1. Abstract

Title

Drug utilization study of dexamfetamine in European countries

Date: 28 May 2021

Keywords

Drug utilisation study, dexamfetamine, multi-country

Rationale and background

The MAH's dexamfetamine product is on the market in Germany, the UK, the Netherlands, Finland, Denmark, Sweden, Iceland and Norway. A drug utilisation study to follow the use of prescribed dexamfetamine in the European Countries using multiple data sources had been proposed during the marketing authorization application (MAA) as part of the risk management plan (RMP).

In this drug utilization study, retrospective data from patient-level and prescription databases covering the time period from Q1 2015 to Q4 2019 (up to 5 years post product launch) was analysed and presented in annual reports. This is the final of consecutive reports produced during five years and contains analyses of prescription data from the years 2015 to 2019. Due to the different approaches for the DUS and the structured literature review, findings regarding abuse, misuse, overdose, diversion and dependence associated with dexamfetamine are presented in a separate report (1). Both reports are summarized in an executive summary (see Annex 1).

Research question and objectives

This is a retrospective database analysis to provide data on drug utilization on an annual basis for up to 5 years. Objectives are

- to describe how dexamfetamine was prescribed by physicians in Europe
- to evaluate off-label use and prescribed overdoses by physicians in Europe, defined as
    - Prescription for an indication other than AD/HD
    - Age <6 years or ≥18 years
    - Prescribed overdose
- to collect data on abuse, misuse, overdose, diversion and dependence related to individual dexamfetamine use (addressed in a separate report)

Study design

This is a multi-country DUS using retrospective data from databases. A study approach was chosen to gather drug utilization data for dexamfetamine in multiple data sources from European target countries. For this final report, data from the following countries were analysed: Germany, the UK, the Netherlands, Finland, Denmark, Sweden and Norway.

Setting

Secondary data collected in an outpatient setting from European countries was used. The overall observation time will cover the period from Q1 2015 to Q4 2019. For this final report, data from Q1 2015 to Q4 2019 from the respective databases were analysed.

Subjects and study size, including dropouts

The target population consisted of patients who were documented in the country-relevant database with at least one prescription of dexamfetamine during the study period. No exclusion criteria were applied.

In the case the sample size of 100 cases per single target country was not reached for the annual reports, a cumulative analysis of two consecutive years was performed.

Variables and data sources

Patient and prescriber characteristics, prescription pattern, duration of treatment and development of dependence syndrome were analysed. Two longitudinal (IMS® Disease Analyzer/Germany; CPRD/UK), two cross-sectional databases (IMS® Medical Index/Germany, UK, Netherlands; Multirec/Finland) and three national registries (publicly available version of Danish National Prescription Registry/Denmark, NorPD/Norway, Swedish Prescribed Drug Register/Sweden) were used as data sources for this study.

Results

This final report provides results regarding dexamfetamine utilisation on patient and prescription level for Germany, the UK, the Netherlands, Finland, Denmark, Sweden and Norway.

In Germany, 1,704 prescriptions of the year 2019 were available for analysis in the cross-sectional database (IMS® Medical Index); 62% of prescriptions were recorded for patients between 6 and 17 years and 37% for adult patients. Half of prescriptions (50%) were issued for licensed indication and for 40% the indications was unknown or missing. Of the prescriptions, 17 (1%) were for children below six years. The dose recommendation was within the authorised limit for the majority of dexamfetamine prescriptions (97%). Considering age, indication and maximum dose, less than half of the prescriptions (43%) were issued off-label, mainly due to being filled for adults and non-licensed indications. Dependence syndrome associated with stimulants was recorded during treatment with dexamfetamine in one of 97 patients in 2019 in the longitudinal EMR database (IMS® Disease Analyzer).

In Germany, from 54 (year 2015) to 1,704 (2019) prescriptions were available for analysis in the cross-sectional database (IMS® Medical Index); from 59% to 66% of the prescriptions were recorded for patients between 6 and 17 years and from 35% to 41% for adult patients.

