Title	**Drug Utilization Study with Intuniv® in Australia**
Protocol version identifier	Final version 1.0
Date of last version of protocol	New protocol
Active substance	Pharmacotherapeutic group: Antiadrenergic agents, centrally acting ATC code(s): C02 AC02 Active substance: guanfacine hydrochloride
Medicinal product	Intuniv® Modified release tablets 1mg, 2mg, 3mg and 4mg
Product reference	AUSTR 275278 1mg AUSTR 275313 2mg AUSTR 275314 3mg AUSTR 275315 4mg
Marketing authorisation holder(s)	Shire Australia Pty Limited Level 39 Grosvenor Place 225 George Street Sydney, NSW 2000 Australia
Research question and objectives	The overall objective is to provide data on an annual basis for 3 years in Australia to evaluate drug utilization and monitor off-label use of Intuniv®. Primary objective: • To characterize patients who are prescribed Intuniv® with a specific focus on compliance with: o Indication o Patient age relative to the product information o Visits and measurements performed during the first year of treatment Secondary objectives: • To describe prescribing patterns of Intuniv® • To monitor the effectiveness of the risk minimization measures based on the outcomes measured in the drug utilization study
Country of study	Australia
Author	QuintilesIMS, Germany

Marketing authorisation holder(s)	Shire Australia Pty Limited Level 39 Grosvenor Place 225 George Street Sydney, NSW 2000 Australia
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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
AMPCo	Australasian Medical Publishing Company
AMSRS	Australian Market & Social Research Society
ATC	Anatomical Therapeutic Chemical
CoE	Centre of Excellence
DUS	Drug Utilisation Study
EPR	Electronic Patient Records
ESOMAR	European Society for Opinion and Market Research
GDS	Global drug safety
ICD	International Classification of Diseases
PhD	Doctor of Philosophy
PBAC	Pharmaceutical Benefits Advisory Committee
PI	Product Information
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TGA	Therapeutic Goods Administration
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

3 RESPONSIBLE PARTIES

Sponsor: Shire Pharmaceuticals

Project team:
Project Manager: [redacted] PhD, [redacted]; Shire (e-mail: [redacted]);

Global Pharmacovigilance and Risk Management:

[redacted], PhD; Shire (e-mail: [redacted])

[redacted], PhD; Shire (e-mail: [redacted])

Contractor: QuintilesIMS

QuintilesIMS is a member of Medicines Australia and adheres to their Code of Conduct. QuintilesIMS Market Research personnel are members of the Australian Market & Social Research Society (AMSRS) and follow the Code of Professional Behaviour.

Project team:
The project will be managed by the QuintilesIMS Centre of Excellence (CoE) in Retrospective Studies. As team members are likely to change over the project period of 3 years, no individual names are listed here. All project tasks will be performed by adequately qualified staff, including experienced senior project coordinators, epidemiologists, and medical experts.

Statistical analysis will be conducted by QuintilesIMS in-house global and local experts. These teams have many years combined experience of analyzing and drawing statistically robust findings from longitudinal and cross-sectional patient data.

4 ABSTRACT

Title	Drug Utilization Study with Intuniv® in Australia
Rationale and background	Shire Pharmaceuticals plans to launch Intuniv® for treatment of ADHD in children and adolescents in Australia in 2018. Shire Pharmaceuticals will conduct a drug utilization study for three years as part of the risk management plan for Intuniv® in Australia.
Research question and objectives	The overall objective is to provide data on an annual basis for 3 years in Australia to evaluate drug utilization and monitor off-label use of Intuniv®. Primary objective: • To characterize patients who are prescribed Intuniv® with a specific focus on compliance with: o Indication o Patient age relative to the product information o Visits and measurements needed during the first year of treatment Secondary objectives: • To describe prescribing patterns of Intuniv® • To monitor the effectiveness of the risk minimization measures based on the outcomes measured in the drug utilization study
Study design and data sources	This is a drug utilization study using retrospective database analysis. A single database with all relevant information is not available. Therefore, data from the NostraData database, a longitudinal patient-level prescription database, will be supplemented with data from a physician survey.
Population	Patients who have been prescribed Intuniv® at least once during the reporting period.
Variables	• Indication of use (diagnosis) • Patient characteristics (e.g., age, gender, presence/absence of contraindications) • Patterns of drug use (e.g., daily dose, first time user, repeat user, treatment duration, gaps, discontinuation of attention deficit hyperactivity disorder (ADHD) therapy and switches, co-prescriptions of ADHD medication) • Prescriber information (specialty, graduation year, gender, location, region) • Frequency of monitoring of weight, blood pressure and heart rate

