had previously been noted. The purpose of the additional risk minimisation activities is to support and foster appropriate Strattera prescribing and patient monitoring of cardiovascular parameters. In particular, the physician communications, including associated checklists and measurement recording chart, are intended to inform physicians of the cardiovascular or cerebrovascular disorder contraindication and the recommendation to monitor blood pressure and heart rate in all patients at baseline and during treatment with Strattera.

An initial assessment of paediatric patient prescribers was completed and results were reported in 2012. The second assessment of paediatric patient prescribers was completed in Q4 2013 and was reported in Q1 2014. As a follow-up to the approval of the adult indication, this assessment will evaluate awareness, knowledge, and adherence among HCPs treating adult patients. The same survey used for the previous assessments will be used but will be adapted to adult prescribers.

8. Research question and objectives

Research question 1:

- Are HCPs that prescribe Strattera or manage/monitor adult patients using Strattera aware of the cardiovascular risk minimization measures and are they adherent with the SmPC recommendations to monitor or manage cardiovascular risk?

The main objective of this a survey is to assess the knowledge and awareness of Strattera risk minimisation measures among psychiatrists who prescribe Strattera or monitor adult patients treated with Strattera. This includes an assessment of awareness and adherence to the SmPC requirements specific to cardiovascular risks and monitoring including:

- Severe cardiovascular/cerebrovascular disorder contraindication
- Warnings and precautions
- The recommendation to monitor blood pressure and heart rate in patients at baseline and during their treatment with Strattera

Research question 2:

- Are HCPs that prescribe Strattera or manage/monitor adult patients using Strattera aware that Strattera risk minimisation tools are available?

The secondary objective includes an assessment of awareness of the available risk minimisation tools, which include:

- Physician's guide for assessing and monitoring cardiovascular risk when prescribing Strattera
- Checklist for actions to take before prescribing/dispensing or administering Strattera
- Checklist for monitoring to manage cardiovascular risks with Strattera treatment
- Measurements recording chart for blood pressure and heart rate.

9. Research methods

9.1. Study design

This is a cross-sectional survey to be administered in Denmark, Sweden, the Netherlands, Spain, and the UK among psychiatrists who prescribe Strattera and/or monitor adult patients treated with Strattera. These countries were selected based on their large market share of Strattera prescriptions. Psychiatrists will be identified via open recruiting using a panel of HCPs within the GfK SE network who have agreed to participate in research surveys. Psychiatrists will be invited to participate by phone and email and if they agree, an email will be sent with the link to the online survey.

9.2. Setting

Psychiatrists that prescribe and/or monitor adult patients on Strattera will be invited to participate via email and/or phone to complete the online survey. The survey is designed to take no more than 10 minutes. Participating HCPs will have the option of receiving compensation for their time. The amount varies by country and is determined by the standard maximum allowed for each country by local laws and as determined by Lilly's process for fair market value.

9.3. Variables

This assessment will evaluate knowledge and awareness of Strattera risk messages specific to cardiovascular risks and monitoring as well as adherence to the SmPC. Knowledge, awareness, and adherence will be evaluated and results will be expressed as proportions. Summary tables will include descriptive statistics and no formal hypothesis testing was conducted.

9.4. Data sources

The data for this assessment will be obtained using an online survey of psychiatrists from Denmark, Sweden, the Netherlands, Spain, and the UK.

9.5. Study size

As reflected in Table 9.1, sample sizes in this assessment have been adjusted to reflect the limited number of prescribers that treat adult patients with ADHD. At the time of protocol development, the adult indication for Strattera has been launched for less than 1 year in most countries being surveyed. Primary care physicians and general practitioners were not included in this survey because they have already been surveyed twice regarding the same knowledge, awareness, and adherence. Only the psychiatrists treating adult ADHD patients have not yet been assessed. The sample size was determined based on confidence in obtaining the projected number of respondents within each country, which, in turn, was based on the source adult psychiatrist population that can provide meaningful insight for this survey.

Table 9.1. Target Number of Completed Surveys by Country

Target groups	Denmark (N)	Netherlands (N)	Spain (N)	Sweden (N)	UK (N)	Total (N)
Psychiatrists	30	40	70	40	70	250

In a random sample (assumes no clustering or stratification) of 250 psychiatrists who complete the survey, the true value of interest (for example, awareness of medical information) lies within the lower and upper confidence level around the observed value as described in Table 9.2. If, for instance, the observed value of physicians' awareness of the medical information was observed at 90%, the true value is estimated to lie within a +/-3.7% range around the observed 90%.

Table 9.2. Expected 95% Confidence Level

Sample Size	Observed Value (e.g. Awareness)	Lower 95% Confidence Level	Upper 95% Confidence Level
250	50%	43.8%	56.2%
250	60%	53.9%	66.1%
250	70%	64.3%	75.7%
250	80%	75.0%	85.0%
250	90%	86.3%	93.7%

9.6. Data management

Surveys will be completed online and data will be stored on a secure server. Survey participants must log in using unique login identification. Every effort will be made to protect participant confidentiality. Participant identifiers will not be disseminated or placed on any reports from this study. Analyses will be conducted with anonymised data. Unless authorized by the participant (for example, in the case of adverse event [AE] or product complaint reporting), only anonymised data will be made available to Lilly in accordance with privacy protection rules as dictated by applicable regulations.