In the longitudinal database, from 122 (2015) to 209 (2019) patients and from 493 (2015) to 990 (2019) prescriptions were available for analysis in the longitudinal database (IMS® Disease Analyzer); from 30% to 46% of the patients in the GP panel, from 98% to 100% in the paediatrician panel and from 67% to 79% in the psychiatrist panel were between 6 and 18 years and from 50% to 65% of the patients in the GP panel, 0% in the paediatrician panel and from 21% to 33% in the psychiatrist panel were for adult patients 19 years or older. Considering age, indication and maximum dose, from 18% to 20% of the prescriptions were issued off-label, mainly due to being filled for patients with no recorded ADHD diagnosis (17%-19%) and for adults (5%-6%). Of the prescriptions, less than 1% were for children below six years across all

study years. Dependence syndrome associated with stimulants was recorded during treatment with dexamfetamine in one patient in each year 2016, 2017, 2018 and 2019 in the longitudinal EMR database (IMS® Disease Analyzer).

In the longitudinal database (CPRD), 1,800 prescriptions were recorded in 2019. After the exclusion of prescriptions for the second licensed indication (narcolepsy) of dexamfetamine in the UK, 1,254 prescriptions remained. With regard to the licensed indication, age group and maximum dose of dexamfetamine in the treatment of AD/HD, 78% were issued off-label, mainly due to prescriptions to adults (75%). None of the patients was children below six years. Of the prescriptions, 28% had no diagnosis of ADHD recorded and 3% had a dose recommendation above the authorised limit (overdose) for dexamfetamine. None of the patients developed dependence syndrome associated with stimulants during treatment in the longitudinal database.

For the UK, in the longitudinal database used (CPRD), from 131 (2017) to 217 (2019) patients and from 1,125 (2017) to 1,800 (2019) prescriptions were reported between 2015 and 2019. From 19% to 30% of the prescriptions were issued for patients between 6 and 18 years and from 70% to 81% for adult patients older than 18 years. With regard to the licensed indication, age group and maximum dose of dexamfetamine in the treatment of AD/HD, 73% to 82% were issued off-label, mainly due to prescriptions to adults (69%-80%). From 27% to 35% prescriptions were for patients that did not have a diagnosis of ADHD recorded. In each year, less than 12 patients (≤1%) were children below six years. From 1% to 7% of prescriptions had a dose recommendation above the authorised limit (overdose) for dexamfetamine. In 2015, 2016, 2018 or 2019, none of the patients developed a dependence syndrome associated with stimulants during treatment in the longitudinal database, but in 2017 less than 6 developed a dependence syndrome.

For the Netherlands, for prescriptions in the combined years 2018 and 2019 of the cross-sectional database (IMS® Medical Index), 22% of the 153 recorded prescriptions were issued for patients between 6 and 17 years and 78% for adult patients. Prescriptions for the treatment of AD/HD (64%) and, to a lesser extent, of conduct disorder (26%) were the most frequent indications in 2018 and 2019. Off-label use of dexamfetamine was frequent (91%) and was mainly driven by prescriptions in adults (78%), indications other than AD/HD (36%) and to a much lesser degree by prescribed overdoses (6%).

For the Netherlands, from 62 (year 2016) to 91 (2019) prescriptions were recorded each year (IMS® Medical Index), from 22% (years 2018 and 2019 combined) to 27% (years 2016 and 2017 combined) of the prescriptions were issued for patients between 6 and 17 years and from 73% to 78% for adult patients. Off-label use of dexamfetamine was frequent (87%-91%) and was mainly driven by prescriptions in adults (73%-78%), indications other than AD/HD (36%-37%) and to a much lesser degree by prescribed overdoses (3%-6%). There were no prescriptions to children with an age below 6 years.

In Finland, 247 prescriptions were available 2019 for analysis in the Multirec database; none of the prescriptions were for children below six years, 7% of prescriptions were recorded for patients between 6 and 17 years and 93% for adult patients. The majority of prescriptions (95%) were issued for AD/HD. Off-label use of dexamfetamine in AD/HD patients was high (93%) and mainly driven by prescriptions in adults (93%) and to a much lesser degree by prescribed overdoses (9%).

In Finland, from 118 (year 2016) to 247 (2019) prescriptions were available for analysis in the Multirec database; none of the prescriptions were for children below six years, from 2% to 8%

of prescriptions were recorded for patients between 6 and 17 years and from 92% to 98% for adult patients. Off-label use of dexamfetamine in AD/HD patients was high (92%-98%) and mainly driven by prescriptions in adults (92%-98%) and to a much lesser degree by prescribed overdoses (7%-19%). From 1% to 5% did not have a diagnosis of AD/HD recorded with their prescription. There were no prescriptions to children with an age below 6 years.

