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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 VYVANSE® (lisdexamfetamine dimesilate) in Australia for Binge Eating Disorder

Keywords

Lisdexamfetamine, drug utilization study, prescriber survey, retrospective database analysis, off-label use

Rationale and Background

Shire Pharmaceuticals (now Takeda Australia) received marketing approval for VYVANSE for treatment of binge eating disorder (BED) in Australia on 22 January 2018. This drug utilization study (DUS) conducted for three years with annual reporting is part of the risk management plan for VYVANSE in Australia.

Research Question and Objectives

To evaluate drug utilization of VYVANSE with a special interest in BED and to monitor its off-label use on an annual basis for 3 years in Australia.

Primary Objectives

- To characterize patients who are prescribed VYVANSE, with a specific focus on compliance with
  - The indication
  - Patients' age relative to the product information
  - Visits and measurements performed during the first year of treatment

Secondary Objectives

- To describe prescribing patterns of VYVANSE for BED
- To monitor the effectiveness of the risk minimization measures described in the risk management plan (RMP) based on the outcomes measured in the DUS

Study Design and Data Sources

This is a DUS using 2 data sources, including longitudinal secondary patient level data of a dispensing database (NostraData) and data obtained from repeated cross-sectional surveys among physicians. A single database with all relevant information does not exist. Therefore, data from the NostraData dispensing database, a longitudinal patient-level prescription database, were supplemented with data from a physician survey.

Setting

The study was conducted in an out-patient setting. For this third (final) report, the observation period was from 01 March 2020 to 28 February 2021 for the annual reporting and from 01 March 2018 to 28 February 2021 for the cumulative reporting period for the NostraData database. The reporting period for the physician survey was from 06 Apr 2020 to 28 May 2020. The overall observation period of the study covers the 3-year period from launch of VYVANSE for BED in February 2018 to February 2021.

Subjects and Study Size, Including Dropouts

The study population included patients who had been prescribed VYVANSE at least once during the observation period without evidence of use of VYVANSE for attention deficit

hyperactivity disorder (ADHD) treatment. For the physician survey, data from a total of approximately 100 patients reported by psychiatrists and 50 patients treated by other specialties expected to treat patients with BED (general practitioners (GPs), pediatricians, endocrinologists) were collected in accordance with the amended study protocol (version 2.0 dated 11 Oct 2019).

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

- *NostraData database*
  - Annual reporting period (March 2020 – February 2021):
    - 53,156 patients, 318,281 prescriptions (main analysis: all patients with at least one prescription for VYVANSE)
    - 10,275 patients, 60,417prescriptions (sensitivity analysis 1: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by pediatricians or child psychiatrists)
    - 5,518 patients, 31,017 prescriptions (sensitivity analysis 2: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by prescribers other than psychiatrists)
    - 8,521 patients, 50,870 prescriptions (sensitivity analysis 3: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by pediatricians or child psychiatrists, exclusion of patients with first prescription for VYVANSE at <18 years of age)
  - Cumulative reporting period (March 2018 – February 2021):
    - 75,044 patients, 744,154 prescriptions (main analysis: all patients with at least one prescription for VYVANSE)
    - 8,622 patients, 56,284 prescriptions (sensitivity analysis 1: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by pediatricians or child psychiatrists)
    - 5,072 patients, 30,811 prescriptions (sensitivity analysis 2: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by prescribers other than psychiatrists)
    - 7,066 patients, 46,250 prescriptions (sensitivity analysis 3: exclusion of patients with prescription records of ADHD medication and with prescriptions for VYVANSE by pediatricians or child psychiatrists, exclusion of patients with first prescription for VYVANSE at <18 years of age)
- *Physician survey 2021:*
  - 104 patients reported by 23 psychiatrists and 50 patients reported by 11 physicians of other specialties (GPs, pediatricians, endocrinologists)

Variables

Both data sources:

- Data on patterns of drug use
  - Prescribed or calculated average daily dose (ADD)
  - First time/repeat use
  - Treatment duration
  - Discontinuation of Vyvanse therapy

  - Switches from/to Vyvanse
  - Co-prescriptions of medications of interest
- Prescriber specialty

Additionally, in the physician survey:

- Indication of use (diagnosis)
- Presence/absence of contraindications
- Patient characteristics
  - Age
  - Gender
- Frequency of monitoring of cardiovascular status (blood pressure, heart rate)