Study size	<u>Prescription database:</u> All prescriptions for Intuniv® available in the NostraData database in Australia (70% coverage of the Australian pharmacies) will be analysed. <u>Physician survey:</u> It is planned to collect data for 100 patients, who have been prescribed Intuniv® at least once during the study period, provided by representative physicians expected to treat patients with ADHD.
Data analysis	Descriptive analysis of all variables will be performed. The description of missing data for each outcome of interest will be provided. For continuous variables the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented. Categorical variables will be displayed with frequencies and percentages. A detailed statistical analysis plan (SAP) will be agreed on prior to the start of the analysis.
Milestones*	Intuniv® launch date / begin of observational period: February 2018 Start of data collection: February 2019 End of data collection: May 2021 First study report: August 2019 Second study report: August 2020 Last (third) study report: August 2021

*Milestones will depend on the actual launch date of Intuniv®.

5 AMENDMENTS AND UPDATES

Not applicable.

6 MILESTONES

Milestone*	Planned date
Intuniv® launch date:	February 2018
Start of data collection:	February 2019
End of data collection:	May 2021
First study report:	August 2019
Second study report:	August 2020
Last (third) study report:	August 2021

*Milestones will depend on the actual launch date of Intuniv®.

7 RATIONALE AND BACKGROUND

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder primarily characterized by the "co-existence of attentional problems and hyperactivity, with each behaviour occurring infrequently alone" and several inattentive or hyperactive-impulsive symptoms present prior to age 12 (2, 3). ADHD is the most commonly studied and diagnosed psychiatric disorder in children, affecting about 3 to 5% of children globally (4, 5) and diagnosed in about 2 to 16% of school-aged children (5). In an Australian national survey, the prevalence of ADHD in children and adolescents aged 6 to 17 was found to be 11.2% (6). ADHD is a lifetime disorder (7) with 30 to 50% of individuals diagnosed in childhood continuing to have symptoms into adulthood (7, 8). These symptoms include significant social, emotional and academic problems as well as low self-esteem, poor peer relationships, delinquency and substance abuse (5).

Causes of ADHD

The exact causes of ADHD are not known, although many studies suggest that there is a large genetic influence (9). Like many other psychiatric illnesses, ADHD results from a combination of factors. In addition to genetics, scientists are investigating possible effects of environmental factors, brain injuries, nutrition and the social environment on the development of ADHD (10).

Treatment of ADHD

Currently available treatments focus on reducing the symptoms of ADHD and improving social and emotional functioning. Treatments include medication, various types of psychotherapy, education and training, or a combination of treatments.

Most commonly, ADHD is treated with stimulant medications, which are designed to have a calming effect on children with ADHD. Many types of stimulant medications are available. In general, their mechanism of action is on catecholaminergic neurons in the brain, ultimately

leading to an increase of extracellular dopamine and norepinephrine levels in the prefrontal cortex (11).

The two stimulant active ingredients used in the treatment of ADHD in Australia are amphetamines (dexamphetamine and lisdexamfetamine) and methylphenidate. Methylphenidate is available as a short-acting preparation (e.g. Ritalin®) and as a long-acting or extended release preparation (e.g., Ritalin LA®, Concerta®). The mode of action of methylphenidate is not completely understood, but its effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine (11). In Australia, one amphetamine is available under the generic name dexamphetamine as instant release sulfate tablets. Additionally, in 2013 lisdexamfetamine dimesilate (Vyvanse®) was launched in Australia. Vyvanse® is the therapeutically inactive prodrug of dextroamphetamine. It is gradually hydrolysed into L-lysine and the pharmacologically active dextroamphetamine. Amphetamines block the reuptake of norepinephrine and dopamine into the presynaptic neuron and, in contrast to methylphenidate, increase the release of these monoamines into the extraneuronal space (11, 12).

Nonetheless, a subset of ADHD patients will either fail to respond to stimulants or has side effects that preclude their use (e.g., tics, severe loss of appetite, marked insomnia). For such patients, non-stimulant agents serve as second-line treatment. The first non-stimulant medication (Strattera®) was approved in the United Kingdom (UK) in 2004, and in Germany in 2005. In 2009, Shire Pharmaceuticals launched extended-release guanfacine (Intuniv®), a novel non-stimulant drug, in the United States and Canada. In 2016, Intuniv® was launched in nine European countries (Belgium, Denmark, Finland, Germany, Ireland, Netherlands, Norway, Sweden, United Kingdom). Intuniv® is a long-acting, once-daily formulation of guanfacine (a selective alpha-2A-adrenergic receptor agonist) indicated for treatment of ADHD in children and adolescents ages 6 to 17 years. Intuniv® has demonstrated improvement of a range of ADHD symptoms that can be disruptive, such as inattention, hyperactivity, impulsivity, and extensive loss of temper (13). Intuniv® is not a controlled substance, which sets it apart from most other ADHD drugs.

