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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
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1. ABSTRACT

Title

Drug Utilization Study with Intuniv in Australia

Keywords

Guanfacine, drug utilization study, retrospective database analysis, off-label use

Rationale and Background

Shire Australia (now Takeda Australia) has launched Intuniv for treatment of ADHD in children and adolescents in Australia in February 2018. Takeda is conducting a drug utilization study (DUS) 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 objectives:

- To characterize patients who are prescribed Intuniv with a specific focus on compliance with:
  - Indication
  - Patient age relative to the product information
  - 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 DUS

Study Design and Data Sources

This is a DUS 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, was supplemented with data from a physician survey.

Setting

Patients who have been prescribed Intuniv at least once during the reporting period. For this third (final) study report, the observation period was from 01 February 2020 to 31 January 2021 for the annual and from 01 February 2018 (the launch date in Australia) to 31 January 2021 for the cumulative reporting period.

Subjects and Study Size, Including Dropouts

The following numbers of patients and prescriptions are included in this third (final) report.

- NostraData database:
  - Annual reporting period: 21,028 patients, 152,837 prescriptions
  - Cumulative reporting period: 27,461 patients, 260,460 prescriptions
- Annual physician survey (2021): 26 physicians, 104 patients.

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

Results

This report presents final results of a DUS for Intuniv in Australia based on longitudinal prescription data (NostraData database) and on a survey among physicians. Here, we present the results of the combined cumulative 3-year period in the database and three survey rounds performed yearly (2019-2021). The annual number of Intuniv prescriptions reported in the NostraData database has continuously increased during the 3-year period after Intuniv launch in Australia: from 12,343 prescriptions in 3,869 patients in the first annual period to 93,192 prescriptions in 15,021 patients in the second annual period and to 152,837 prescriptions in 21,028 patients in the third annual period of the study. In the survey, data for 100 patients from 20 physicians was reported in the first survey round (2019), for 100 patients from 19 physicians in the second (2020) and for 104 patients from 26 physicians in the current third round (2021).

In the NostraData database, the analysis of the cumulative data shows that Intuniv was most frequently prescribed by pediatricians (about 60% of prescriptions); around 12% of Intuniv prescriptions were written by psychiatrists and around 15% by general practitioners (GPs).

In the previous survey rounds, the proportion of pediatricians varied between 85% in 2019, 47% in 2020 and 69% in 2021; proportion of GPs was 0% in 2019, 37% in 2020 and 15% in 2021. In each survey round, approximately 15% of participants were general psychiatrists or child and adolescent psychiatrists.

In the physician survey, ADHD was the main indication for treatment with Intuniv for 97% of patients in 2019, for 89% of patients in 2020 and 97% in 2021. In 2021, one further patient (1%) was prescribed Intuniv for ADHD in combination with anxiety and 2 further patients (2%) solely for anxiety. Data on diagnosis were not available in the database.

Results of this final analysis reveal that 17% of patients with age information available in the Nostra database (about 60% of the patients had information available) were outside the indicated age range for Intuniv of 6-17 years. The number of patients outside the indicated age range obtained via the survey was between 2% (2019) and 13% (2021). In the database, 1.5% (cumulative period) of all patients with age information available were below 6 years of age; no patients under 6 years at treatment initiation were reported in the physician survey in 2019 and 2021, only 1 patient (1%) was reported in 2020. The proportion of adult users of Intuniv was similar in the database (about 15% of all patients with available age information) and in the survey (2% in 2019, 12% in 2020, and 13% in 2021).

Intuniv is contraindicated in patients with a history of hypersensitivity to Intuniv, its excipients or other products containing guanfacine. In addition, special warnings and precautions for use of Intuniv should be considered in patients with certain comorbidities (e.g. somnolence, sedative events, syncope/fainting, hyper-/hypotension or bradycardia). Comorbid conditions of interest from the medical history were documented in 6% to 13% of the patients

in the survey; most frequent comorbidities were somnolence (3% to 5%) and hypertension (0% to 2%).

