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- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.

1.0 ABSTRACT

Title

Drug utilization study of Intuniv (guanfacine extended release) in European countries

Keywords

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

Rationale and Background

Shire Pharmaceuticals (now part of Takeda) has launched Intuniv in 14 countries in Europe from January 2016 onwards. Intuniv is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents 6-17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Takeda is conducting a drug utilization study for up to five years as part of the risk management plan for Intuniv. Data is provided across 4 reports on an annual basis.

Research Question and Objectives:

The study's overall research question and objective is to characterize patients who are prescribed Intuniv, to describe prescribing patterns among physicians and to evaluate if additional risk minimization measures that had been provided to physicians were successfully implemented and effective.

Primary objectives:

- To characterize patients who are prescribed Intuniv with a specific focus on:
  - Indications other than ADHD
  - Children less than 6 years of age
  - Adults
  - Patients who did not have any first-line stimulant treatment prior to their first prescription of Intuniv
  - Prescribed overdose of >7mg/day or of >4mg/day for patients ≤12 years of age
- To describe prescribing patterns of Intuniv among physicians

Secondary objective:

To measure the effectiveness of the additional risk minimization measures (educational materials for healthcare professionals) in order to assess compliance with the indication and with visits and measurements needed during the first year of treatment.

Study Design

This is a multi-country drug utilization study which consists of two parts. One part is a retrospective database study using different longitudinal patient level data sources of 6 countries, Denmark, Germany, Norway, Spain, Sweden and the UK. The results of this study are described in this report. The second part is a prescriber survey conducted in 4 countries in which longitudinal patient level data do not exist or are difficult to access, Belgium, Finland, Ireland and The Netherlands. The prescriber survey is described in a separate protocol and the results of the analysis are described in a separate report.

Setting

Patients with at least one prescription of Intuniv in the selected databases during the reporting period were evaluated. For the fourth and last report, the observational period is from the country specific launch date to December 2021.

The UK formally left the European Union (EU) on 31 January 2020 and became a third country. During a transition period from 1 February to 31 December 2020, the EU pharmaceutical law continued to apply to the UK. From 1 January 2021, the EU pharmaceutical law applies to the UK in respect to Northern Ireland only. Since the UK was already included in the study, the MAH continued to collect and report the data from the UK and present it as part of the study report.

Subjects and Study Size, Including Dropouts

The following number of patients and prescriptions are included in the fourth and last report.

Denmark:

This report includes the annual data for Denmark from 2019 (originally planned for the third report) and 2020 and the cumulative data from 2016 to 2020.

- Annual data 2019: 594 patients; 3,779 prescriptions
- Annual data 2020: 806 patients; 5,516 prescriptions
- Cumulative data 2016-2020: 1,350 patients; 15,358 prescriptions

Germany:

- Annual data 2021:
  - Pediatrician panel (PP): 218 patients; 1,405 prescriptions
  - Neurologist/ psychiatrist panel (NPP): 264 patients; 1,425 prescriptions
  - General practitioner (GP) panel (GPP): 35 patients; 127 prescriptions
- Cumulative data 2016-2021:
  - PP: 508 patients; 6,220 prescriptions
  - NPP: 529 patients; 5,531 prescriptions
  - GPP: 73 patients; 307 prescriptions

Norway:

- Annual data 2020: 734 patients; 4,722 prescriptions
- Cumulative data 2016-2020: 1,341 patients; 14,167 prescriptions

Spain:

- Annual data 2021: 207 patients; 2,086 prescriptions
- Cumulative data 2017-2021: 356 patients; 6,381 prescriptions

Sweden:

- Annual data 2020: 10,286 patients; 61,086 prescriptions
- Cumulative data 2016-2020: 17,791 patients; 174,539 prescriptions

United Kingdom:

- Annual data 2021: 373 patients; 2,992 prescriptions
- Cumulative data 2016-2021: 691 patients; 10,095 prescriptions

Variables and Data Sources

Indication of use (diagnosis), patient characteristics (age, gender, and comorbidities), data on patterns of drug use (dosing, first time user, repeat user, duration, discontinuation of ADHD therapy and switches), prescriber specialty, frequency of monitoring weight, blood pressure, and heart rate, if information is available in the data source.