9.7. Data analysis

Data analyses will be descriptive and will entail tabular displays of mean values and the frequency distribution of item responses. Awareness, knowledge, and adherence will be evaluated and results will be expressed as proportions and means. Summary tables will include descriptive statistics for continuous variables (means) and categorical variables (frequencies, percentages). Results will be analysed on an item-by-item or variable-by-variable basis. These descriptive statistics will allow for the assessment of how proportions vary for each of the items evaluated. No formal hypothesis testing will be conducted.

The risk minimisation measures will be considered successful if a majority of psychiatrists participating in the survey are aware of and prescribe Strattera in accordance with the cardiovascular/cerebrovascular contraindications, warnings and precautions, and the

recommendation to monitor blood pressure and heart rate in all patients at baseline and during treatment with Strattera.

9.8. Quality control

All fieldwork suppliers undergo ongoing evaluation and quality control. The following quality control mechanisms are implemented for all quantitative surveys (among others):

- Error prevention by intelligent programming (filtering, error messages among others)
- Consistency checks of the respondents' individual data files regarding plausibility ("data logic") and completeness
- Re-contacting respondents after the interviews in order to keep evidence that interviews are really done by the agreed (panel) participants

Under suspicion of any irregularities (for example, detection of equivocal response patterns or consecutive answers of the same multiple choice answer), the data file will be tentatively excluded from analysis and further investigated by the responsible project manager.

In order to minimize bias in the survey instrument, the sample of survey participants, and other survey procedures, the following measures will be taken, as appropriate:

- Evaluation of survey to ensure that questions are not ambiguous or leading
- Randomisation of response options presented in a list to reduce positional bias
- Monitoring of regional spread of respondents to minimise regional bias
- Exclusion of participants employed or contracted by regulatory bodies (such as the European Medicines Agency [EMA]), Lilly, or the vendor conducting survey
- Quality control measures: for example, exclusion of flatliners (always ticking same answer options in statement batteries, and so on)
- Assessment of demographic information provided by respondents in order to assess geographical representation. If over representation of any one area is identified, additional sampling from other areas may be necessary for a more balanced sample.

9.9. Limitations of the research methods

Potential limitations to using this online survey include:

- Non-response bias. This is an inherent limitation in the survey study design and in this case cannot be controlled. This limitation should not impact the ability to achieve the objective of this assessment.
- Exclusion of psychiatrists not comfortable with or without access to the internet. In order to reduce the probability of this occurrence, psychiatrists will be given the option to conduct the survey with an interviewer if they refuse to complete it online.
- Social desirability response bias where psychiatrists may respond positively rather than truthfully. In order to reduce the probability of this type of bias, surveys are anonymous, questions are not leading, and are designed to elicit truthful responses.

- Sample is not random. Psychiatrists will be selected from panel lists of those who have agreed to participate in market research. Given the specific target population, this cannot be controlled.

These limitations are acknowledged and given the nature of the data collected should not greatly impact the conclusions drawn from the data collected from respondents. Efforts, where possible, will be made to address and reduce the impact of these limitations, see bullets above.

9.10. Other aspects

Not applicable.

10. Protection of human subjects

Observational studies are submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all prospective observational studies are submitted to at least 1 independent body (for example, ERB) per country for review and to confirm that the study is considered non-interventional in that country. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region and country or countries where the study is being conducted, as appropriate.

Every effort will be made to protect participant confidentiality. Participant identifiers will not be disseminated or placed on any reports from this study. Analyses will be conducted with anonymised data. Unless authorised by the participant (for example, in the case of an AE or product complaint report), only anonymised data will be made available to Lilly in accordance with privacy protection rules as dictated by applicable regulations.

GfK Health, which is conducting this survey on behalf of Lilly, is strictly committed to the highest standards of privacy protection and confidentiality and of the code of conduct of pharmaceutical market research as defined by European Pharmaceutical Market Research Association (EphMRA) and Arbeitskreis Deutscher Markt- und Sozialforschungsinstitute e.V.- work council of German market research agencies (ADM). GfK Health is part of EphMRA, ADM, European Society for Opinion and Marketing Research (ESOMAR), and Berufsverband Deutscher Markt- und Sozialforscher - Association of German market researchers (BVM).

11. Management and reporting of adverse events/adverse reactions

Adverse Event Collection for Prospective Observational Studies

Adverse events or product complaints will be documented according to Lilly's reporting requirements and reported to Lilly within the timeframe specified by Lilly. The survey participant will also be informed that someone from Lilly may call back to obtain additional information about the AE or product complaint.

Adverse Event Reporting Timing for Prospective Observational Studies

GfK study personnel will report to Lilly any AE in temporal association with Strattera within 1 day of awareness of the event via AE collection form used by GfK.

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Additionally, GfK personnel will report the following information for Lilly drug(s), regardless of whether there is an associated serious or nonserious AE:

- pregnancy exposures
- breast-feeding exposures
- overdoses
- misuse
- abuse
- off-label use
- medication error
- lack of drug effect
- suspected transmission of infectious agent

Study personnel will report adverse reactions in temporal association with Lilly drugs and with any non-Lilly drugs to the appropriate party (for example, regulators or Lilly) as they would in normal practice as required by applicable laws, regulations, and practices.

12. Plans for disseminating and communicating study results

A final report will be submitted in a future Strattera Periodic Safety Update Report (PSUR) as an EU appendix. In the event of negative finding, results will be communicated to regulatory bodies in the appropriate timeframe.

13. References

None.