There was no documentation of use of other ADHD drugs prior or parallel to the first prescription of Intuniv recorded for 21% of the patients in the database and for 13% of first-time users in the survey 2019, 14% in 2020 and 9% in 2021. Patients who were prescribed another ADHD medication concomitantly with the first recorded prescription of Intuniv were not considered as potential off-label users as they may likely have received another monotherapy before initiating treatment with Intuniv.

Treatment with Intuniv was discontinued by 54% in the cumulative period in the database, but only by 8% (2020) to 11% (2019, 2021) of patients in the survey.

The daily dose was calculated based on the dose instruction recorded on the dispensed prescription (prescribed daily dose: PDD) or calculated by taking into account the number of prescribed pills, their strength and the calculated treatment duration (average daily dose: ADD) for data from the NostraData database. For the survey, only information on PDD was reported.

The ADD based on all prescriptions for a patient in the database except the last prescription was 2.1 mg/day (cumulative period) when considering the time between dispensing dates of the first and of the last prescription (approach 1). When adding all prescription periods, including prescriptions that had been dispensed in parallel (approach 2), the mean ADD was 2.1 mg/day in the cumulative study period. The maximum dose of 7 mg was exceeded in the database for 0.5% of patients based on the calculations of approach 1; this proportion was <0.1% when using approach 2.

The mean PDD per prescription in the database was 2.4 mg/day. In the survey, the mean PDD varied between 1.1 mg/day in 2020 and 1.5 mg/day in 2021 for the first and between 2.3 mg/day (2020) and 2.8 mg/day (2021) for the most recent prescription prior to data collection. Considering the PDD, the proportion of patients with a prescribed overdose was low in both data sources. In the database, PDD >7 mg/day was documented for 0.5% of patients in the cumulative period; (0.7% in the age groups 13-17 years and 18-25 years; 1.0% in patients aged >25 years). In the age group 6-12 years, a daily dose >4 mg is not recommended in the product information, but a dose >4 mg was documented for 1.0% of patients in the cumulative data period (PDD >4 mg/day and ≤7 mg/day for 0.6% and >7 mg/day for 0.5% of patients). In the survey, a PDD outside the recommendation was not reported for any of the patients at the time of treatment initiation and was documented for 2 patients (2%) for the most recent prescription of Intuniv in 2020 and 2021.

The overall proportion of patients with potential off-label use of Intuniv was 29% in the cumulative period of study in the NostraData database. This proportion was similar in the physician survey 2021 (29%) and varied in the previous survey rounds between 16% in 2019 and 34% in 2020. The most frequent reason for potential off-label use in both data sources (about 20% in the database; 13% in the survey waves 2019 and 2021, 20% in the survey round 2020) was no evidence of treatment with psychostimulants prior to Intuniv. However, it is not known if those patients were prescribed Intuniv because stimulants or atomoxetine were not suitable, which would allow first-line prescription of Intuniv in accordance with label.

Data on monitoring measures was available in the survey only. Monitoring of blood pressure, heart rate and body weight was performed for about 70% to 92% of patients during the first 2 months of treatment with Intuniv. This proportion was lower in 2021 than in the previous run of the survey (2020) but higher than in 2019 for heart rate and weight monitoring. Of the measurements, weight monitoring was performed most frequently (85% to 92% of patients),

followed by blood pressure monitoring (75% to 89%) and heart rate monitoring (70% to 88%) across the three survey waves. Around 50% to 94% of patients were monitored during the time between the third and the twelfth month (blood pressure: 75% to 94% of patients, heart rate: 50% to 88%, weight: 75% to 92% across three survey rounds). Around 70% to 96% of patients were monitored after the twelfth month of treatment with Intuniv. The mean number of measurements per patient for each parameter varied from 1.1 to 2.3 during the first 2 months and from 1.3 to 2.6 per patient during the time between the third and the twelfth month. A low sample size for analysis of treatment periods between the third and the twelfth month and after the twelfth month of treatment should be taken into consideration when interpreting the results for these periods.