In Denmark, 1,105 patients with approximately 12,900 prescriptions from the Danish registry were available for analysis in 2019. Overall, 46% of 1,105 patients with prescriptions for dexamfetamine were between 6 and 17 years and 54% were adults, whereas up to five of the patients were below 6 years.

In Denmark, from 382 (year 2015) to 1,105 (2019) patients with approximately 3,800-12,900 prescriptions from the Danish registry were available. Overall, from 29% to 46% of the patients with prescriptions for dexamfetamine were between 6 and 17 years and from 54% to 70% were adults, whereas less than eight of the patients were below 6 years in each year.

In Sweden, 55,581 prescriptions of 9,594 patients were available in 2019 for analysis in the Swedish prescription register; less than 0.1% of the prescriptions were for children below six years, 4% of prescriptions were recorded for patients between 6 and 17 years and 96% for adult patients. The majority of prescriptions (87%) were issued for AD/HD. Off-label use of dexamfetamine in AD/HD patients was high (97%) and mainly driven by prescriptions in adults (96%).

In Sweden, from 7,273 (year 2015) to 55,581 (year 2019) prescriptions and from 1,868 to 9,594 patients were available in the Swedish prescription register; less than 0.1% of the prescriptions were for children below six years, from 3% to 4% of prescriptions were recorded for patients between 6 and 17 years and from 96% to 97% for adult patients. Off-label use of dexamfetamine in AD/HD patients was high (96%-97%) and mainly driven by prescriptions in adults (96%-97%) and to a much lesser degree by prescribed overdoses (9%-20%). Less than 0.1% of the prescriptions were for children with an age below 6 years. From 11% to 13% did not have a diagnosis of AD/HD recorded with their prescription.

In Norway, 28,930 prescriptions of 3,219 patients were available 2019 for analysis in the Norwegian prescription register; four prescriptions were for children below six years. Of all prescriptions, 3% were recorded for patients between 6 and 17 years and 97% for adult patients. The majority of prescriptions (85%) were issued for patients with a diagnosis of AD/HD. Off-label use of dexamfetamine in AD/HD patients was high (96%) and mainly driven by prescriptions for adults (96%).

In Norway, from 1,811 (year 2015) to 28,930 (2019) prescriptions of 682 (2015) to 3,219 (2019) patients were available in the Norwegian prescription register; less than 7 prescriptions were for children below six years in each year. Of all prescriptions, from 1% to 4% were recorded for patients between 6 and 17 years and from 97% to 99% for adult patients. The majority of prescriptions (72%-85%) were issued for patients with a diagnosis of AD/HD. Off-label use of dexamfetamine in AD/HD patients was high (96%-99%) and mainly driven by prescriptions for adults (96%-99%).

Discussion

This final report provides findings on the utilisation of dexamfetamine in Germany, the UK, the Netherlands, Finland, Denmark, Sweden and Norway. In particular in Finland and the Netherlands, the results are based on a relatively small number of patients and prescriptions (n<250). Therefore, results shall be evaluated carefully. Overall, only few patients are exposed to dexamfetamine in all countries compared to the high (3.5%) prevalence of AD/HD in children and adolescents (2).

In this study, dexamfetamine prescriptions in children below 6 years were observed very rarely. In all countries studied, the proportion of adult AD/HD patients receiving dexamfetamine is considerably high with respect to the licensed use in children and adolescents only. This may be due to increased awareness of the persistence of AD/HD into adulthood, its indicated use only after first line and the approval of several other AD/HD drugs for the treatment of AD/HD in adults (methylphenidate, lisdexamfetamine).

With the exception of anecdotal cases in Germany and the UK, no evidence was found in the study regarding the development of dependence to dexamfetamine. Prescription of doses over 40 mg/day were observed rarely, with the exception of Sweden.

When comparing off-label use over the course of the study, no major change or trend outside normal annual fluctuations could be observed in any country. This final report of the DUS covers in some of the target countries prescription data right from the launch as a starting point.

Marketing Authorisation Holder(s)

MEDICE Arzneimittel Pütter GmbH & Co. KG
Kuhloweg 37
58638 Iserlohn
Germany

Names and affiliations of principal investigator

(PRIVACY), Medice Arzneimittel Pütter GmbH & Co. KG, Iserlohn, Germany