Background and rationale of the current study

Shire Pharmaceuticals plans to launch Intuniv® in Australia in 2018. In order to evaluate drug utilization and monitor inappropriate use of Intuniv® in Australia, Shire Pharmaceuticals proposed to conduct a drug utilization study as part of the risk management plan for Intuniv® in Australia.

The indication for Intuniv® given in the Australia Product Information (PI) (1):

Intuniv® is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years old, as monotherapy (when stimulants or atomoxetine are not suitable, not tolerated or have been shown to be ineffective) or as adjunctive therapy to psychostimulants (where there has been a sub-optimal response to pyschostimulants). Intuniv must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures.

Based on this label, inappropriate use of Intuniv® may include the following:

- Use for patients with a diagnosis other than ADHD
- Use for children less than 6 years of age
- Use in adults (≥ 18 years of age)
- Prescribed overdose > 7 mg/day for patients > 12 years, or > 4 mg/ day for children ≤ 12 years
- If monotherapy with Intuniv®, no prior treatment with stimulants or atomoxetine

In this drug utilization study, electronic patient-level dispensing data and patient medical record data, covering a period of 3 years post-product launch will be analyzed. Annual study reports will be generated by QuintilesIMS, sent to Shire, and then submitted to the Therapeutic Goods Administration (TGA).

This protocol specifies the objectives of the study, describes the methodology and data sources, outlines the plans for statistical analysis, and details the tasks and timelines for the project.

8 RESEARCH QUESTION AND OBJECTIVES

Overall objective

The overall objective is to provide data on an annual basis for 3 years in Australia to evaluate drug utilization and to monitor off-label use of Intuniv®. The planned study is part of the risk management plan for Intuniv®, which had been offered by Shire Pharmaceuticals.

The primary objective of the study is:

- To characterize patients who are prescribed Intuniv®, with a specific focus on compliance with
  - Indication
  - Patients' age in accordance with the product information
  - Visits and measurements needed during the first year of treatment

The secondary objectives of the study are:

- To describe prescribing patterns of Intuniv®
- To monitor the effectiveness of the risk minimization measures based on the outcomes measured in the drug utilization study (DUS).

9 RESEARCH METHODS

9.1 Study design

This is a drug utilization study using retrospective database analysis. A single longitudinal data source that would represent the Australian ADHD population adequately and contain variables needed to monitor off-label use is not obtainable. Therefore, this study will combine data from two sources of patient-level drug utilization data for Intuniv®:

- NostraData database: longitudinal patient level prescription database
- Physician survey: de-identified patient data provided by representative physicians in Australia

In the NostraData database, actual prescription data are collected, which allows generation of information on drug usage. However, these prescription data do not contain patient variables such as age and indication needed to monitor potential off-label use. Therefore, these data must be supplemented with another data source. The physician survey will provide the data not included in the NostraData database. More detailed information on the prescription database and physician survey is given in Section 9.4.

9.2 Setting

Prescription database:

All prescriptions for Intuniv® available in the NostraData database in Australia will be analysed. Currently, about 70% of all Australian pharmacies provide data for NostraData. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv®.

Physician survey:

It is planned to collect data for 100 patients in Australia, who have been prescribed Intuniv® at least once during the study period, provided by representative physicians expected to treat patients with ADHD, as described in section 9.4.2.

The overall observational period will cover 36 months after the launch date.

9.3 Variables

The study aims to characterize patients who are prescribed Intuniv® and describe prescribing patterns of Intuniv® among physicians in Australia.

The following information will be obtained from the NostraData database:

- Direct prescription information
    - Patient information
        - First-time user
        - Repeat user
        - Number of prescriptions per patient
    - Prescriber information
        - Physician specialty

    - Co-prescriptions of other ADHD medication (methylphenidate, lisdexamfetamine, dex/dextro/amphetamine, atomoxetine)
    - ADHD treatment prior to Intuniv® (methylphenidate, lisdexamfetamine, dex/dextro/amphetamine, atomoxetine)
    - Prescribed dose
- Information derived/calculated from the NostraData database:
    - Duration of exposure
    - Discontinuation of treatment
    - Treatment gaps
    - Switch of therapy (from / to Intuniv®)
    - Average daily dose

The following information will be collected through the physician survey:

- Patient information (age, gender)
- Prescriber information (specialty, graduation year, gender, location, region)
- Prescription information
    - Duration of treatment
    - Co-prescription of other ADHD medications
    - First time user
    - Repeat user
    - Discontinuation of therapy
    - Treatment gaps
    - Switch of therapy (from / to Intuniv®)
    - Prescribed daily dose
- Disease-related information
    - Date of diagnosis
    - Indication of use (diagnosis) according to WHO ICD 10 classification
- Presence / absence of contraindications
- Physician practice patterns with regard to monitoring of:
    - Blood pressure
    - Heart rate
    - Weight

9.4 Data sources

The following data sources will be used:

- NostraData database:
    - Longitudinal patient level prescription database
- Physician survey:
    - De-identified patient data provided by a representative sample of physicians known to treat patients with ADHD – predominantly paediatricians and

psychiatrists selected to be representative of prescribing patterns in Australia. The physicians will be instructed to select the patient record based on the last patient they have seen, for whom at any time in the last 12 months they have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit).