The following data sources were used:

- Longitudinal patient level databases
  - Electronic medical records database
    - IMS Disease Analyzer (Germany)
    - IMS LPD (Spain)
    - IMRD (IQVIA Medical Research Data incorporating THIN, a Cegedim Database, UK)
  - National registries (Denmark, Norway, and Sweden)
- Prescriber survey
  - Belgium
  - Finland
  - Ireland
  - Netherlands

Results

The results presented here are based on the cumulative data (maximum period 15 Jan 2016 -31 Dec 2021. For country-specific periods please see Table 1).

Across the countries studied, the percentage of patients with a documented ADHD diagnosis ranged from 71% in Denmark to 94% in PP and NPP Germany and Spain.

Between 62% (Denmark) and 83% (Spain) of patients were male. Children aged 6 to 12 years were the largest patient group in most countries: Germany: PP: 69%, NPP: 68%, GPP: 48%; Norway: 58%; Spain: 60%; Sweden: 44% and UK: 55%. In Denmark, 28% of patients were children up to 12 years. About a quarter to a third of the patients were adolescents (aged 13 to 18 years) in all countries: Denmark: 27%; Germany: PP: 29%, NPP: 30%, GPP: 47%; Norway: 27%, Spain: 37%; Sweden: 30% and UK: 38%.

Comorbidities of interest, mostly anxiety disorders, were documented in around 5% to 28% of the patients with a history of at least 365 days in the database prior to the first prescription of Intuniv: Denmark (19%), Germany (PP: 9%, NPP: 5%, GPP: 11%), Norway (9%), Spain (7%), Sweden (28%) and UK (14%).

For 49% (German GPP) to 97% (Denmark) of the patients with an available history of at least 365 days prior to the first prescription of Intuniv psychostimulants were recorded in the databases in Denmark, Germany, Norway, Spain, Sweden and UK.

Average daily dose (ADD) ranges were between 1.4 mg/day (German GPP) and 2.5 mg/day (Spain).

Regarding potential off label use:

- No documented ADHD diagnosis in patients with an enrolment history of at least 365 days in the database was recorded in a total of 44 patients in the 3 panels in Germany (PP: n=25 of 426 patients,

(6%); NPP: n=10 of 365 patients, (3%); GPP: n=9 of 47 patients, (19%), in 393 patients (29%) in Denmark, in 229 patients (17%) in Norway, in 23 patients (7%) in Spain, in 1,692 patients (10%) in Sweden and in 73 patients (12%) in UK.

- In all countries, 0% to <1% of patients were younger than 6 years, that is, <1% (1 patient) in Norway, <1% (1-4 patients) in Denmark, <1% (5 patients; PP: n=3, <1%; NPP: n=2, <1%) in Germany, <1% (1-5 patients) in UK, <1% (2 patients) in Spain and <1% (160 patients) in Sweden.
- There was a high percentage of adult users observed in Denmark (45%, n=608) plus 25% in Sweden (n=4,369) and 14% in Norway (n=193). A lower percentage of adult users was observed in the EMR data, i.e., 3% (n=10) in Spain, ~6% (40-44 patients) in UK and 1% to 6% in Germany (PP: 1%, n=5, NPP: 2%, n=12; GPP: 6%, n=4).
- For patients with an enrolment history of at least 365 days in the database, no records on psychostimulants prior to the initiation of Intuniv were found for a total of 175 patients in the 3 panels in Germany (PP: n=129 of 426 patients, 30%; NPP: n=22 of 365 patients, 6%; GPP: n=24 of 47 patients, 51%), for 35 patients (3%) in Denmark, for 77 patients (6%) in Norway, for 30 patients (9%) in Spain, for 2,378 patients (13%) in Sweden and for 102 patients (17%) in the UK.
- Considering the calculated ADD, the maximum dose according to the Summary of Product Characteristics for Intuniv was exceeded for 15 patients in Germany (PP: n=11, 2%; NPP: n=4, 1%; GPP: n=0, 0%), 23 patients (2%) in Denmark, 44 patients (3%) in Norway, 227 patients (1%) in Sweden and 13 patients (2%) in the UK. In Spain, no patient with a calculated ADD exceeding the maximum dose was recorded.
- In Germany and the UK, prescribed doses written by the physicians on the prescriptions were also available. For 50 patients in Germany (PP: n=18, 4%, NPP: n=31, 6%, GPP: n=1, 1%), a dosage exceeding the recommended range was documented. In the UK, for 13 patients (2%) a dosage exceeding the recommended range was documented.
- Recording of monitoring of weight, blood pressure and heart rate during the first year of therapy was only available in the databases for Germany and the UK. In Germany, for 0% to 13% of patients' measurements were recorded during the 2 months after the index date (date of the first prescription of Intuniv in the database), for 0-16% of patients in the time period 3-12 months after the index date, and for 6% to 18% of patients in the time period ≥13 months after index date. In the UK, for <16% of patients, measurements were recorded during the 2 months after the index date. Blood pressure and weight were monitored for 38% of patients in the UK in the time period 3-12 months after the index date and 39% during the time period ≥13 months after the index date.