Results

In this third (final) report, data of 744,154 prescriptions for 75,044 patients extracted from the NostraData database were included in the main analysis for the cumulative reporting period. Approximately 50% of prescriptions were issued by pediatricians, 28% by psychiatrists and 15% by GPs. Other prescribers (4%) included neurologists (0.4%) and endocrinologists (0.2%) and for 3% specialty was not available in the database. When sensitivity analyses were applied to exclude patients likely to have received VYVANSE for ADHD (by excluding patients with prescription records for ADHD medication other than VYVANSE at any time, or with at least one VYVANSE prescription prior to launch of VYVANSE BED, or by excluding patients with VYVANSE prescriptions by certain specialties, as specified above), the sample size was reduced by 89% (from 75,044 to 8,622 patients) in sensitivity analysis 1, by 93% (from 75,044 to 5,072 patients) in sensitivity analysis 2 and by 91% (from 75,044 to 7,066 patients) in sensitivity analysis 3 in the cumulative reporting period

In the physicians' survey, data of 104 patients reported by 23 psychiatrists and of another 50 patients reported by 11 physicians of other specialties were analyzed. Corresponding figures in the 2019 survey were 100 patients reported by 30 psychiatrists and 50 patients reported by 15 physicians of other specialties. In the 2020 survey, 100 patients were reported by 23 psychiatrists and 50 patients by 8 physicians of other specialties. The mean number of patients treated with VYVANSE for indications other than ADHD within 12 months prior to the survey by psychiatrists varied between 6.1 ± 10.3 (median 4) in 2019, 7.6 ± 7.0 (median 4) in 2020 and 7.3 ± 5.3 (median 5) in 2021. On average, 13.5 ± 24.9 (median 5) patients in the survey round 2019, 14.6 ± 9.7 patients (median 15) in 2020 and 14.6 ± 16.6 patients (median 5) in 2021 were treated with VYVANSE - by physicians other than psychiatrists - for indications other than ADHD.

In three consecutive survey rounds performed in 2019, 2020 and 2021, psychiatrists reported BED as the main indication for 73%, 69% and 64% of patients, respectively; obesity for 14%, 11% and 7%, respectively; and other indications for 13%, 20% and 29%, respectively. The most frequently reported other diagnosis was depression. Of patients reported by other specialties across the three survey waves, only 36% (2020) to 44% (2021) of patients were prescribed VYVANSE for BED as the main indication, 32% (2021) to 48% (2019) for obesity and 10% (2019) to 26% (2020) for other indications such as oppositional defiant disorder or autism spectrum disorder.

In the survey, at the time of treatment initiation, 89% (2019) to 98% (2021) of patients reported by psychiatrists were in the indicated age group for BED of 18 to 55 years, 1% (2021) to 10% (2019) were >55 years and 1% (2019, 2021) to 3% (2020) were <18 years. Of the patients reported by other specialties, 40% (2021) to 58% (2019) were 18–55 years and

42% (2019) to 60% (2021) <18 years of age. In the NostraData database, data from the cumulative reporting period showed that slightly more than one third (38%) of patients with available age information were adults between 18 and 55 years and almost two thirds (60%) were under 18 years. Based on the sensitivity analyses in which patients likely to have received VYVANSE for ADHD were excluded, the percentage of patients between 18 and 55 years of age increased and ranged from 67% in sensitivity analysis 1 to 94% in sensitivity analysis 3. The percentage of patients <18 years of age decreased to 29% (sensitivity analysis 1) and 19% (sensitivity analysis 2).

The majority of patients reported in three survey rounds by psychiatrists were female (75% to 79%). Among patients reported by other specialties, proportions of female and male patients were closer to equal (50%, 64% and 46% were females in 2019, 2020 and 2021, respectively). Data for the cumulative study period from the NostraData database showed similar proportions of female and male patients in sensitivity analyses in which patients likely to have received VYVANSE for ADHD were excluded (48% to 52% were female). In the main analysis, including patients with ADHD, which is more prevalent in males, only 39% were female in the cumulative period of study.

Around two thirds of all patients in the survey rounds 2019 and 2020 (64% to 67% by psychiatrists, 58% to 74% by other specialties) were new users; this proportion was lower in 2021 (51% by psychiatrists and 38% by other specialties). In the NostraData database, the proportion of new users was 77% in the cumulative reporting period; in the most recent annual period, the proportion of new users in the database (47%) was similar to those in the survey performed in 2021.