9.4.1 Longitudinal prescription databases

The NostraData database is a longitudinal prescription database containing prescription information at the patient level based on retail pharmacy data, including treatment initiation and renewals; however, no hospital-based pharmacies are included. NostraData Australia currently includes data from approximately 70% of all Australian pharmacies.

In the NostraData database, information is collected about medication dispensed, dose, form, strength, prescriber type and cost. Pharmacy patient ID is also collected; therefore, patients can be tracked over time within the same pharmacy. This ID, coupled with the number of prescriptions being dispensed, enables classification of whether an individual is a new patient, switching patient, or repeat patient. Additional detail enables classifying which products the patient has switched between and the prescriber type driving these trends.

In this study, NostraData database data are used at the patient level. Thereby all patients and scripts will be tracked to determine the number of patients who have been initiated on Intuniv® per 12 month period, the number of patients switching between products, number of repeats and the number of discontinuations. Information on Intuniv® dose, treatment duration and specialty of treating physician will also be extracted. Suspected overdose as potential off-label use could be calculated based on the number of prescription renewals and dose thereon. The recommended maximum daily dose for Intuniv® is 7 mg/day for patients > 12 years, or 4 mg/day for children ≤ 12 years (1). Prescriptions, if any, by physicians outside the expected specialties could also be detected.

A limitation of these prescription data is the lack of information on diagnoses and age, which would be important to monitor potential off-label use. These data will be obtained from the physician survey described in Section 9.4.2.

9.4.2 Physician survey

De-identified patient data provided by representative physicians randomly selected throughout Australia will be used to supplement information acquired from the prescription database. The information will be collected electronically using a web link. Similar surveys have been used successfully for Pharmaceutical Benefits Advisory Committee (PBAC) submissions in the past. For this survey, a retrospective analysis of relevant patient record extracts will be performed by physicians to provide a detailed understanding of the true use of Intuniv®, patient's age, treatment pathways, treatment duration and time since diagnosis as well as co-prescriptions and co-diagnoses.

Physician sample

Recruitment will occur from the total population of healthcare practitioner groups who are most likely to treat patients with ADHD. Physicians will be screened as described in more detail below. Suitable lists of physicians (e.g., OneKey lists) will be used for this study to ensure that an unbiased sample of physicians is selected. The lists will be supplemented by the Australasian Medical Publishing Company (AMPCo) list of relevant physicians, which is generated in part from the Australian Medical Association membership.

Sample

It is planned to collect medical record extracts of 100 patients per year who have been prescribed Intuniv® by up to 100 physicians. Due to the low prescribing base, no quotas by physician types will be set. As many patient medical records (anticipated maximum: 100 records) from as many prescribing physicians who are willing to participate will be collected.

Recruitment

Physician recruitment will be undertaken by an experienced independent field team. A fax or e-mail invitation will be sent at the end of the first year after the launch of Intuniv® to physicians who may be suitable for participation in the survey. The invitation will include questions on:

- Number of patients currently personally treated or managed for ADHD in the physician's primary practice location
- Number of patients they have prescribed/initiated Intuniv® within the last 12 months

The responses from this invitation will allow QuintilesIMS to determine how many patient records will be requested from each physician. Only physicians who have prescribed Intuniv® will be included for the abstraction of patient records for this drug utilization study. Physicians with fax invitation will also be asked to provide their e-mail address if they may be interested in participating in a survey.

Previous experience indicates a response rate of around 10% for specialists with this type of research (prior to any further screening criteria being applied).

Technique

An online physician survey is considered most appropriate for the data collection for this study. Qualifying physicians will be sent a link to the study by e-mail. They will be requested to complete the survey using information from patient records.

The physicians will be instructed to select the patient records of up to 10 patients starting with the last patient they have seen, for whom at any time in the last 12 months they have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit).

Follow-up phone calls and emails will be conducted to physicians who have agreed to participate, but who do not complete the online form.