Discussion

The third and final study report provides an overview of Intuniv utilization and potential off-label use based on data from a longitudinal prescription database and a physician survey in Australia in the third year after launch of Intuniv. In addition, data from the database for the cumulative period of three years since launch was analyzed. Generally, the results from the NostraData database suggest a considerable increase of Intuniv prescribing in Australia in the second and third annual period since launch in February 2018.

The majority of patient information obtained via the survey indicated those who were prescribed Intuniv had a documented ADHD diagnosis. Most patients started Intuniv after treatment with another ADHD drug. The remaining patients may have either received Intuniv as first line therapy because stimulant or atomoxetine was not suitable for them, or it may have been prescribed off-label. A distinction between these two scenarios was not possible in the database and, as a consequence, overestimation of potential off-label use was possible.

The results of this study show that Intuniv is mostly prescribed to the indicated age group of 6-17 years. Very few children below 6 years were prescribed. The percentage of adult patients varied between the two data sources over the study periods and was generally in the same range in the NostraData database (around 15%) and in the physician survey rounds 2020 and 2021 (12% to 13%); however, low proportion of adults was reported in the first survey wave in 2019 (2%).

In accordance with published information (6), the majority of patients were male.

Dosage instructions given by the physician were mostly within the recommended range for all patients. Calculated ADD also suggests that over 99% of the patients were treated as recommended. However, exact dosing of Intuniv is based on weight rather than age, and data on weight are not available. Therefore, although unlikely, some unrecognizable overdosing could have occurred in patients with low body weight who received the maximum dose allowed in their age category. On the other hand, some of the patients may have had a body weight that required a dose above 7 mg/day to achieve the range of 0.05 to 0.12 mg/kg/day.

For most patients, monitoring of blood pressure, heart rate and body weight in compliance with the product information was performed during the first year of treatment with Intuniv (75% to 87% during the first 2 months; 81% to 92% during the time between the third and the twelfth month). After the twelfth month of therapy monitoring was reported for 83% to 96% of patients. In the first two months of treatment, the average number of body weight measurements (1.8 to 2.0 across three survey rounds) was as recommended in the product information and, between the third and twelfth month of treatment, the average number of body weight measurements (1.3 to 2.6 across three survey rounds) was slightly lower than recommended.

Conclusion

Overall, the findings indicate that – compared to the first annual period since its launch – Intuniv prescribing in Australia has increased considerably in the second annual period and to a lesser extent in the third period.

In summary, the findings of the final study report regarding indication, treatment and prescribing patterns and potential off-label use of Intuniv are consistent through the three study periods. In all three reporting periods, the majority of patients had been diagnosed with ADHD. Most treatment initiators received Intuniv as a second-line treatment.

The prescribed dose of Intuniv in almost all patients in both data sources was within the recommended range. Less than 1% of patients with Intuniv prescriptions in the database and only 0%-1% in the survey were children <6 years of age. Lower compliance was observed regarding use of Intuniv in adult patients.

The availability of data regarding monitoring of blood pressure, weight and heart rate during treatment suggest that these additional risk minimization measures were performed periodically mostly as recommended in the product information.

In conclusion, Takeda maintains that the educational materials for Intuniv were effective for all relevant risks and no changes are required to educational materials at this time. In particular, there were only anecdotal cases of patients below 6 years, low numbers of adult users and rare use in indications other than ADHD or with doses higher than recommended. For a considerable number of patients, there was no evidence of prior treatments with other ADHD drugs. It remains unclear to what extent this is due to use in a non-recommended situation (as first-line treatment), a recommended situation (stimulants or atomoxetine were not appropriate), or incomplete historical information on previous treatments in these patients and should therefore be interpreted with caution. The data from this study indicate no change in the benefit-risk profile for the product.

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