The mean treatment duration including treatment gaps reported in the survey rounds 2019 and 2020 was around 6 months (median 3 months) among patients reported by psychiatrists and varied between 7 months (2020) and 11 months (2019) among patients reported by other specialties. In the 2021 survey, the mean treatment duration was longer with around 13 months (median 9 months) by psychiatrists and around 20 months (median 16 months) by other specialties. In the database, when excluding potential ADHD patients in the three sensitivity analyses, mean treatment duration in the cumulative study period ranged from 225 to 249 days (median 135 to 150 days / 4-5 months) including gaps, or 183 to 197 days (median 120 days / 4 months) when gaps were excluded. For comparison, in the main analysis of the database where all prescriptions were considered, the mean duration of exposure to VYVANSE for the cumulative reporting period was around 384 days (median 246 days / 8 months) including treatment gaps, or around 296 days (median 180 days / 6 months) when treatment gaps were excluded.

In the physician survey, treatment with VYVANSE was discontinued by around one fifth of patients (19% by psychiatrists and 21% by other specialties in 2019, 19% and 28% in 2020, 20% and 14% in 2021). In the NostraData database, discontinuation rate in the cumulative study period was 60% among all patients prescribed VYVANSE; it was around 45% in the three sensitivity analyses.

In the three rounds of the survey, the majority of the reported patients (78% to 82% by psychiatrists, 67% to 76% by other specialties) had received psychotherapy prior to initiating treatment with VYVANSE. Although there is no other approved medication for BED in Australia, a switch to VYVANSE from another medication was reported for 43% to 54% of the patients in the survey (43% to 57% by psychiatrists and 44% to 50% by other specialties); around 25% of all patients switched within 30 days after discontinuation of prior medication. Switch from VYVANSE to another medication was reported for 27%, 18% and 36% of all patients who discontinued treatment with VYVANSE in the survey rounds 2019, 2020, 2021, respectively; 43% to 67% of treatment discontinuers switched to psychological or nutritional

non-drug treatment and 18% to 33% to no other treatment. In the NostraData database, switches were only evaluated for specific medications (monoamine oxidase inhibitor [MAOI], selective serotonin reuptake inhibitor [SSRI] and serotonin–norepinephrine reuptake inhibitor [SNRI]), with a switch to VYVANSE observed for approximately 0.2% of patients in the main analysis and for 1% of patients in the sensitivity analyses in the cumulative data. A switch from VYVANSE to MAOI, SSRI or SNRI was observed in approximately 2% of patients in the main analysis and in 3% to 4% in the sensitivity analyses.

Based on the survey results from psychiatrists, the main co-treatments in patients with ongoing VYVANSE treatment were psychotherapy (51% to 61% of patients in three survey rounds), SSRI (34% to 38%), SNRI (19% to 25%) or another central nervous system (CNS) stimulant (6% to 10%). Co-treatments reported by other specialties were psychotherapy (46% to 97% of patients in three survey rounds), SSRI (12% to 28%), SNRI (0% to14%) or Guanfacine hydrochloride (3% to 5% of patients). Overall, 15% to 45% of patients treated by other specialties received concomitant medication; this proportion ranged from 60% to 65% among patients treated by psychiatrists.

Based on the NostraData database results, the primary concomitant drug treatment in the main analysis were other CNS stimulants (41% of patients in the cumulative reporting period) and SSRIs (23% of patients). In the sensitivity analyses, co-prescriptions of VYVANSE and SSRI were found for around one fourth of patients (26% to 29% in the cumulative period), and of VYVANSE and SNRIs for 9% to 10% of patients. No co-prescriptions for other CNS stimulants were observed in the sensitivity analyses, consistent with the exclusion criteria.

The mean prescribed daily dose (PDD) of the most recent VYVANSE prescription in the survey reported by psychiatrists varied between 45 mg and 48 mg (median 50 mg). As expected, PDD was lower for the first VYVANSE prescription, with a mean ranging from 30 mg to 32 mg and median 30 mg. Values reported by other specialties were in a similar range. In the main analysis of the database, the mean PDD was 44.6 ± 17.3 mg (median 50) in the cumulative study period. In the sensitivity analyses of the cumulative data, the mean PDD was similar to the main analysis (45 to 46 mg), with the median of 50 mg.

Physicians in the survey had been asked to specifically report patients who were prescribed VYVANSE for indications other than ADHD, to allow focusing on the population for the second approved indication for VYVANSE, BED. Therefore, when interpreting the survey results regarding potential off-label use shown below, it should be noted that an estimated 89% - 93% of patients (based on NostraData results for entire study period) who were prescribed VYVANSE for its primary indication, ADHD, were excluded from being reported in the physician survey. Accordingly, the results of the survey only apply to patients who were prescribed VYVANSE for BED or for non-approved indications.