Discussion

This fourth and final study report of the Intuniv DUS includes the data analyses from the retrospective databases from 6 countries. It provides an overview of Intuniv utilization based on data obtained in the real-life outpatient setting in Germany, Denmark, Norway, Spain, Sweden and UK.

In each country, most patients who were prescribed Intuniv had a documented ADHD diagnosis (ranging from 71% to 94% across the 6 countries). For 70% to 98% of the patients with an enrolment history of at least 365 days in the database, prior prescriptions of psychostimulants were documented in the databases, with the exception of the GPP in Germany (49%). This suggests that most patients had already tried an ADHD therapy with a stimulant prior to starting Intuniv, in line with the therapeutic indication approved in the EU. Some of these patients without prior ADHD treatment may have had a contraindication to psychostimulants, which would allow first line treatment with Intuniv.

The results of the current analysis show that Intuniv is mostly prescribed to the indicated age group of 6 to 17 years. Most of the patients were males. Less than 1% of the children younger than 6 years of age were prescribed Intuniv. Relatively high percentages of adult users of Intuniv were reported in Denmark, Norway and Sweden, which was consistent with the three previous reports. The reason for this finding is not known, but could be due to possible differences in the attitude towards medical treatment of psychiatric diagnoses in different countries or due to differences in actual reimbursement practices for continuers of Intuniv from adolescence to adulthood

Dosage instructions given by the physician were mainly within the recommended range for all patients. Calculated ADD also suggests that the patients were mainly treated within the recommended dosage range.

Information on monitoring of blood pressure, heart rate and weight was available in the databases from Germany and the UK. According to the results, these examinations had not been recorded as frequently as indicated in the product information, although this might not be due to non-compliance with the requirements, but rather due to incomplete documentation. In all other countries covered by this report information on monitoring of blood pressure, heart rate and weight were not available in the respective data sources. Further information regarding data monitoring is covered by the survey which was conducted in parallel to this database study.

Conclusion

Overall, the findings indicate that, in most countries, Intuniv is prescribed mainly within the label – to the indicated age group and to patients with ADHD who had previously been treated with a stimulant medication. Prescribed use in patients younger than 6 years of age did not exceed 1% of patients across all reported countries.

Lower prescriber compliance was observed regarding use of Intuniv in adult patients in Denmark, Norway, and Sweden in comparison to Germany, Spain, and the UK. Comparing this fourth and final report to the previous three reports, the overall number of patients and prescriptions increased, but there were no relevant changes in distribution over different age groups or regarding potential off-label use.

Regarding the secondary objective of describing the effectiveness of the additional risk minimization measures, prescriber compliance regarding measurements of weight, heart rate and blood pressure indicated during the first year of treatment cannot be confirmed, which might not be due to non-compliance with the requirements but rather due to incomplete documentation. This would be in accordance with the survey results, which show that monitoring of blood pressure, weight and heart rate was performed, but were recorded at lower frequencies than indicated in the product information.

appropriate discontinuation procedures.

The benefit-risk ratio for Intuniv remains positive.