The questionnaire

The questionnaire reflects the objectives of this study and will be designed by QuintilesIMS in consultation with Shire. The areas to be covered include the following:

- Patient age and gender
- Physician specialty, graduation year, gender, location, region
- Diagnosis/indication (including non-ADHD/off-label indications)
- Date of diagnosis
- Last treatment prior to Intuniv® (switch-in to Intuniv®)
- Treatment details for Intuniv® – total daily dose to determine average daily dose, if initiation, switch or addition, current treatment duration; gaps, re-prescriptions

- Other treatments for ADHD prescribed while on Intuniv® (co-prescriptions, non-drug treatment)
- If currently still being treated with Intuniv® (if not, what kind of treatment was prescribed after Intuniv®, if any)
- Other psychiatric comorbidity
- Monitoring performed with regards to the requirements in the product information during treatment with Intuniv® (measurement of weight, blood pressure, heart rate)

This approach would cover all questions important for the detection of off-label use of Intuniv® (i.e., use for patients diagnosed for disease other than ADHD, use for children less than 6 years of age, use for adult patients, prescribed overdosage, prescription to patients with contraindications).

It is anticipated that physicians will spend around 15-20 minutes per patient extracting this information from their records and then recording the responses.

Physicians will be appropriately reimbursed for their time taken to complete the chart review.

All respondents will be de-identified and responses will remain confidential, in line with the European Society for Opinion and Market Research (ESOMAR) and the Australian Market Research Society (AMSRS) Code of Professional Behaviour.

Furthermore, no patients will be identified. Physicians will be asked to provide information on patient diagnoses and treatments, but no identifiable details (as per the Privacy Act).

9.5 Study size and feasibility

Prescription database:

All prescriptions for Intuniv® available in the NostraData database in Australia will be analysed. Currently, about 70% of all Australian pharmacies provide data to NostraData. The exact number of prescriptions to be analyzed will depend significantly on the market share of Intuniv®.

Physician survey:

It is planned to collect data for 100 patients, who have been prescribed Intuniv® at least once during the study period, provided by representative physicians expected to treat patients with ADHD, as described in section 9.4.2. The sample size of approximately 100 is appropriate to determine proportions at a margin of error of 10% within a 95% Confidence Interval.

9.6 Data management

The study will be conducted according to the standard operating procedures of QuintilesIMS. The datasets extracted from the Australian NostraData database will be stored at QuintilesIMS Australia and at QuintilesIMS Bangalore. Data obtained from the physician survey will be checked in terms of consistency during data entry using automatic checks and before data analysis. Once validated and quality-checked, the physician survey database will be locked. Survey data will also be stored at QuintilesIMS Australia.

9.7 Data analysis

9.7.1 General statistical considerations

Descriptive analyses will be performed based on the prescriptions contained in the NostraData database from each 12-month reporting period. The use of Intuniv® will be analysed using the prescriptions collected during the 3-year assessment period.

All prescription information of Intuniv® dispensed from February 2018 up to January 2019 will be extracted from the prescription database for the first report. Extractions will take place once per year for 3 years. The last annual extraction will include data covering the period from approximately February 2020 to January 2021, and cumulative data from February 2018 to January 2021.

Data from the NostraData database and physician survey will not be directly combined. Study tables will reference the data source used for each set of results.

9.7.2 Potential for sampling bias

Prescription data:

All analyses will be performed using NostraData data, which provides about 70% coverage of all Australian pharmacies. Potential bias may nevertheless result if the total uptake of Intuniv® prescriptions is very low.

Physician survey:

In order to avoid any selection bias to the best possible extent, physicians will be randomly recruited using nationally representative external lists, such as OneKey lists, as described in Section 9.4.2.

The prescriber sample selected will be described by specialty, graduation year, gender, location and regions.

Data extractions will include patient medical records from paediatricians, psychiatrists and child and adolescent psychiatrists with at least one prescription of Intuniv® during the previous 12 months. As a result, in case prescribers of Intuniv® were different from the "universe of prescribers", the prescriber sample could deviate from prescribers in general.

9.7.3 Descriptive analysis

Reports will include descriptive statistics of all parameters analyzed. As part of this analysis, the description of missing data for each outcome of interest will be provided.

Indication of use, patient characteristics, patterns of drug use, average daily dose, co-prescriptions and co-diagnoses will be described. Distribution of number of prescriptions and treatment duration will be evaluated.

For continuous variables the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be presented. Categorical variables will be displayed with frequencies and percentages. Analyses will be performed using appropriate statistics software (e.g., SAS v9.2 or higher).

A detailed statistical analysis plan (SAP), that could support independent replication of the study results, will be agreed on prior to the start of the analysis. Table shells and examples of figures that will be produced will be included in the SAP.

Exact definitions of all variables (e.g. details on the calculation of average daily dose), the categories of variables to appear in the tables (e.g. age), and subgroup analyses of patients will also be included in the SAP.