Among the patients reported in the survey performed in 2021 who were prescribed VYVANSE for indications other than ADHD, an indication of BED was reported by psychiatrists for 64% of patients and by other specialties for 44% of patients. In other words, 36% of patients reported by psychiatrists and 56% of patients reported by other specialties were prescribed VYVANSE for non-approved indications. The proportion of patients prescribed VYVANSE for non-approved indications varied between 27% and 31% by psychiatrists and between 58% and 64% by other specialties in the 2019 and 2020 survey rounds, respectively.

Excluding ADHD indications, an age at initiation <18 years was reported for 1% to 3% of patients by psychiatrists and for 42% to 60% of patients of other specialties in three survey rounds. Patients >55 years of age were reported by psychiatrists (10%, 4% and 1% in 2019, 2020 and 2021, respectively), but not by the physicians of other specialties (0% in all three survey rounds).

Conditions contraindicated with the use of VYVANSE were evaluated prior to the first prescription and were reported in the survey by psychiatrists for 54% (2019) to 60% (2021) of patients and for 18% (2020) to 40% (2020, 2021) by other specialties.

No off-label use due to concomitant treatment with MAOI was reported with the exception of 1 patient (2%) reported by other specialties (2019) and 1 patient (1%) by psychiatrists (2021). No use with a PDD >70mg/day was identified with the exception of 1% of patients treated by psychiatrists in the survey performed in 2019 and 4% (2 patients) by other specialties in the current survey round (2021). In the database, a PDD >70mg/day was reported for 1% or less of the patients and concomitant treatment with MAOI for 0.1% of patients in the cumulative study period.

In summary, excluding ADHD indication, off-label use for any reason (indication other than BED, age <18 years or >55 years, contraindicated conditions, PDD >70 mg or concomitant use of MAOI) was identified for 63%, 72% and 70% of patients reported by psychiatrists in the survey rounds 2019, 2020 and 2021. Corresponding proportions among patients treated by other specialties were 92%, 72% and 86%, respectively.

The cardiovascular status of patients based on heart rate and blood pressure should be monitored during the first 12 months of treatment with Vyvanse. Physician's office visits during the first 12 months of treatment with VYVANSE were reported for 100% of patients in all three survey rounds with, on average, 4.4 ± 4.9 (2020) to 7.0 ± 6.4 (2021) visits per patient by psychiatrists and 3.4 ± 1.5 (2021) to 4.7 ± 3.7 (2019) by other specialties. Overall, in the physician survey, cardiovascular monitoring was reported for most patients in all three rounds (2019, 2020, 2021). Blood pressure and heart rate was monitored in 57% to 73% of patients treated by psychiatrists and in 86% to 98% by other specialties. On average, within the 12 months after initiation of VYVANSE, 3.3 ± 3.5 to 4.2 ± 4.9 measurements of blood pressure and 3.1 ± 2.5 to 4.3 ± 4.9 measurements of heart rate had been conducted by psychiatrists; similar results were reported for patients prescribed VYVANSE by other specialties (3.0 ± 1.3 to 4.3 ± 9.9 measurements of blood pressure and 2.5 ± 1.3 to 3.9 ± 2.1 measurements of heart rate).

Discussion

Information obtained via the survey indicated that the majority of patients reported by psychiatrists (around 70%) had a documented diagnosis of BED; this proportion was lower for patients by other specialties (around 40%). Up to half (32% to 48%) of the patients treated by physicians other than psychiatrists received VYVANSE for treatment of obesity. It is conceivable that the indications obesity and BED are conflated to some degree. The indication for VYVANSE was analyzed as documented by physician. Overestimation of "obesity" due to combined indications of BED and obesity may nevertheless be possible.

The results of the survey show that, among psychiatrists, VYVANSE is mostly prescribed to the indicated age group of 18 to 55 years (up to 98% of patients); this proportion was lower among other specialties (40% within 18 to 55 years), mainly due to prescriptions to patients younger than 18 years.

Gender distribution of patients differed between the data sources. In the physician survey, three fourth of patients (75%) prescribed VYVANSE by psychiatrists and up to 64% prescribed VYVANSE by other specialties were female, in line with the data available from literature (higher prevalence of BED among females than among males) (6). In the database, among patients with gender information available, approximately 60% were male in the main analysis. This is perhaps due to a high percentage of patients with ADHD, which is more prevalent in males. Data from the sensitivity analyses of the database results excluding

probable ADHD patients shifted this toward a more equal gender distribution (48% to 52% female), in the direction expected for the BED population.

The mean PDD of the first and the most recent VYVANSE prescriptions in the survey reported by all physicians were within the expected range. This was also confirmed in the database analysis. Prescribed overdosing was rare: PDD >70 mg/day was reported for less than 1% of prescriptions in the database and for 0% to 1.3% of the most recent prescriptions in the survey.