9.8 Quality control

Quality control will be conducted at several levels

- To ensure nationally representative site selection for the physician survey, a robust, up-to-date, complete and representative list of Australian physicians will be used (e.g., OneKey lists). OneKey lists are generated by several thousand pharmaceutical company representatives visiting physicians and sending updates to this database on a daily basis. All updates are validated by telephone by a team of data integrity personnel to ensure accuracy. The database was established in the 1980s and is subscribed to by most major pharmaceutical companies. Recruitment of physicians will occur from the total population of general psychiatrists, child and adolescent psychiatrists and paediatricians in Australia.
- For site selection, all efforts will be undertaken to ensure that the sample is also representative by location- by state, metropolitan versus non-metropolitan areas and private versus public settings. Quotas will be set to ensure appropriate representation.
- At the site management level in case of the physician survey, significant effort will be expended to collect complete and valid data. Follow-up phone calls will be conducted to physicians who have agreed to participate but who do not complete the questionnaire. Logic checks will also be applied.
- The NostraData database includes patient/prescription information extracted directly from retail pharmacy computers to ensure completeness of the data. Each patient has an individual patient ID per pharmacy coupled with the number of prescriptions and the information given therein. For confidentiality reasons, de-identification of data is performed by a third party on behalf of QuintilesIMS.

9.9 Limitations of the research methods

Panel composition and representativeness

It could be argued that the physicians who participate in the physician survey may have different practice behaviour than other physicians who do not take part in such activity. In the planned physician survey, participating physicians will be randomly recruited using complete and representative lists of Australian physicians who treat patients with ADHD. The selected prescriber sample will be described by gender, graduation year, location and regions and compared with prescribers in general. In each stratum of the participating physicians' specialties, the number of prescriptions provided will be compared to the number of prescriptions in the database to detect substantial over- or undersampling of physicians.

Missing diagnoses

In the prescription database, information on patient age, gender and diagnosis is not provided. However, in the physician survey, patient age and gender will be collected and the indication for Intuniv® will be asked in an open-ended manner that will detect indications other than ADHD. Data from the Electronic Patient Records (EPR) will be treated as confidential.

10 PROTECTION OF HUMAN SUBJECTS

This study is non-interventional and the prescription data analysis is based on secondary data. No identifying data are collected in any of the planned approaches. Both databases (prescription database and database for the physician survey) are/will be developed following local data privacy regulation.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional study design which is based on retrospective data collection. In the event adverse reactions to Intuniv® are identified during the course of the study, QuintilesIMS will report them using the Shire AE Report form within one business day of discovery to Shire Global Drug Safety (GDS) department at [redacted] as per company policy on safety reporting.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

If Intuniv® is launched in February 2018 (please refer to Milestones), the first study report will be sent to Shire in August 2019. Annual reports will be sent thereafter. The last report will be sent in August 2021. All reports will be submitted to the TGA. In case Intuniv® is launched later than February 2018, reporting times will be postponed accordingly.

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APPENDIX 1: QUESTIONNAIRE

Drug utilization study of Intuniv® in Australia

Front Screen

Intuniv® (guanfacine extended release) PATIENT RECORD SURVEY

Thank you for agreeing to take part in this survey.

QuintilesIMS is conducting this survey among specialists who have prescribed Intuniv® (guanfacine hydrochloride modified release) to patients in the last 12 months. The purpose of this survey is to gather data to describe the way in which this treatment option is being used. The information you provide will remain anonymous and will only be used in an aggregated manner.

The aggregated results will be provided in a report to the Therapeutic Goods Administration (TGA) for a review on the utilisation of this treatment.

We ask that you have on hand the records of patients you manage to whom you have prescribed Intuniv® in the last 12 months. We request that you complete up to 10 such patient records.

You will be reimbursed for your time for each patient record that you complete (as a single payment after completion of all records).

If you have any questions about the research, please do not hesitate to contact us at the details provided below.

We are required to pass onto our client, details of adverse reactions and product complaints that are stated during the course of studies and screening. What you state will, of course, be treated in confidence. Should you raise during the completion of the questionnaire an adverse event in a specific patient, we will need to report this, even if it has already been reported by you directly to the company or the regulatory authorities. If an adverse reaction is stated, are you willing to waive the confidentiality given to you under the Market Research Codes of Conduct specifically in relation to any adverse reactions or product complaints stated during the completion of the questionnaire?

- Yes, I agree to waive confidentiality specifically in relation to any adverse reactions or product complaints stated during the completion of the questionnaire (All other information I provide will remain confidential.).
- No, I do not agree to waiving confidentiality specifically in relation to any adverse reactions or product complaints stated during the completion of the questionnaire (I may still complete the questionnaire and will remain anonymous.).

Physician Demographics and Practice Information

D1 Physicians age category

D1. What is your graduation year (first medical degree)?

Pre 1959	( )
1960-69	( )
1970-79	( )
1980-89	( )
1990-99	( )
2000-09	( )
2010+	( )

Data: single punch

D2 Physicians gender

D2. What is your gender?

Female	( )
Male	( )

Data: single punch

D3 Physicians setting

D3. In which state do you work the majority of your time?

NSW/ACT	( )
VIC/TAS	( )
QLD	( )
SA/NT	( )
WA	( )

Data: single punch

D4 Physicians practice type

D4. What is your practice type (%time spent)?

Private	%
Public	%
Community mental health	%

Data: single punch

D5 Physicians office location

D5. In which area are you serving the majority of your time?

Capital city	( )
Regional	( )
Rural	( )

Data: Single punch

D6 Physicians main specialty

D6. What is your main medical specialty?

General practice (GP)/family physician	( )

Child & Adolescent Psychiatrist	( )
Psychiatrist	( )
Paediatrician	( )
Neurologist	( )
Other, please specify: _____	( )

Data: single punch
Data: list of physicians' specialties.

D7 Physicians experience

D7. For approximately how long have you been working in this specialty?

for |__|__| years

Data: open numeric.

INFORMATION ABOUT RECENT PATIENTS

Explanatory text

Please try to recall the most recent patients who were prescribed **Intuniv®** in the last 12 months.

Please select the patient record based on the last patient you have seen, for whom at any time in the last 12 months you have prescribed Intuniv® (whether or not Intuniv® was prescribed at that last visit).

Please begin from the patient you have seen most recently and complete the questionnaire to the greatest degree of detail possible, and preferably without any omission. Be assured that all patient data requested is fully anonymous and will be collated with data provided by other respondents' and presented to the study sponsor in an aggregated and fully anonymised form.

Data: Repeat P1-P26 for up to 10 patients.

Patient 1: (Patient 2, 3, 4, 5, 6, 7, 8, 9, 10)

P1 Patients gender

P1. Patient's gender:

- o Male
- o Female

Data: Single punch

P2 Patient's age current

P2. Please provide the patient's current age

Age (years) |__|__|

Data: Open numeric years 1-99

P3 Indication

P3. What is this patient's main indication for which Intuniv® has been prescribed?

- o As treatment of ADHD
- o As treatment of anxiety
- o As treatment of hypertension
- o Other, please specify_____

Data: Single punch

Data: randomize order of indications – "Other" should not be randomized; always to be the last option

In case P3="As treatment of ADHD" is ticked, proceed with P4 else go to P5.

P4 Indication ICD

P4. Indication: What is this patient's exact diagnosis of ADHD (WHO ICD-10) for which Intuniv® has been prescribed?

- o F90.0 - Disturbance of activity and attention
- o F90.1 - Hyperkinetic conduct disorder
- o F90.8 - Other hyperkinetic disorders
- o F90.9 - Hyperkinetic disorder, unspecified
- o F98.8 - Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence (e.g. Attention deficit disorder without hyperactivity)
- o Other, please specify.....

- Unknown

Data: Single punch

Data: randomize order of indications – "Other, Unknown" should not be randomized; always to be the last options

P5 Date of most recent prescription

P5. Please provide the approximate date of the most recent Intuniv® prescription for this patient:

Month (MM) |__|__| Year (YYYY) |__|__|__|__|

Data: Open numeric month 1-12, year: current year or the year before

P6 Daily dose

P6. Which total daily dose of Intuniv® did you prescribe?

At the time of **most recent prescription**:

|__|__| mg as total daily dose

Data: Open numeric mg 1-99

P7 Treatment gaps

P7. Have there been any gaps (defined as > 30 days) in the patient's Intuniv® treatment?

- Yes
- No
- I do not know/recall

Data: Single punch

If no/do not recall continue with P9

P8 Treatment duration

P8. Total treatment duration (excluding treatment gaps) until now:

Treatment duration (months) |__|__|__|

Data: Open numeric months 1-999

P9 On treatment with Intuniv®

P9. Is treatment of this patient with Intuniv® currently ongoing?

- Yes
- No
- I do not know/recall

Data: Single punch

If no/do not recall continue with P13

ONLY ASK THE FOLLOWING QUESTION in case P3="ADHD":

P10 Co-treatments for ADHD

P10. What other treatments for ADHD is the patient currently prescribed?

- ☐ Methylphenidate
- ☐ Lisdexamfetamine
- ☐ Dex/dextro/amfetamine
- ☐ Atomoxetine
- ☐ Other ADHD medication
  - please specify_____
- ☐ Non-drug treatment (psychological, educational and social)
- ☐ None

Data: Multi-punch; except of "none": single punch; randomize option except of "other, none"

P11 Monitoring at current visit

P11. Which of the following examinations were performed at the last visit in your office?