Around one half to two thirds of patients in the survey and three fourths of patients in the database during the cumulative period were new users. The mean treatment duration from the survey ranged from around 6 months in 2019 and 2020 to 13 months in 2021 among patients reported by psychiatrists and from 7 months (2020) to 20 months in 2021 for patients reported by other specialties. In the database, the mean treatment duration including gaps was around 7 to 8 months in all sensitivity analyses in the cumulative period, when potential patients with ADHD were excluded. This treatment duration was longer than the initial treatment period of 3 months recommended in the Product Information for BED, but shorter than the mean treatment duration when ADHD patients were also included (mean approximately 13 months in the cumulative period).

VYVANSE is indicated for moderate to severe BED in adults when non-pharmacological treatment is unsuccessful or not available. In line with this indication, the survey data show that 78% to 82% of patients reported by psychiatrists and 67% to 76% of patients reported by other specialties underwent psychotherapy prior to treatment with VYVANSE. Treatment with other medications prior to VYVANSE was reported for 43% to 54% of patients in the survey. Treatment discontinuation with VYVANSE was reported by approximately one fifth of patients, with around one half to two thirds of them switching to psychotherapy or non-drug nutrition treatment and around one fifth to one third switching to other medication. Currently there is no approved prescription treatment for BED in Australia other than VYVANSE, and the trend of switching to VYVANSE from other medications or from VYVANSE to other medications may suggest that clinicians explored other medications for the intended indications.

Psychotherapy was indicated as the main co-treatment in the survey by both psychiatrists (51% to 64%) and other specialties (46% to 97%). The broad variability in percentages among co-treated among other specialties could be the low number of reporting physicians other than psychiatrists (8 to 15 per reporting period), which was further reduced by the requirement that patients need to have ongoing treatment with VYVANSE for analysis of co-treatment. The most common concomitant medications were SSRIs or SNRIs. Other CNS stimulants reported for 4%-10% of all patients may be indicative of treatment for ADHD, which suggests that some of the patients reported in the survey may be patients with ADHD, even if ADHD was not reported as the main indication for prescription of VYVANSE in these patients. However, due to data protection reasons, it is not possible to follow up on individual patients for further clarification. In the main analysis of the database, the most common drug co-treatments were CNS stimulants (including stimulant ADHD medication), followed by SSRIs, Guanfacine hydrochloride and SNRI. In the sensitivity analyses, where patients with ADHD medications had been excluded, SSRIs were found to be dispensed for approximately one fourth of the patients and SNRIs for approximately 10%.

Monitoring of cardiovascular outcomes was conducted for the majority of patients reported in the survey, indicating an awareness of the physicians of cardiovascular risks for these patients. Monitoring was performed with, on average, 3 to 4 measurements per patient during the first 12 months of treatment.

Conclusion

In summary, findings regarding indication, age, prescribing patterns and potential off-label use of VYVANSE are consistent throughout the three study reports (interim report 1, interim report 2, final report). Overall, the results indicate that psychiatrists prescribe VYVANSE in accordance with the label with regards to dosage and mostly also for age and indication. The majority of patients managed by psychiatrists received Vyvanse for treatment of BED; when excluding prescriptions for ADHD treatment, there were only a few reports of patients <18 years of age by psychiatrists and few patients (4%) were >55 years. Lower compliance with regards to indication and age was observed for patients reported by other specialties, who frequently prescribed VYVANSE for indications other than BED (56%-64% of patients), or to patients <18 years of age (42%-60%). Better physicians' compliance is also needed with regards to reports of contraindications (54%-60% of patients by psychiatrists, 18%-40% by other specialties) that slightly increased at psychiatrists during the study period. Although not contraindicated, better compliance is needed with co-prescriptions of SSRI and SNRI, which were observed in one third of patients in the database and in the survey. The mean treatment duration, with more than 6 months both in the survey and in the sensitivity analyses of the database, was longer than the recommended initial treatment period of 3 months period listed in the Product Information.

For all patients, additional physician visits were reported during the first 12 months of treatment in addition to treatment initiation indicating compliance with the recommendation to regularly assess if there is an ongoing requirement for treatment with VYVANSE. The data on blood pressure and heart rate monitoring during the first 12 months of treatment confirmed physicians' compliance with, and awareness of the potential cardiovascular risks associated with the use of VYVANSE in the population of patients with BED.

In accordance with the product information, prescriptions of Vyvanse for BED should be initiated by psychiatrists. Despite the relatively high rate of off-label prescribing of Vyvanse by non-psychiatrists, we believe the results discussed in this report, as a whole, do not indicate a change in the benefit-risk profile for this product, which remains positive.

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