- ☐ Measurement of weight
- ☐ Measurement of blood pressure
- ☐ Measurement of heart rate
- ☐ None of these

Data: Multi-punch; randomize options; except of "none of these": single punch

HISTORIC INFORMATION

P12 Date of diagnosis

P12. On which date did this patient first present (either to you or someone else) with the diagnoses for which Intuniv® was prescribed?

- o Day (DD) |__|__| Month (MM) |__|__| Year (YYYY) |__|__|__|__|
- o Unknown

If year=current year, then at least month and year

Else only year mandatory

P13 Initation date of Intuniv®

P13. When was this patient first prescribed Intuniv® (either by you or someone else)?

- o Day (DD) |__|__| Month (MM) |__|__| Year (YYYY) |__|__|__|__|
- o Unknown

If year=current year, then at least month and year

Else only year mandatory

P14 Patients age at first prescription

P14. Please provide the patient's age at the time of the first prescription:

Age (years) |__|__|

Data: Open numeric years 1-99

P15 Comorbidities

P15. Prior to the first prescription of Intuniv®, did the patient experience any of the following conditions?

- ☐ Hypotension
- ☐ Hypertension
- ☐ Bradycardia
- ☐ Somnolence
- ☐ Sedative events
- ☐ Syncope/fainting
- ☐ Other, please specify
- ☐ None

Data: Multi-punch; except of "none": single punch; randomize option except of "other, none"

P16 Total daily dosage

P16. Which total daily dose of Intuniv® did you prescribe:

At the time of **first prescription** (starting dose/frequency):

|__|__| mg as total daily dose

□ Unknown

Data: Open numeric mg 1-99

In case of "Unknown": single punch;

P17 Prior ADHD treatment

P17. Was the patient treated with other ADHD medication prior to Intuniv®?

- o Yes
- o No
- o I do not know/recall

Data: Single punch

If no continue with P20

P18 Switch in to Intuniv®

P18. Was the prior ADHD treatment stopped >days 30 prior to Intuniv treatment?

- o Yes
- o No (Switch)
- o I do not know/recall

Data: Single punch

P19 Prior ADHD treatment

P19. What treatment(s) for this indication did the patient use prior to Intuniv®?

- ☐ Methylphenidate
- ☐ Lisdexamfetamine
- ☐ Dex/dextro/amfetamine
- ☐ Atomoxetine
- ☐ Other ADHD medication
  - o please specify_____

Data: Multi-punch

ONLY ASK FOLLOWING QUESTION IF P9=NO:

P20 Switch-out from Intuniv®

P20. You mentioned that the patient had discontinued Intuniv® treatment. What treatment(s) for this indication was this patient switched to following discontinuation of Intuniv®?

- ☐ To Methylphenidate
- ☐ To Lisdexamfetamine
- ☐ To Dex/dextro/amfetamine
- ☐ To Atomoxetine
- ☐ To other ADHD medication
  - o please specify_____
- ☐ To non-drug treatment (psychological, educational and social)
- ☐ To none
- ☐ Unknown

Data: Multi-punch; except of "none": single punch; randomize option except of "none"

MONITORING

P21 Practice visits

P21. How often did the patient approximately visit your office within the last 12 months following the first prescription of Intuniv®?

|__|__| times

Data: Open numeric times 1-99

P22 Monitoring type and count

P22. How often were the following examinations performed during the first 60 days after the first prescription (initiation) of Intuniv®?

☐ Measurement of weight |__|__| times

☐ Measurement of blood pressure |__|__| times
☐ Measurement of heart rate |__|__| times

Data: Multi-punch; randomize options; Open numeric times 0-99

ONLY ASK FOLLOWING QUESTION IF Today-P14>2 months:

P23 Monitoring type and count

P23. How often were the following examinations performed between the 3rd and the 12th months after the first prescription (initiation) of Intuniv®?

☐ Measurement of weight |__|__| times
☐ Measurement of blood pressure |__|__| times
☐ Measurement of heart rate |__|__| times

Data: Multi-punch; randomize options; Open numeric times 0-99

ONLY ASK FOLLOWING QUESTION IF Today-P14>1 year:

P24 Monitoring type and count

P24. How often were the following examinations performed between the 13th months after the first prescription (initiation) of Intuniv®and now?

☐ Measurement of weight |__|__| times
☐ Measurement of blood pressure |__|__| times
☐ Measurement of heart rate |__|__| times

Data: Multi-punch; randomize options; Open numeric times 0-99

P25 Additional information

P25. Which additional information and recommendations did you provide to this patient when prescribing Intuniv® at the time of prescription?

Please specify:
.....
.....
.....

Data: open text, to be coded

Thank you for your participation in this survey

QuintilesIMS Team